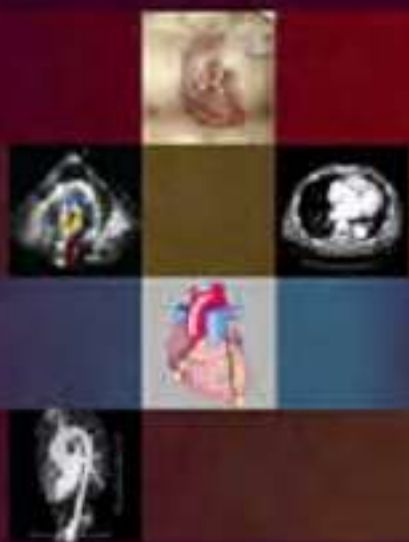


Allen Jeremias
David L. Brown

CARDIAC INTENSIVE CARE

2ND EDITION



Cardiac Intensive Care

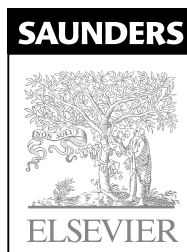
Second Edition

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Dedicated to my parents, Dr. Andreas and Susanne Jeremias, who always supported me in every endeavor and made me who I am today; and to my grandfather, Dr. Nicolaus Jeremias, whose unwavering dedication to patient care has set the standard that I aspire to.

Allen Jeremias

This edition is dedicated to my mentor, Kanu Chatterjee, MBBS, on the occasion of his retirement from the Division of Cardiovascular Medicine at University of California, San Francisco, where he inspired and taught generations of trainees the art, science, and humanity of medicine.

David L. Brown

Foreword

The care of acutely ill cardiac patients has evolved over the past 40 years through a series of landmark developments and milestones. Coronary intensive care began in the 1960s with the introduction of electrocardiogram (ECG) monitoring for patients with acute myocardial infarction (MI). ECG monitoring coupled with the introduction of antiarrhythmic interventions (cardioversion, defibrillation, and lidocaine) led to a dramatic decrease in the mortality of patients with acute MI, largely through a reduction of in-hospital ventricular dysrhythmias. This was the first major milestone in the care of patients with acute MI. At this time, hemodynamic dysfunction and pump failure emerged as the leading causes of death in acute MI.

In the early 1970s, the introduction of bedside pulmonary artery catheterization, by Willie Ganz and Jeremy Swan at the Cedars-Sinai Medical Center, made possible accurate assessment of hemodynamic dysfunction in critically ill cardiac patients. This landmark development spawned a new era of coronary care that led to better assessment and management of pump dysfunction, stimulating the introduction of afterload-reducing therapy for heart failure. Around the same time, the concept of infarct size as a major determinant of ventricular dysfunction and prognosis began in the experimental laboratory, triggering a search for interventions to limit infarct size in experimental animals. The results of various therapies in this regard were inconsistent in the laboratory and in the clinical arena.

The next major milestone came in the late 1970s and early 1980s, when the role of coronary thrombosis as the proximate cause of acute MI became firmly established through the landmark study of Marcus DeWood, then a trainee in cardiology. With this observation and the elegant early experimental work of many investigators, the importance of timely reperfusion as a powerful method for infarct size limitation was recognized. The focus on reperfusion, initially with intracoronary and subsequently with intravenous thrombolysis and more recently with primary angioplasty, as a means of reducing infarct size and decreasing mortality revolutionized contemporary care of patients with developing MI.

This advance represented another major milestone in coronary care. All this stepwise progress over the years has led to a substantive and steadily declining mortality for patients with acute MI. The past several years have witnessed an explosion in our knowledge of vascular biology, atherogenesis, plaque disruption and thrombosis, and the concept of acute coronary syndromes. These concepts have led to dramatic improvements in our ability to diagnose and manage patients with unstable angina with potent antithrombotic strategies ranging from aspirin and heparin to platelet receptor antagonists and direct thrombin inhibitors to angioplasty and stent implantation.

Throughout this progress, coronary care units evolved from specialized areas catering to patients with acute ischemic syndromes to a place where we now take care of the ever-increasing population of patients with other critical cardiovascular illnesses, such as acute and severe chronic heart failure, chronic pulmonary hypertension, life-threatening cardiac dysrhythmias, aortic dissection, and other diagnoses. A modern coronary care unit is, in reality, a cardiac intensive care unit.

This second edition of *Cardiac Intensive Care*, presented in a new full-color design, edited by Allen Jeremias, MD, MSc, and David L. Brown, MD, provides a state-of-the-art compendium summarizing all of the progress that has been made in the diagnosis, assessment, and treatment of patients with critical cardiac illnesses over the past several years. The 52 chapters and 3 appendices are written by experienced authors who have made important contributions in their respective fields. Nine new chapters have been added in this new edition dealing with topics including quality assurance and improvement, physical examination, mechanical treatments for acute ST segment elevation MI, non-ST segment elevation MI, and management of post-cardiac surgery patients. The convenience of full-text online access at expertconsult.com is an added bonus.

The editors have captured the essence of what is the state-of-the-art in a rapidly evolving and dynamic field. The contents of this text provide a nice blend of pathophysiology and the more pragmatic issues of actual intensive cardiac care. In addition to dealing in detail with the issues of acute cardiac problems, this text provides a broader perspective by including many useful chapters that deal with critical care issues of a more general nature, such as airway and ventilator management, resuscitation, dialysis, and ultrafiltration. The editors and the authors are to be commended for having produced an up-to-date and useful treatise on cardiovascular critical care.

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Preface



Since the publication of the first edition of *Cardiac Intensive Care*, there have been considerable changes in the level of care and the complexity of therapies provided in the cardiac intensive care unit (CICU). To reflect these changes appropriately, the second edition of *Cardiac Intensive Care* has not only been updated, but also completely restructured with many new chapters. Given that most CICU admissions are still related to coronary artery disease and its acute manifestations, one major focus of this text remains the diagnosis and therapeutic options for patients with acute coronary syndromes. Section III, Coronary Artery Disease, is divided into Acute Myocardial Infarction, Complications of Acute Myocardial Infarction, and Complications of Percutaneous Interventional Procedures. We recognize, however, the ever-increasing multifaceted disease states that are cared for in the CICU and have included sections on Noncoronary Diseases, Pharmacologic Agents in Cardiac Intensive Care Unit, and Advanced Diagnostic and Therapeutic Techniques.

The evidence base for practice in the CICU is expanding rapidly, placing high demands on the daily “rounders.” The field of cardiovascular medicine has expanded to subsume multiple subspecialties and a multitude of procedures, including percutaneous coronary intervention, percutaneous valve procedures,

peripheral arterial procedures, atrial and ventricular ablations, pacemaker and defibrillator implantations, and cardiac imaging. The cardiac intensivist is required to make informed decisions about the potential benefit versus the risks of referring patients for these procedures and to interpret the data derived from these procedures adequately. In addition, adding to the dynamic environment, optimal patient care in the CICU is delivered via a multidisciplinary approach involving physicians, nurses, ethicists, respiratory therapists, nutritionists, physical therapists, and social workers. The goal of this second edition of *Cardiac Intensive Care* is to provide a comprehensive, conceptual, yet practical and evidence-based text for all specialties involved in patient care in a CICU.

The editors thank Natasha Andjelkovic from Elsevier for her tireless efforts and her ongoing encouragement throughout this endeavor. Additionally, we express our deep appreciation to all the contributing authors. Without their expertise, dedication, and time commitment, this book would not have been possible.

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Evolution of the Coronary Care Unit: Past, Present, and Future

Jason N. Katz, Richard C. Becker

Origins of the Coronary Care Unit
Validating the Benefits of the Coronary Care Unit
Economic Impact of the Coronary Care Unit
Critical Care in the Coronary Care Unit

Describing the Contemporary Coronary Care Unit—
the Duke Experience
Future Trends and Continued Evolution in the
Coronary Care Unit
Conclusion

ORIGINATING DURING a time of great technical and investigative discovery, the coronary care unit (CCU) has emerged as one of the most important advances in the care of patients with acute coronary syndromes. Despite the notion that the CCU has revolutionized the management of myocardial infarction (MI), however, widespread proliferation and acceptance of the CCU as “standard of care” has not been met with universal support. Complicating matters further, the CCU has changed considerably over the past several decades, bringing to light unresolved issues of patient triage, medical ethics, physician and nurse training, cost, and resource use. This chapter reviews the evolutionary history of the CCU, from its inception in the early 1960s to its contemporary role in the care of often critically ill patients with cardiovascular disease (Fig. 1-1). Future trends in cardiac care also are addressed, with particular attention given to ways in which the CCU may remain a viable entity within a continuously changing health care system.

Origins of the Coronary Care Unit

Several seminal reviews of acute MI—a highly fatal disease at the time—served to highlight the critical need for improved methods of health care delivery.^{1,2} Outside of morphine and comfort care measures, there was little available in the clinician's armamentarium to spare patients with acute MI from death or prolonged convalescence. Treatment of MI at the time has been described as “benign neglect,”³ and even minimal forms of patient exertion were discouraged.

Focus on Resuscitation

The first reasonable therapy to combat complications of myocardial ischemia finally became available after the successful implementation of open-chest^{4,5} and, later, closed-chest

defibrillation.^{6,7} After reporting on the effective open-chest defibrillation of a patient who developed life-threatening ventricular arrhythmia in the setting of MI, Beck and colleagues⁵ prophetically reported that “this one experience indicates that resuscitation from a fatal heart attack is not impossible and might be applied to those who die in hospital ... and perhaps to those who die outside the hospital.” Following closely on the heels of these discoveries and the demonstrated efficacy of closed-chest massage,⁸ the concept of the CCU as a vehicle for successful resuscitation began to take shape.

Julian, the senior medical registrar of the Royal Infirmary of Edinburgh, first articulated the idea of the CCU. In his original presentation to the British Thoracic Society in 1961,⁹ Julian described five cases of cardiac massage used in resuscitation attempts for patients with acute MI. He concluded that “many cases of cardiac arrest associated with acute myocardial ischaemia could be treated successfully if all medical, nursing, and auxiliary staff were trained in closed-chest massage, and if the cardiac rhythm of patients ... were monitored by an electrocardiographic linked to an alarm system.” His vision for the CCU was founded on four basic principles, as follows:

1. Continuous electrocardiogram monitoring with arrhythmia alarms
2. Cardiopulmonary resuscitation with external defibrillator capabilities
3. Admission of patients with acute MI to a single unit of the hospital where trained personnel, cardiac medications, and specialized equipment were immediately available
4. The ability of trained nurses to initiate resuscitation attempts in the absence of immediate physician presence

At roughly the same time, several clinician investigators in North America developed specialized units devoted exclusively to the treatment of patients with suspected MI. In Philadelphia,

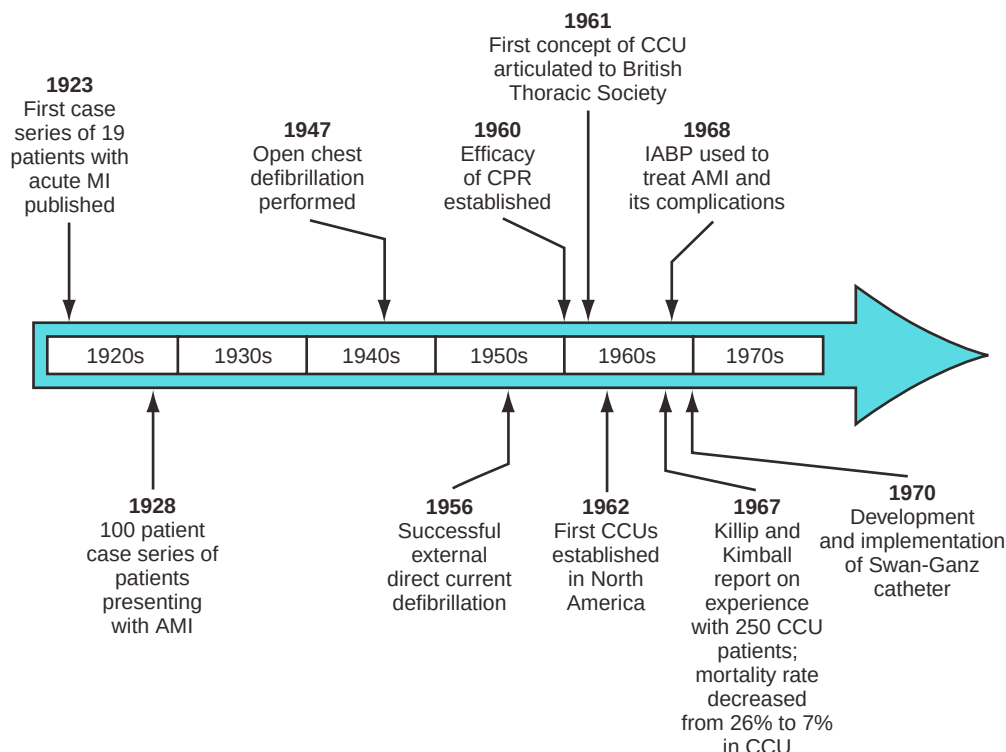


Figure 1-1. Timeline of landmark events in the evolution of the coronary care unit (CCU). AMI, acute myocardial infarction; CPR, cardiopulmonary resuscitation; IABP, intra-aortic balloon pump.

Meltzer¹⁰ created a two-room research unit with an aperture in the wall through which defibrillator paddles could be passed from one patient to the other. In Toronto, Ontario, Brown and associates¹¹ erected a four-bed unit with an adjacent nursing station for the care of MI patients. Arrhythmia surveillance was provided using a converted electroencephalogram unit with electrocardiogram amplifiers. Although Brown's initial observations suggested no immediate decline in mortality associated with more attentive coronary care,¹¹ these preliminary findings did little to temper the growing enthusiasm for these specialized units.

Day,¹² a contemporary of Meltzer, Brown, and Julian, began building mobile crash carts in the attempt to resuscitate acute MI patients being monitored on the general medical floors. Similar to his colleagues, Day astutely recognized that delays in arrhythmia detection on these general wards significantly limited the success of resuscitation attempts. As a result of his observations, an 11-bed unit was established at Bethany Hospital in New York staffed by "specially-trained nurses who could give the patient with coronary disease expert bedside attention, interpret signs of impending disaster, and quickly institute CPR."¹² Day is largely credited with introducing the term *code blue* to describe resuscitation efforts for cyanotic patients with cardiac arrest and, perhaps more importantly, the term *coronary care unit*.

Shift in Paradigms—Prevention of Cardiac Arrest

Until this point, the benefit of specialized care in the CCU was predominantly related to recognition of peri-infarction arrhythmias that were incompatible with life, and the successful termination of such events. It seemed clear to physicians of the time

that the development of malignant arrhythmias posed the greatest threat to patients sustaining acute cardiac injury, and perhaps the early recognition and prompt therapy for early prodromata of cardiac arrest might have a significant impact on patient survival. The focus of the CCU moved from one of resuscitation to a more preventive role. Julian¹³ described this transformation as the "second phase" in the evolution of the CCU.

In the late 1960s, Killip and Kimball¹⁴ published their experience with 250 acute MI patients treated in a four-bed CCU at New York Hospital–Cornell Medical Center. Credited largely with the MI classification scheme that now bears their name, in which the presence or absence of heart failure or shock had significant prognostic implications, these two investigators also showed that aggressive medical therapy in the CCU seemed to reduce in-hospital mortality from 26% to 7%. This led Killip and Kimball to proclaim in their landmark report that "the development of the coronary care unit represents one of the most significant advances in the hospital practice of medicine."¹⁴ Not only did it seem that patients with acute MI had improved survival if treated in a CCU, but also all in-hospital cardiac arrest patients seemed more likely to survive if geographically located in the CCU.

"Although frequently sudden, and hence often 'unexpected,' the cessation of adequate circulatory function is usually preceded by warning signals."¹⁴ With these words, Killip and Kimball, collectively, with the influential findings of Day, Meltzer, Brown, and others, ushered in the rapid proliferation of CCUs throughout the world, with a categorical focus on the prevention of cardiac arrest.

Truly at the forefront of this new paradigm in coronary care were Lown and colleagues,¹⁵ who elaborately detailed the key

components of the CCU at the Peter Bent Brigham Hospital. “From the opening of the unit,” they reported, “the focus has been the prevention of cardiac arrest.” The foundation of their CCU revolved around employment of a “vigilant group of nurses properly indoctrinated in electrocardiographic pattern recognition and qualified to intervene skillfully with a rehearsed and well-disciplined repertoire of activities in the event of a cardiac arrest.”¹⁵ With a CCU mortality of 11.5% and an in-hospital mortality of 16.9%, these investigators concluded that an aggressive protocol emphasizing arrhythmia suppression after MI could virtually eradicate sudden and unexpected fatalities. Although more contemporary data refuting the notion of preventive antiarrhythmic therapy in MI fail to support the early premise of Lown and others,¹⁶ their debatable yet compelling results allowed the concept of the CCU to continue to flourish.

Several other developments in the late 1960s through the mid-1980s, including the use of intra-aortic balloon counterpulsation,¹⁷ the implementation of flow-directed catheters capable of invasive hemodynamic monitoring,¹⁸ and the use of systemic thrombolysis for the treatment of coronary thrombosis,¹⁹ helped to advance the frontiers of the CCU. Along with these dramatic changes in the care of patients with acute MI came a remarkable transformation in the face and philosophy of the CCU. At the same time, questions and controversies began to emerge regarding the benefits and proper use of these specialized and costly units.

Validating the Benefits of the Coronary Care Unit

Although use of a CCU for the management of patients with acute MI became more commonplace, many still questioned their true impact. These critics pointed to the dubious nature of the early comparisons between CCUs and the general medical wards, most of which were purely observational and experiential reports, and all of which unquestionably lacked the scrupulous scientific and analytic techniques of contemporary clinical research. Adding further fuel to the controversy was a study by Hill and associates²⁰ in the late 1970s comparing outcomes of patients with suspected MI managed at home with outcomes of patients managed in the hospital setting. These investigators found no significant differences in mortality for the two groups, although skeptics cite design flaws, power limitations, and dynamic advances in hospital-based care as major confounders to this study. Nonetheless, results such as these led many, including Cochrane,²¹ to exclaim, “... the battle for coronary care is just beginning.”

Much of the data in support of the CCU was largely observational. As previously described, Killip and Kimball¹⁴ attributed a nearly 20% decline in mortality to the successful implementation of their CCU. Other nonrandomized data from a Veterans Administration population²² and several Scandinavian studies^{23,24} corroborated the early uncontrolled observations of Killip, Kimball, Day, and others. These trials all showed lower mortality rates and greater resuscitation success in acute MI patients when treated in a CCU setting.

Goldman and Cook²⁵ attempted to ascribe the epidemiologic decline in mortality rates from ischemic heart disease in the United States to the presence of CCUs. From 1968-1976,

estimates suggested a decline in mortality of approximately 21%. Using complex statistical analyses and mathematical modeling, the authors surmised that nearly 40% of the decline could be directly attributable to specific medical interventions, with the CCU being one of the premier contributors. They suggested that approximately 85,000 more people would be alive at the end of 8 years because of the presence of CCUs than would have otherwise been alive; in other terms, the CCU may have accounted for approximately 13.5% of the decline in coronary disease-related mortality.²⁵ Epidemiologic estimates from other investigators seemed to corroborate these findings.²⁶

On an even broader scale, Julian¹³ and Reader²⁷ contemplated that the steady decline in mortality among people 35 to 64 years old in the United States, Australia, and New Zealand since 1967 (the advent of CCUs) may have been a direct effect of the specialized care received in the CCU. More contemporary data, in patients treated during the “thrombolytic era,” have suggested that one highly significant independent predictor of 30-day mortality among acute MI patients was treatment isolated to an internal medicine ward.²⁸ Despite the retrospective nature of this analysis, the findings seemed to underscore the importance of treating acute MI in the setting of an intensive CCU.

Although there are significant limitations to the available data, a plethora of nonrandomized studies seems to support the beneficial role of the CCU in the management of patients with acute cardiac ischemia. A truly randomized, prospective study evaluating the role of the CCU is likely impossible, given the current (albeit arguable) burden of proof in support of these units. Key opinion leaders in the field of cardiovascular medicine have nearly unanimously endowed the CCU as “the single most important advance in the treatment of acute MI.”^{29,30}

Economic Impact of the Coronary Care Unit

Evaluation of the economic impact of the CCU poses a significant challenge, and no single study has directly addressed this issue. Not only is it difficult to measure true costs in a dynamic health care system, but also evolutionary changes in the CCU (with concomitant changes in resource use, therapeutic procedures, and medication administration) makes fiscal assessments quite unwieldy.

If one were to draw correlates with other contemporary critical care units, perhaps cost could be put into some perspective. Because they are places of high resource use and high expenditure, intensive care units (ICUs) contribute significantly to the economic burden of health care facilities and, on a broader scale, to the economic burden of societal health care. Although ICUs constitute less than 10% of hospital beds in the United States, estimates suggest that ICUs consume more than 20% of total hospital costs and nearly 1% of the U.S. gross domestic product.^{31,32} It has been suggested that ICU costs have increased by nearly 200% in the years 1985-2000.³³

The argument over whether or not CCUs are comparable to ICUs, or, perhaps more importantly, whether or not they should be, is addressed later in this chapter. Data exist to support similarities in resource use, morbidity and mortality, and in-hospital length of stay^{34,35}—all of which have significant economic impact and need to be addressed in more rigorous scientific analyses of CCU populations.

Critical Care in the Coronary Care Unit

The landscape of the CCU has evolved over the last several decades. As a result of more sensitive diagnostic tools, advanced pharmacotherapeutics, and novel interventional techniques, cardiologists now have the ability to alter the natural history of MI significantly. Consequently, the mortality rates for acute MI in several contemporary acute coronary syndrome databases have steadily declined.³⁶⁻³⁸ At the same time, however, the presence of other cardiovascular diseases and noncardiac critical illness seems to be increasing in today's CCU. An aging U.S. population, acute and chronic sequelae of nonfatal MI, comorbid medical conditions, and complications of implantable devices all result in increased susceptibility to critical illness in high-risk patients. Many, if not all, of these patients are likely to be admitted to the CCU. What were previously purely resuscitative and preventive units for patients with MI have now arguably transformed into critical care units for patients with cardiovascular disease. Some authors have suggested that perhaps even the name "coronary care unit" has become a misnomer in today's health care environment; Julian¹³ has advocated more recently that the CCU could instead be more appropriately called the *cardiac care unit*. Others have suggested that the distinction between contemporary CCUs and ICUs has become blurred—largely resulting from an increased cardiac critical care burden.³⁹

In a single-day descriptive analysis of U.S. critical care units, Groeger and colleagues³⁴ highlighted mortality statistics, resource use data, and patient characteristics of modern CCUs; results which were remarkably comparable to composite data from contemporary medical ICUs.^{34,35} Another more recent investigation concluded that severity of illness, quantified by a classic physiologic measure of critical illness (the APACHE [Acute Physiology, Age, and Chronic Health Evaluation] II score), was the greatest independent predictor of in-hospital mortality in a CCU cohort of patients—suggesting that risk stratification in the CCU could be conducted in a manner similar to other ICUs, where the APACHE II score has been well established.⁴⁰

Although limited observational data suggest that current CCU patients have become more complex from a critical care perspective, there are no large contemporary analyses that corroborate these findings on a broader scale. If the CCU has indeed evolved into an ICU for cardiac patients, re-examination of the role of the CCU, and the role of the cardiologists staffing these units, is warranted. Whether the CCU is a beneficial tool in its current stage of evolution is unknown. In a retrospective study of patients admitted to a CCU in Lazio, Italy, investigators found no significant differences in in-hospital mortality between CCU and non-CCU admissions for patients with cardiac diagnoses other than acute MI or arrhythmia.⁴¹ Additionally, a growing body of evidence now exists to support the benefits of critical care specialists to improve the care of ICU patients,⁴²⁻⁴⁴ and there has been some suggestion that the CCU may benefit from similarly requisite critical care physician training.³⁹

Describing the Contemporary Coronary Care Unit—the Duke Experience

Several contemporary databases have been used to describe operational and demographic features of ICUs in the United States.^{34,45-47} These rich datasets have been used to help

establish practice guidelines, to generate hypotheses for novel clinical research efforts, and to accelerate quality improvement initiatives in critical care medicine. The datasets contain very limited information on CCUs, however, and there have been no concerted efforts to illustrate or define, through similar registries, the role of the modern CCU.

In an effort to better understand the current practice model of a CCU in today's academic health care system, the authors of this chapter have created a single-center database containing 2 decades' worth of diagnostic, procedural, demographic, and outcome-related variables from the Duke University Medical Center CCU. Unadjusted, descriptive results are illustrated in Figures 1-2 and 1-3. These graphs highlight the growing critical care burden and increased implementation of critical care resources in the CCU at Duke, and it is our hope that this database will result in numerous novel hypothesis-generating analyses, and stimulate collaborative multicenter investigations to better understand the continued evolution of the CCU.

Future Trends and Continued Evolution in the Coronary Care Unit

Multiple nonrandomized studies seem to support the beneficial role of the CCU in the management of patients with acute MI. As a result, there has been a rapid proliferation of these specialized units in the United States and worldwide since their introduction into the medical vernacular more than 4 decades ago. At the same time, data support significant evolutionary changes within contemporary CCUs. Observational studies suggest that although the mortality for acute MI has steadily declined, there is a greater burden of noncoronary cardiovascular disease and critical illness. For these particular patients, the role and impact of CCU care are uncertain. This uncertainty has numerous implications related to patient outcomes, resource use, and costs of care. As we continue to work toward better defining the changing landscape of the CCU and its place within the current health care system, there are several key topics that need to be addressed.

Multidisciplinary Clinical Integration and the Coronary Care Unit Model

Because of the multiplicity and complexity of critical care delivery, and the advancing critical care burden in the contemporary CCU, the development of practice models for efficient and effective patient care will be an important part of the continued evolution of the CCU. At the same time, landmark documents from the Institute of Medicine have attacked several "dysfunctional" processes of past and current health care systems, with particular attention focused on the elimination of "isolationist decision-making and ineffective team dynamics" that may put patient care at risk.^{48,49} A careful appraisal of the role of multidisciplinary care in the CCU will therefore be a vital component of future study.

Currently, several models of health care delivery are employed in ICUs—the open model, the closed model, and hybrid models. All of these critical care platforms have distinct advantages and disadvantages from patient-care and systems-based perspectives. In a closed ICU model, all patients admitted to an ICU are cared for by an intensivist-led team that is primarily responsible for making clinical decisions. In a contemporary CCU, this

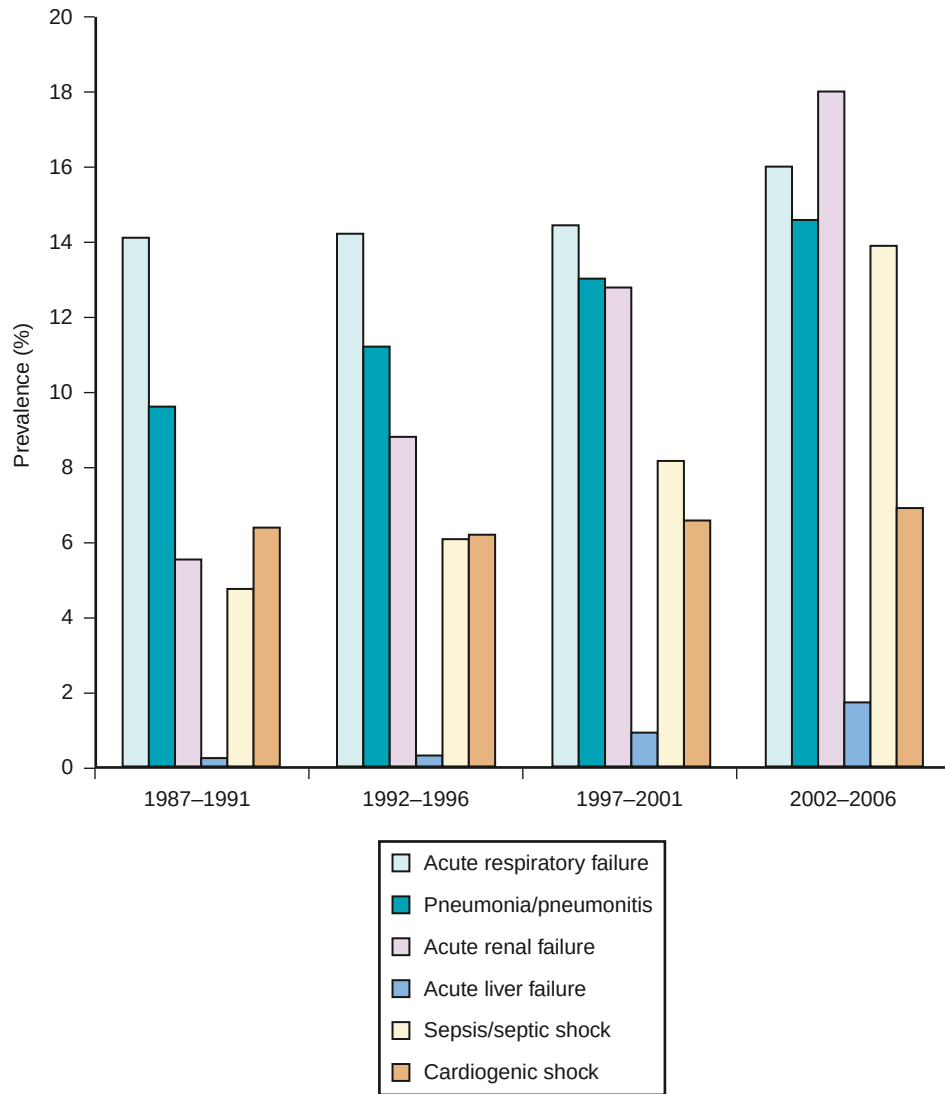


Figure 1-2. Unadjusted trends in selected critical illness in the Duke University Medical Center coronary care unit (unpublished data, 1987-2006).

leader might be a general cardiologist, a cardiologist with critical care expertise, or an intensivist adept in the care of patients with complex cardiovascular illness. In an open ICU model, the patient's primary physician determines the need for ICU admission and discharge and makes all management decisions. As its name suggests, a hybrid or transitional ICU model is a blend of the two more traditional critical care delivery models. The burden of evidence seems to support a closed or hybrid ICU format for delivering high-quality, cost-effective care compared with the open model,^{50,51} and descriptive studies of current practice patterns show greater implementation of these health care delivery systems in the United States.⁴⁵

Governing bodies for the major critical care medicine organizations universally espouse the benefits of multidisciplinary critical care.^{52,53} It is believed that shared responsibility for ICU team leadership is a fundamental component for providing optimal medical care for critically ill patients. A multidisciplinary approach to CCU management, in light of the growing patient complexity, seems equally reasonable. Potential members of

CCU teams, all of whom would be intimately connected in the day-to-day care of patients, might include a cardiologist, intensivist, pharmacist, respiratory therapist, critical care nurse, and social worker or case manager (Fig. 1-4). The goal of this integrated approach would be to provide the highest quality care, while limiting adverse events, curbing ineffective resource use practices, and providing an efficient patient transition out of the intensive care setting.

Nursing and Clinician Training Requirements

In today's CCU, in contrast to the CCU of the 1960s, having nurses trained in the vigilant detection of life-threatening arrhythmias and educated in the implementation of cardiopulmonary resuscitation and defibrillation is no longer sufficient. Most CCUs employ nurses with the most rigorous critical care backgrounds. With growing numbers of patients who have cardiovascular disease, many of whom will require admission to the CCU during their lifetimes, there is a significant need for training more nurses skilled in cardiovascular and critical care. At the

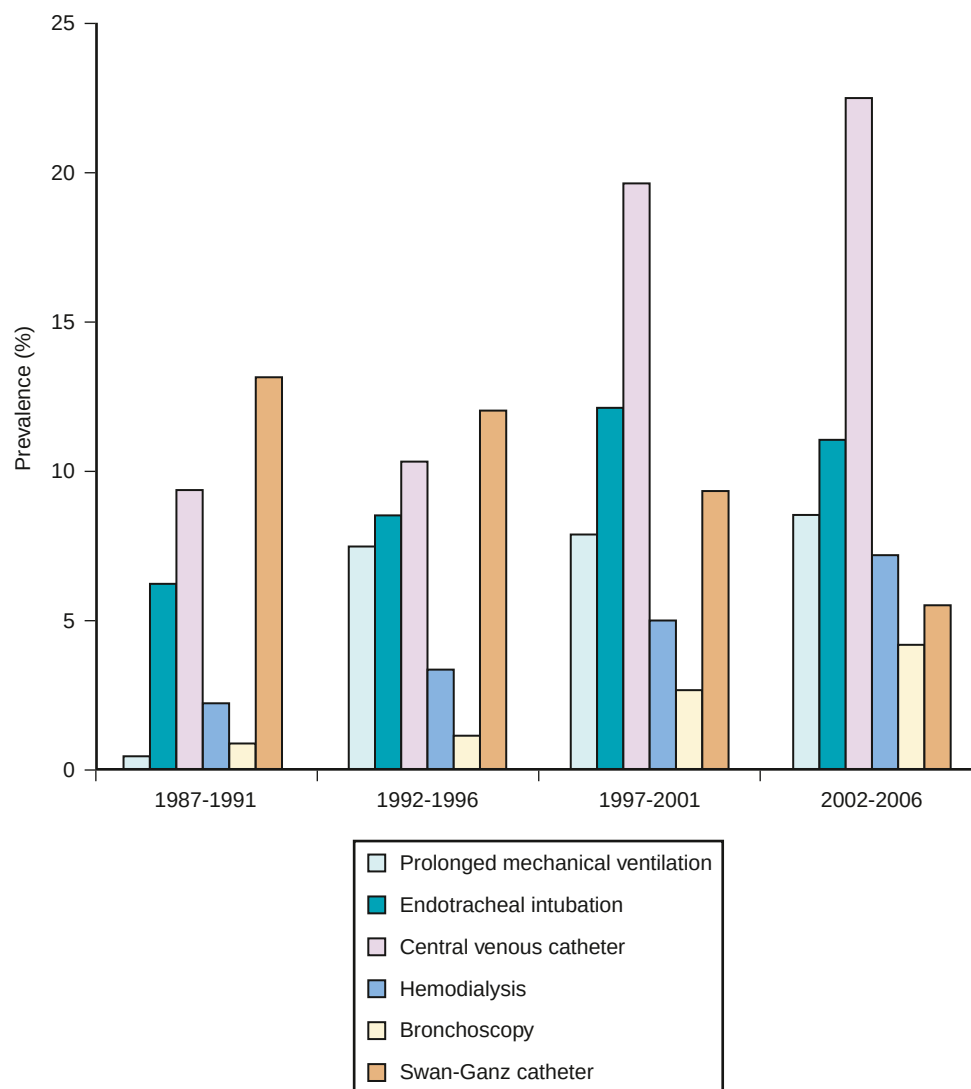


Figure 1-3. Unadjusted trends in selected critical care procedures in the Duke University Medical Center coronary care unit (unpublished data, 1987-2006).

same time, the burden of nursing shortages⁵⁴ raises a difficult proposition for the continued viability and growth of CCUs in the United States. It is imperative that these issues be fundamentally addressed because the CCU nurse is arguably the most influential component of the multidisciplinary team from an operational perspective.

As alluded to previously, the diversity of critical illness in today's CCU poses many challenges to the general cardiologists that most commonly staff these units. Whether we provide these clinicians with requisite skills in critical care delivery (in the form of continuing medical education), or we train cardiologists with advanced specialization in critical care medicine, or we demand obligatory intensivist input in the care of all critically ill CCU patients, there are many unresolved issues that have direct implications to the future role of CCU clinicians. There is a significant amount of pressure for all critical care units to be staffed by appropriately trained intensivists,⁵⁵ largely the result of numerous nonrandomized studies pointing to the benefits that these clinicians have on the care

of patients with critical illness.^{43,44} CCUs may be targeted for such reform in the future.

Technology Needs in Today's Coronary Care Unit

Beyond the continuous telemetry monitoring and defibrillator capabilities advocated by Julian, Brown, and others, contemporary CCUs have considerably more technologic requirements, including the ability to provide noninvasive and invasive hemodynamic monitoring, mechanical ventilation, fluoroscopic guidance for bedside procedures, continuous renal replacement therapy, methods for circulatory support (e.g., intra-aortic balloon counterpulsation, percutaneous and implantable ventricular-assist devices, extracorporeal life support), and portable echocardiography. Additionally, the development of clinical information systems for standardization of care, for monitoring outcomes metrics, and for quality assurance purposes has become widely supported. These clinical information systems often include electronic clinician order entry and real-time nursing data entry as well.

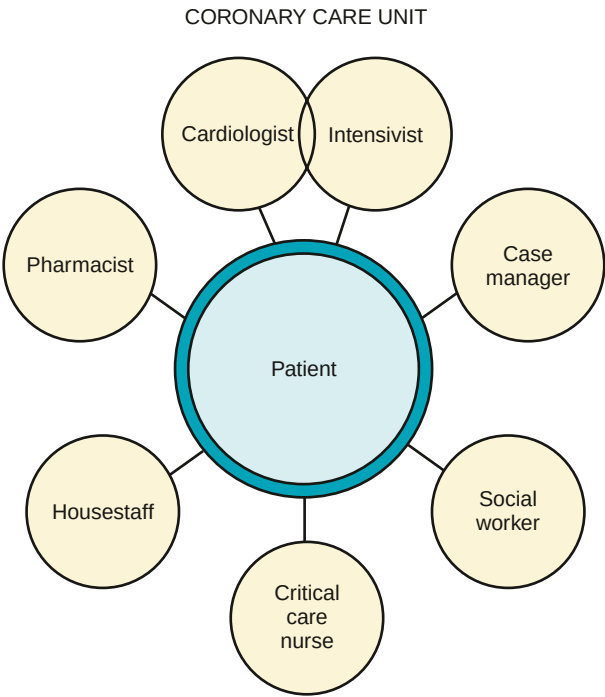


Figure 1-4. Proposed components of a multidisciplinary coronary care unit (CCU) team. Future training models may develop clinicians who have expertise in critical care and cardiovascular medicine—characteristics of an ideal CCU team leader.

Finally, there has been a growing enthusiasm for telemedicine, especially for more rural health care facilities with limited resources for critical care. This technology has also been advocated as a way to navigate the impending crisis of insufficient critical care specialists to meet the growing demands for their skills,⁵⁶ and has a potentially viable role in the operation of many U.S. CCUs.

Platforms for Coronary Care Unit–Based Critical Care Research

The evolution of the CCU also provides a fertile environment from which to conduct novel research. Existing platforms for CCU-based critical care investigation have included the ongoing development and implementation of mechanical circulatory support devices, the creation of models for the study of sepsis-associated myocardial dysfunction, and the execution of clinical analyses to study the impact of bleeding and transfusion on patient outcomes. The potential for future platforms in basic, translational, genomic, and clinical study is seemingly limitless, and the generation of knowledge culminating from such research will inevitably lead to improvements in patient care—the result of more efficient CCU operational models, standardization of cardiac critical care delivery, creation of physician decision-support tools, and advanced personnel training. Key components for developing a successful, translatable, and reproducible platform of CCU-based critical care research include the creation of uniform computerized databases for efficient data abstraction, the organization of dedicated cardiac critical care research teams, and the establishment of focused multicenter and international research networks with the necessary tools for implementing novel research constructs.

Table 1-1. Potential Platforms for Coronary Care Unit (CCU)–based Critical Care Research

Systems-of-care studies and analyses of organizational models in the CCU
Novel biologic markers for noncoronary cardiovascular critical illness
Device development (e.g., minimally invasive hemodynamic monitoring)
Risk stratification, creation of expanded physiologic scores, and appropriate triage practices
Economic analyses of CCU-based critical care delivery
Practice patterns for pharmacotherapy in the CCU and drug development for cardiovascular critical illness
Genomic studies of critical illness susceptibility in CCU patients
Optimal mechanical ventilation strategies for cardiac patients, and effective weaning protocols
Role of telemedicine, medical informatics, and other electronic innovations in the CCU
Development and implementation of novel training models to improve cardiac critical care delivery
Effectiveness of multidisciplinary clinical integration in the CCU
End-of-life issues in CCU populations
Application of current critical care quality metrics for CCU quality-of-care initiatives

Additionally, contributions from academic organizations, government agencies, philanthropic groups, and industry to provide funding and other resources for project support and investigator career development in the field of cardiovascular critical care will be crucial. Table 1-1 lists potential research areas for future study.

Conclusion

Although the future role of the CCU is uncertain, the potential viability of these units is quite remarkable. Much as the CCU seems to have revolutionized the care of patients with acute MI, the CCU now has the potential to improve the care of a wide range of cardiovascular patients for decades to come. As the premier setting for the recruitment of patients who populated some of the landmark clinical trials in acute coronary syndromes, the CCU also represents a fertile environment for untapped research opportunities in cardiac critical care. The evolution of the CCU has been a remarkable journey of discovery, and it will be no less intriguing to see what the future holds for these truly specialized units.

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Ethical Issues of Care in the Cardiac Intensive Care Unit

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CHAPTER

2

Western Biomedical Ethics
Practical Guidelines for Ethical Decision Making
Withholding and Withdrawing of Life Support

Cross-Cultural Conflict
Conclusion

Every human being of adult years and sound mind has a right to determine what shall be done with his own body.

U.S. Supreme Court Justice Benjamin Cardozo¹

CARE IN THE intensive care unit (ICU) represents one of the costliest and most aggressive forms of Western medicine. ICU patients are the sickest and the most unstable, and they often are in no position to participate in medical decision making. In addition, the patient's family and loved ones are often left reeling by the sudden onset and seriousness of the illness. These factors bring to the ICU a host of difficult and troubling ethical issues. Responding wisely in an informed and compassionate manner is an essential part of good critical care medicine.

The primary defining characteristics of cardiac intensive care unit (CICU) patients are cardiovascular instability and life-threatening disease that require intensive monitoring, advanced life-support techniques, or both. These patients often have poor prognoses; a substantial number either do not survive to leave the CICU or do leave the unit but die on the wards without leaving the hospital. Physicians and other health care providers working in critical care must be comfortable working in the presence of death and dying, and must be prepared for the attendant ethical problems that often develop. These issues include, but are not limited to, writing do-not-resuscitate (DNR) orders, negotiating with family members who do not want a patient to be told about a diagnosis of a terminal illness, trying to determine what level of care an irreversibly ill patient without decision-making capacity would choose if able, and withholding or withdrawing life support. As the ability to preserve the physiologic functioning of critically ill patients has improved, physicians, patients, and their loved ones are increasingly faced with the questions of when and how to terminate life-sustaining treatment.

When addressing these issues, physicians are best served by remembering that their primary responsibility is to act in the patient's best interest by maintaining open and honest communication with the patient, the patient's loved ones, and the members of the medical team. Acting in the patient's best interest means providing the best possible medical care for patients who can be saved and facilitating a peaceful and dignified death for patients who cannot.

Economic and resource issues threaten to complicate further the work of ICU physicians. In the United States, CICU beds cost \$2000 to \$10,000 per day. In the current climate of increasing pressures to limit health care costs, the pattern of

high charges accrued by patients with poor prognoses in ICUs has drawn increased scrutiny, and strategies to avoid prolonged futile ICU treatment have been studied.² The practice of providing tens of thousands of dollars' worth of advanced care to ICU patients who have essentially no chance of recovery is ethically problematic because health care resources are limited in terms of dollars, ICU beds, and personnel. With many CICUs routinely filled to capacity, allowing patients with no real chance of improvement to occupy unit beds may prevent other patients with a high probability of benefiting from intensive care from being able to gain access to the CICU. Although we remain generally opposed to physicians withholding potentially beneficial therapies solely for economic reasons, in the current political and economic climate, critical care physicians should become conversant with ICU economics and develop sound stewardship practices with regard to CICU resources.

This chapter provides an overview of the ethical challenges that arise in critical care medicine. After a review of basic principles, guidelines, and methods of biomedical ethics, and a discussion of the ethical problems related to health care economics in the ICU, this chapter focuses on ethical issues related to the withholding and withdrawal of life support. Brief discussions of euthanasia and cross-cultural conflict are also included.

ICU medicine regularly brings us face to face with tragedy. ICU patients and their loved ones are often confronting the worst disasters of their lives. When conflict over medical care develops in this setting, it can be wrenching for all parties involved, including physicians. It is our hope that a firm grasp of the issues addressed in this chapter allows the critical care physician to approach ethical dilemmas in the ICU with confidence and understanding.

Western Biomedical Ethics

As defined by the *Oxford English Dictionary*, ethics represents "the science of morals; the department of study concerned with the principles of human duty," and "the rules of conduct recognized in certain associations or departments of human life."³ Medical ethics addresses two distinct but overlapping areas: the generic issue of what it means to practice medicine in a manner consistent with basic moral values, and the more specific challenge of identifying principles and guidelines for proper physician conduct that can be widely agreed on by the medical profession. Although confidentiality in medicine, as in law, is a strict ethical rule, it derives less from abstract moral values and more from

its necessity for the effective practice of medicine; a psychiatrist who reports a bank robber's after-the-fact confession is violating the profession's ethics, but may not be acting immorally. For the purposes of this chapter, the term *medical ethics* represents guidelines for proper and principled conduct by physicians.

Although Western biomedical ethics dates back to the ancient Greeks,⁴ it developed into a discipline of its own in the 1970s, largely as a result of new dilemmas posed by powerful new medical therapies. As medicine developed and strengthened its ability to maintain physiologic functioning in the face of ever greater insult and injury to the body, patients, and more often their loved ones and physicians, found themselves struggling with the often painful question of when to allow the patient to die. The 1976 New Jersey Supreme Court decision in the case of Karen Ann Quinlan established that advanced life support could be withdrawn from patients who have essentially no chance to regain any reasonable quality of life.⁵ Since that time, a flurry of other legal decisions, state and federal laws, and reports and consensus statements from various medical societies and regulatory commissions have helped define in what manner, under what circumstances, and by whose authority advanced or basic life support can be withdrawn.⁶⁻¹⁶

Various methods for "thinking ethically" have been identified and used during the decades-long evolution of the field of bioethics.¹⁷ We have selected three methods that have been the most influential in bioethical analysis to date, and that are the most helpful for addressing clinical situations in the ICU: (1) principlism, (2) consequentialism, and (3) casuistry. Physicians should not feel compelled to choose one of these methods over the others as their primary way for ethical analysis and reflection, but rather using some combination of the three methods in most cases can be the most helpful.

Principlism

Principlism has a concordance with the Western philosophical theory of deontology. Deontologic arguments hold that actions must be evaluated on the basis of the inherent qualities of the action itself and the motivations or intentions underlying the action. When applied to the clinical setting, deontology asserts that physicians and other health care professionals have specific obligations, moral duties (*deon* in Greek means "duty"), and rules that in most circumstances should be followed and fulfilled.¹⁸ Beauchamp and Childress¹⁹ identified four fundamental principles and duties from which, in their opinion, all other bioethical principles and duties can be derived: autonomy, beneficence, nonmaleficence, and justice. An understanding of these principles allows the physician to approach ethical dilemmas in an organized and thoughtful manner. With medicine in its current inexact state, however, no physician is able to practice without sometimes violating one or more of these fundamental principles. Many ethical dilemmas present a clash between these principles, and in such situations, physicians must choose which principle to uphold and which to relinquish.

Autonomy

Autonomy refers to the patient's fundamental common law right to control his or her own body. As the U.S. Supreme Court ruled in 1891, in a case unrelated to medicine: "No right is held more sacred or is more carefully guarded by the common law than the right of every individual to the possession and control of his own person, free from all restraints

or interference by others, unless by clear and unquestionable authority of law."²⁰ In medical terms, autonomy means the right of self-determination—the right to choose for oneself among the various therapies that are offered. Autonomy also implies a respect for the patient as an adult individual capable of making his or her own decisions. The principle of autonomy is in contrast to paternalism, in which it is presumed that the physician knows best and decides for the patient or leads the patient to the right decision.

Respect for autonomy means that adult patients with decision-making capacity have the right to refuse medical treatment, even if the treatment is life-sustaining. It follows that, except in emergency situations, patients must consent to any treatments they receive, and they must understand the risks and benefits of any proposed therapies or procedures for this consent to be meaningful. Autonomy also demands that physicians inform patients of reasonable alternatives to the proposed therapies without framing the discussion to bias patient's decisions; physicians can and should make recommendations, but these should be distinct from the presentation of objective information about treatment options.²¹

The acuity of the typical ICU patient's illness must not be used as an excuse for failing to obtain formal consent for care in general or for procedures in particular. Physicians have the responsibility to ensure that the medical care provided is in accord with the patient's wishes. Many ICU patients have the decision-making capacity to decide for themselves what level and types of care they wish to accept. For patients lacking decision-making capacity, a close family member or other surrogate decision maker should be identified to help plan an appropriate level of care consistent with the best available knowledge of what the patient would have wanted. Patients do not have the right to demand specific treatments; only the physician has the authority to determine what therapies are medically indicated for a patient.

Minors do not have the same rights as adults and are not granted autonomy by the law to make their own health care decisions. Instead, these decisions generally fall to the minor's parents. U.S. courts have consistently been willing, however, to overrule parents in cases in which there is evidence that the parents' decisions are not consistent with the best interest of the child. Although adult Jehovah's Witnesses can refuse medically indicated blood transfusions for themselves, they cannot make the same refusal on behalf of their children.

Beneficence

The principle of beneficence represents the physician's responsibility and ethical duty to benefit the patient. The physician's duty is to reduce pain and suffering and, where possible, promote health and well-being. At its most basic level, beneficence is necessary to justify the practice of medicine, for if physicians do not benefit their patients, they lose their *raison d'être*. One caution related to the principle of beneficence is that physicians may have a tendency to judge "patient benefit" primarily in physiologic categories related to medical goals and outcomes. From the patient's perspective, benefit may include not only medical outcomes, but also psycho-social-spiritual outcomes, interests, and activities that help to define the patient's quality of life. A recommended intervention with the likelihood of a good medical outcome but that would not allow a patient to continue a significant interest or activity could be judged differently by the patient than by the physician because of differing perceptions of "benefit."

More philosophically, beneficence as a principle in medicine supports the sanctity of human life and asserts the significance of human experience. In this regard, physicians practice beneficence not only by curing diseases, saving lives, or alleviating pain, nausea, and other discomforts, but also by expressing empathy and kindness—by contributing to patients' feeling that they are cared for and that their suffering is recognized. In the ICU, with critically ill patients near the end of life, presence, compassion, and humanity are sometimes the greatest forms of care that a physician has to offer.

Nonmaleficence

Nonmaleficence requires the physician to avoid harming the patient. More colloquially cited as “first, do no harm,” the principle of nonmaleficence warns the physician against overzealousness in the fight against disease. Opportunities to do harm in medicine are innumerable. Almost every medication and procedure that physicians employ can cause adverse effects, and simply being in the hospital and in the ICU puts patients at risk for infection by a more dangerous group of microorganisms than they would likely encounter at home. Unnecessary tests may unearth harmless abnormalities, and the work-up of these may result in significant complications. An unnecessary central venous line may result in a pneumothorax. Unnecessary antibiotics may result in anaphylactic shock, Stevens-Johnson syndrome, acute tubular necrosis, pseudomembranous colitis and toxic megacolon, or subsequent infection by resistant organisms. Physicians tend to feel much more comfortable with taking action than with withholding action; in the face of clinical uncertainty, many physicians are inclined to order another test or try another medication. It is essential that physicians constantly and consistently assess the potential benefits and the potential harms (including financial costs) that may result from each test and treatment they prescribe for each patient.

There are also other harms specific to the ICU. When a patient languishes on life support without a reasonable chance of recovery, the physician violates the principle of nonmaleficence. For a patient, the ICU can be an uncomfortable and undignified setting, filled with unfamiliar and jarring sights and sounds. Being sustained on mechanical ventilation ranges from unpleasant to miserable unless the patient is unconscious or heavily sedated. The only justification for putting patients through such experiences is an expectation that they may return to some reasonable quality of life as determined by the patient's values. When physicians' care serves only to extend the process of dying and prolong suffering, they violate nonmaleficence. In ancient Greece, the *Hippocratic Corpus* described as one of the primary roles of medicine refraining from treating hopelessly ill individuals, lest physicians be thought of as charlatans.²²

Just as physicians may harm their patients by providing excessively aggressive treatments, so physicians may harm patients by withholding care from them. Working with critically ill patients demands tremendous physical and emotional stamina. When a patient remains in the ICU for a prolonged time or their disease is particularly troubling, the physician may be inclined to spend less time with the sick person or to focus on the flow sheet rather than on the patient. Illness is often a lonely and frightening experience, however, and abandonment by the physician adds to the patient's suffering.

Justice

Justice in medical ethics means a fair allocation of health care resources, especially when the resources are limited. In the United States, on the macro-allocation level, we have failed to achieve a just medical system by any standard. The quality and accessibility of medical care available to U.S. citizens remains largely a function of an individual's socioeconomic status. In 2007, approximately 47 million Americans did not have health insurance. Americans in disadvantaged economic, ethnic, or racial groups experience greater morbidity and mortality from illness and die at a younger age in most disease-specific categories than do other Americans. Unequal access to care is sometimes specifically legislated by Congress; impoverished women covered by Medicaid are denied the same access to abortion as middle-class women with private health insurance. Low Medicaid reimbursement rates limit access to physicians. The principle of justice demands that health care resources be allocated not according to the ability to pay, but rather according to need and to the individual's potential for benefiting from care.

On a micro-allocation level, the principle of justice plays a role in the ICU in terms of triage. With a limited number of beds, the physician in charge of the unit must decide which patients have the greatest need for and the greatest potential to benefit from intensive care. Because intensive care represents a very expensive form of medical intervention, consuming greater than 13% of U.S. hospital costs and 4% of total U.S. health care expenditures,²³ there is a strong national interest in curtailing wasteful ICU use. The concepts of futility and rationing help in analyzing the challenge of triage, but as Jecker and Schneiderman^{24,25} have observed, the two terms have different points of reference. Determinations of futility are related to whether identified goals of treatment are achievable.²⁶ Futility can have two distinct meanings, referring to treatment that has essentially no chance of achieving its immediate physiologic purpose or effect, or, alternatively, that has essentially no chance of meaningfully benefiting the patient. Treating a bacterial pneumonia in a brain-dead patient would be considered not futile with the former definition and certainly futile with the latter. The threshold for futility is a contentious subject, and some authors have argued that the impossibility of arriving at widely accepted objective, quantitative standards renders use of the term inappropriate.^{27,28}

Futility differs conceptually from rationing in that futility applies to an individual patient's chances of benefiting from treatment, whereas rationing refers to the distribution of limited resources within a population. Rationing is fair only when it is applied in an even-handed way for patients with similar needs, without regard to race, ethnicity, educational level, or socioeconomic status. Futility affects triage decisions because futile treatment violates the principles of beneficence and nonmaleficence. Such wasteful use of medical care also violates the principle of justice when resources are limited. Rationing comes into play when there are more patients who need ICU care than there are beds, mechanical ventilators, or other critical care resources available. As health care costs continue to increase, physicians may find increasing pressures in the ICU to limit care for patients with poor prognoses. The ethical test in such circumstances is whether rationing is necessary, and whether it is applied in a fair manner (i.e., similar cases are treated similarly). To maintain a clear understanding of what physicians are doing, it is essential that assertions of futility do not become either a

mask behind which rationing or hospital cost-saving decisions can hide or a means of bullying a patient or family into accepting decisions limiting treatment.^{29,30}

The four principles of biomedical ethics can help untangle and clarify many complex and troubling dilemmas. In different cases, each of the individual principles may seem more or less important, but they are all usually in some way pertinent. These principles can come into conflict with each other, which can signify the presence of an ethical dilemma. Practically, the principles can help to pose a series of significant, patient-centered questions for physicians: “Am I respecting my patient’s autonomy?” “Has the patient consented to the various treatments?” “Do I know my patient’s resuscitation status?” “Is my therapeutic plan likely to benefit my patient, and am I doing all I can to improve my patient’s well-being?” “Am I minimizing patient harm?” “Have I identified goals of treatment or care with my patient (or the surrogate), and are those goals achievable?” “Is there an appropriate balance between potential benefit and risk of harm?” “Is my plan of care consistent with principles of social justice?”

Consequentialism

The second method for “thinking ethically” about clinical and ICU situations is consequentialism, which has its root meaning in the Western philosophical theory of teleology (*telos* in Greek means “ends”). Consequentialist reasoning judges actions as right or wrong based on their consequences or ends. This method of reasoning and analysis requires an anticipatory, projected calculation of the likely positive and negative results of different identified options before decisions and actions are carried out.

A physician may be requested by a family members not to disclose a poor prognosis to their hospitalized loved one because, in their view, the disclosure would upset the patient. Because the patient should be at the center of a “calculation of consequences” for this scenario, the first question should be: How will the disclosure or nondisclosure impact the patient positively by way of benefit or negatively by way of harms? The patient is not the only one who would experience consequences as a result of this particular decision, however. Other stakeholders who can be affected positively and negatively include the following:

- The patient’s family: Will they be angry and feel betrayed if the poor prognosis is disclosed, or will they ultimately feel relieved?
- The bedside nurses and other involved health care professionals: Will they feel distress if they are expected to participate in a “conspiracy of silence,” or if the patient asks them a direct question about his or her prognosis?
- The hospital: Will disclosure or nondisclosure be in accord with organizational values such as respect for patients and compassion?
- The wider community and society: How will other and future patients be affected if they come to know that physicians at this particular hospital disclose or do not disclose poor prognoses to patients?

When applying consequentialism, the projected and accumulated benefits and harms for all the involved and interested parties and related to the reasonable options should be weighed against each other with the goal of maximizing benefit and minimizing harm.

One challenge of calculating consequences for the options in a given medical situation is how to be sufficiently thorough in anticipating what the projected outcomes and results might be. For many situations, experienced physicians and other clinicians, using their knowledge of previous cases and building on their collective wisdom, can reasonably project medical, legal, and psycho-social-spiritual consequences for the different options. A more problematic challenge when using consequentialism is determining how much weight to assign each of the various beneficial and burdensome consequences. Should a potential legal risk to the physician and hospital that could result from a specific bedside decision be given more weight than doing what is clearly in a patient’s best medical interests? In the end, after identifying and weighing projected burdens and benefits of reasonable options, physicians using consequentialism would be ethically required to choose and act on the option that is likely to produce the most benefit, and to avoid the option likely to bring the most harm.

Casuistry

The third method of analysis that can lead to ethically supportable actions is termed *casuistry*,³¹ a word that shares its roots with the word *cases*. Although the term may be unfamiliar to many physicians, the method itself is likely to be familiar to them. Casuistry is based on practical judgments about the similarities and differences between and among cases. Medicine and law use this method when they look to previous and precedent cases to provide insight about a new case at hand. When a patient presents to a physician with a specific set of symptoms and complaints, and after the physician analyzes the results of various diagnostic tests, a skilled and knowledgeable physician is usually able to arrive at a specific diagnosis. The diagnosis is based on attention to the details of the patient’s symptoms and the test results, but also on the physician’s training and experience of having personally seen or having read in the published literature about similar or identical cases.

Casuistry in ethical analysis uses a parallel kind of reasoning. According to casuistry, attention must be given first to the particular details, features, and characteristics of the ethical dilemma at hand. Next, the goal is to identify known previous cases that are analogous and similar to the new case, and that had reasonably good and ethically supportable outcomes. If such a previous or paradigm case can be identified for which a consensus exists about right action, this previous case may provide ethical guidance for the new case at hand. A 25-year-old ICU patient with Down syndrome and an estimated cognitive ability of a 2- to 4-year-old is in need of blood transfusions. Her family members are Jehovah’s Witnesses and adamantly object to the transfusions, based on their religious beliefs. Using casuistry and appealing to similar cases, the intensivist notes that there is an ethical and legal consensus related to pediatric patients of Jehovah’s Witness parents to override parental objections to blood transfusions and to act in the patient’s best interests. Because the 25-year-old patient’s cognitive ability is similar to pediatric patients who do not have the cognitive ability to commit themselves knowingly and voluntarily to a set of religious tenets, the ethically supportable option in the pediatric cases (i.e., overriding parental objections to blood transfusions) could be extended to the case at hand.

An additional feature of casuistry is that as cases are compared, and similarities and differences are identified, moral

maxims or ethical rules of thumb can emerge that can also be helpful for current and future cases and dilemmas. Such moral maxims include the following: (1) adult, informed patients with decision-making capacity can refuse recommended treatment; (2) a lesser harm to a patient can be tolerated to prevent a greater harm; and (3) physicians are not obligated to offer or provide treatments that they judge to be medically inappropriate. One challenge of casuistry is to pay sufficient attention to the relevant facts of the new case to be able to identify previous cases that are similar enough to provide guidance for the case at hand.

An effective use of casuistry by physicians and health care teams can lead to the building-up of a collective wisdom and practical experience from which to draw when new ethical dilemmas arise. Parallel again to a physician building up medical experience and wisdom over time, a physician can establish an ethical storehouse of knowledge and insight based on previous cases and dilemmas that he or she has experienced, heard about, or read about.

Practical Guidelines for Ethical Decision Making

In addition to the three methods discussed previously, the following four practical guidelines can facilitate the process of ethical decision making:

1. Recognize patients as partners in their own health care decisions.
2. Establish who has authority for decision making.
3. Establish effective communication with patients and their loved ones through routinely scheduled family meetings.
4. Determine patient values and preferences in an ongoing manner.

Patient Partnership

All decision making—and all health care—must occur with the recognition that patients are partners in their own health care decisions. The American Hospital Association has supported this partnership model for decision making by addressing patient expectations, rights, and responsibilities.³² Among these expectations and rights, the most salient are the right of patients to participate in medical decision making with their physicians, and the right to make informed decisions, including to consent to and to refuse treatment. To exercise these rights, patients need accurate and comprehensible information about diagnoses, treatments, and prognosis. More specifically, patients need a description of the treatment, the reasons for recommending it, the known adverse effects of the treatment and their likelihood of occurring, the possible outcomes of the treatment, alternative treatments and their attendant risks and likely outcomes, the risks and benefits involved in refusing the proposed treatment, and the name and position of the person or persons who would carry out or implement the treatment. In cases in which someone other than the patient has legal responsibility for making health care decisions on behalf of the patient, all patients' expectations and rights apply to this designee and the patient. According to the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, "Ethically valid consent is a process of shared decision-making based upon mutual respect and participation, not a ritual to be

equated with reciting the contents of a form that details the risks of particular treatments."³³

Authority for Medical Decision Making

Establishing the source of authority for making health care decisions for a patient is a common problem in critical care medicine. Although nonsuicidal adult patients with decision-making capacity retain this authority for themselves, many ICU patients are unable to participate in decision making. Whatever the patient's condition, however, he or she remains the only true source of ultimate authority, and the physician must assemble and review the best available evidence of what the patient would want done. If the patient lacking decision-making capacity has prepared a living will or a durable power of attorney for health care, these documents should be obtained and reviewed. Close family members and loved ones also should be consulted; they may have spoken with the patient about what level of care the patient would want in the event of critical illness. In most, but not all, cases, these individuals know the patient best and have the patient's best interest at heart.

Having reviewed the available evidence, the treating physicians should provide care that is consistent with their best understanding of what the patient would have wanted. The physician plays the role of guide and consultant, evaluating a patient's medical problems, presenting and explaining options for diagnosis and management, and facilitating thoughtful decision making. Except in emergencies or when further treatment is clearly futile, physicians should not proceed with management plans until individuals with true authority to consent to or refuse treatment have approved the plans.

Communication

Explaining medical problems and treatment options to patients and their loved ones, determining patient quality-of-life values and desires, and achieving consensus for a management plan all require effective communication skills. Although well-developed communication skills are always an asset in medicine, communication can be particularly difficult and important in the ICU setting. Patients and their loved ones are often anxious or intimidated by the severity of the patient's condition and by the many unfamiliar sights and sounds in the ICU. With many basic life functions taken over by the nursing and medical staff and their various machines and devices, and with visiting hours often limited, patients and their loved ones may feel powerless and experience anxiety or anger from the loss of control. Honest, effective, and recurrent communication can help alleviate these feelings and decrease the alienation that attends ICU admissions.

Effective communication requires the ability to listen attentively,³⁴ and to express empathy, understanding, and compassion. The physician must be able to employ tact without compromising honesty and to acknowledge and respond to strong emotional expressions without withdrawing or becoming defensive or antagonistic. The physician often must read between the lines and recognize subtle cues about what matters most to patients and their loved ones. Effective communication prevents and defuses conflict; helps patients and families work through their anxieties, fears, and anger; and is the most important skill in negotiating the difficult ethical dilemmas that arise in the ICU.

Establishing effective communication requires time and planning. Physicians must remind themselves that although ICU care may become routine for them, it is rarely that way for the patients or their loved ones. Discussions with a patient's family members or loved ones should occur either at the bedside, if the patient is able to participate, or in a private conference or waiting room; the hospital corridor is *not* an appropriate location. Because the patient and his or her loved ones are likely to feel overwhelmed by the patient's illness and by the ICU environment, communication should be simple and to the point, with more technical details provided as requested. Encouraging the various parties to ask questions and express their feelings helps to counteract any intimidation they may feel and communicates to them that the physician cares about their concerns.

Finally, for communication to be effective, information should be conveyed in language and at a level of detail that the listener understands clearly. Medical jargon, an overly sophisticated vocabulary, excessive detail, or an inappropriate emotional tone can defeat what is otherwise a sincere effort at communicating. Physicians should always ask patients or their loved ones to summarize what they have heard; this is an easy way to evaluate their comprehension and to correct any misunderstandings.

Several types of inadequate communication occur regularly in ICUs. The most common problems result either from focusing on trends rather than on the patient's overall condition or from drawing attention to favorable signs when the overall prognosis remains dismal. If a patient is unlikely to survive to ICU discharge but is not deteriorating, describing the patient to family members as stable is likely to mislead them. A more truthful report might be: "Your wife is as sick as any person could be, and the odds are overwhelming that she will not survive." A similar problem arises in telling a couple that their son with multiple organ failure has improved when in fact there has been only a slight reduction in his oxygen requirement and his overall prognosis remains poor. Such inappropriate "good news" may make the physician feel better, but it can be cruelly misleading by engendering false hopes and needlessly interfering with the grieving process. It is essential to tell the truth and to provide accurate prognostic information.

A second common problem is for patients and their families to receive conflicting information or advice from different physicians involved in the patient's care. Alternatively, different consulting services may each address a specific aspect of the patient's care without helping the patient and family to integrate the disparate pieces of data into a coherent overall understanding of the patient's condition, prognosis, and treatment plan. Multidisciplinary care conferences, which include the ICU physician, relevant consulting physicians, nurses, and, when appropriate, social workers and case managers, should be held periodically to ensure that there is a coherent, shared vision of the patient's overall management plan.³⁵ Formal, structured multidisciplinary conferences that include the patient and family and that are held within 72 hours of ICU admission have been shown to reduce the burdens of intensive care for dying patients and allow patients with lower mortality rates access to the ICU.²

The physician has a responsibility to ensure that effective communication has occurred. Not all physicians excel at communicating. When physicians find that effective communication is not taking place and conflict is developing, they should recruit assistance from an ethics consultant or another facilitator, such as a chaplain, social worker, or psychotherapist. Physicians

should think of facilitators as valuable resources and not view their use as an admission of failure. ICU physicians are generally busy with a demanding set of patients. An ICU physician typically has limited time to talk to patients and patients' families, yet these patients often have very high communication needs. Bringing in an ethics consultant or other facilitator to supplement the ICU team's efforts can help meet these needs without overtaxing the ICU physicians.

Working with critically ill and dying patients can be extremely stressful and emotionally draining on a case-by-case basis and as an accumulating problem over time. Physicians may feel burned-out or may seek to protect themselves by creating emotional distance from their patients. Although physicians cannot delegate all communication responsibilities, the assistance of a facilitator can reduce the stress on all parties involved. Not only can facilitators contribute additional communication skills, but they also have more time for establishing rapport and, as third parties with fresh perspectives, can bring new insight to ethical dilemmas. We believe that such facilitators are underused, perhaps because physicians fear a loss of control over their patients. We recommend requesting a facilitator early whenever it seems that ethical decision making may be difficult.

Determining Patients' Values and Preferences

The fourth practical guideline in ethical decision making is determining the patient's values and preferences regarding quality of life and medical care. As noted previously, ICU medicine can be a painful and undignified experience for the patient. Whether and for how long such an ordeal is appropriate are questions that in the end can be answered only by the patient, and depend on the prognosis, on how the patient judges quality-of-life issues, and on how sensitive the patient is to the discomforts and indignities of the illness and hospitalization. These questions become most significant for chronically or terminally ill patients who are dependent on advanced life support. Physicians must strive to learn each patient's views regarding what constitutes a meaningful and acceptable life compared with a mere prolongation of physiologic functioning. Physicians must never assume that they know what the patient would want, especially with individuals of different cultural, ethnic, or religious backgrounds. Patients have different preferences about how aggressively they wish to be treated and when they want their physicians to forego life-sustaining treatment. Patients' views often change over time, even during the course of the same hospitalization, so patients' perspectives should be reviewed on a regular basis. Whenever possible, discussions with patients about these matters should occur with family members and loved ones present so that all parties have the same understanding of the patient's desires; otherwise, if the patient later loses decision-making capacity, the family may balk at following the patient's wishes.

When patients do not have decision-making capacity, physicians must turn to surrogate decision makers, advance directives, or both. Decisions about life support and end-of-life care are among the most personal decisions to be made. For surrogate decision makers, being asked to make such decisions on a loved one's behalf frequently elicits feelings of grief, guilt, confusion, and being overwhelmed. Physicians can perform a tremendous service for their patients' families and loved ones by discussing resuscitation status, life support, and terminal care issues with patients before they lose decision-making capacity. Patients are not generally eager to hold such discussions;

however, this is no excuse for not broaching the subject, especially with patients who have life-threatening diseases.³⁶

Withholding and Withdrawing of Life Support

Withholding or withdrawing life support is one of the most difficult actions that a physician may have to perform. Having been trained to prolong life and overcome disease, a physician may feel like a failure when allowing a patient to die whose life could have been prolonged with life support. Physicians do not possess omnipotence, however. Death is the natural conclusion to life; although death is often viewed as an enemy in the hospital, it is also sometimes a colleague. For severely ill patients with irreversible conditions, the only choices available may be a prolonged and miserable dying versus a more rapid, comfortable, and dignified death. In these cases, death can represent an end to suffering, can prevent a life that has been happy from ending with prolonged misery, and can allow survivors to mourn and proceed with their lives. A painless and dignified death is sometimes the best a physician has to offer; there is no shame in such an admission.

Legal Precedents

Legal guidelines for withholding and withdrawing life support come predominantly from state court rulings; federal guidance has been minimal in this regard. State court rulings apply only within that state's boundaries, however; they have no legal standing in other states. Although the right to refuse medical treatment is protected by common law and by the U.S. Constitution, the exact limitations of this right and the conditions under which life support can be withdrawn from patients lacking decision-making capacity vary from state to state. In particular, significant variability exists among states regarding what courts accept as clear and convincing evidence that a patient without decision-making capacity would want life support withdrawn. As in all human affairs, various court rulings can be arbitrary, reflecting the background, politics, and moral beliefs of the judges who made the rulings. Physicians and hospitals must be familiar with their state's stance on the question of withholding or withdrawing life support. Although malpractice and criminal actions resulting from withholding or withdrawing life support have been extremely rare, this likely stems from the extreme reluctance, bordering on refusal, of physicians and hospitals to terminate life support contrary to the wishes of the patient's family. Instead, legal action tends to result from a medical team's refusal to withdraw treatment.

Patients with Decision-Making Capacity

The right of adult patients with decision-making capacity to refuse advanced life support and medically supplied nutrition and hydration is well established in the United States through case law and hospital policies.³⁷ The case of *Bouvia v. Superior Court*³⁸ concerned a young, quadriplegic woman with cerebral palsy who was experiencing unrelenting pain and requested that the hospital withhold her medically supplied tube feedings so that she could die. The hospital refused. In its 1986 ruling, the California State Court of Appeals found that "to insist on continuing Bouvia's life ... at the patient's sole expense and against her competent will, thus inflicting never ending physical torture

on her body until the inevitable, but artificially suspended, moment of death ... invades the patient's constitutional right of privacy, removes her freedom of choice and invades her right to self-determination."

Patients Lacking Decision-Making Capacity

The 1976 Karen Ann Quinlan case⁵ helped spur the development and dissemination of biomedical ethics. This groundbreaking case involved a 22-year-old woman who was in a persistent vegetative state. Her father, who had been appointed her legal guardian, requested that mechanical ventilation be withdrawn, asserting that she would not have wanted to be kept alive under such circumstances. Her physicians refused to comply. The case was ultimately decided by the New Jersey Supreme Court, which evaluated "the reasonable possibility of return to cognitive and sapient life as distinguished from ... biological vegetative existence."⁵ The decision indicated that advanced life support provided a clear benefit to the patient only if it would result in "at very least, a remission of symptoms enabling a return toward a normal functioning, integrated existence." The court ruled that life support could be withdrawn from patients if they had essentially no chance of regaining any reasonable quality of life.

The New Jersey Supreme Court's ruling based Quinlan's right to be removed from the ventilator on her constitutional right to privacy. In the absence of any indication from the patient herself of her preferences or values, the court found that the family and physicians were entitled to exercise substituted judgment on the patient's behalf, with the family's decision taking precedence over that of the physicians. When Quinlan's ventilator was withdrawn, she was able to breathe on her own and lived for an additional 10 years, never regaining any cognitive function.

The major challenge in cases such as *Quinlan* involving patients lacking decision-making capacity is deciding who is the appropriate decision maker. Although state courts have consistently recognized the right of patients to refuse treatment, including medically supplied nutrition and hydration, they have been much less consistent with regard to the question of how decisions should be made for patients who cannot decide for themselves.³⁹⁻⁴⁴ Some states have permitted families to make decisions to withdraw life-sustaining treatment from patients lacking decision-making capacity, whereas other states have required that there be clear and convincing evidence that the patient himself or herself would not have wanted such treatment. States allowing surrogate decisions in the absence of clear and convincing evidence about what the patient would have wanted have tended to follow a standard of either substituted judgment or best interest. The substituted judgment standard allows a surrogate to make his or her best judgment of what the patient would have decided if the patient were competent. The best interest standard applies when it remains unclear what the patient would have decided. In this eventuality, the surrogate and the medical team base the decision on the patient's best interest.

The concept of proportionate treatment can help guide best interest decision making: "Proportionate treatment is that which, in the view of the patient, has at least a reasonable chance of providing benefits to the patient, which benefits outweigh the burdens attendant to the treatment. Thus, even if a proposed course of treatment might be extremely painful or intrusive, it would still be proportionate treatment if the prognosis was for complete cure or significant improvement in the patient's

condition. On the other hand, a treatment course which is only minimally painful or intrusive may nonetheless be considered disproportionate to the potential benefits if the prognosis is virtually hopeless for any significant condition.”⁴⁴

Many states have codified the substituted judgment standard, enacting laws that give families the right to make decisions on behalf of patients lacking decision-making capacity. For patients who did not identify a surrogate decision maker before they lost decision-making capacity, most states identify a hierarchy among relatives so that it is clear who the decision maker should be. Most of these statutes apply only to patients who are terminally ill, however.⁴⁵

From a legal and ethical perspective, no distinction is made between nutrition and hydration provided through a medical device (e.g., a gastrostomy or nasogastric tube or intravenous line) and other forms of life-sustaining treatment such as mechanical ventilation. As one California court ruled, “... medical procedures to provide nutrition and hydration are more similar to other medical procedures than to typical human ways of providing nutrition and hydration. Their benefits and burdens ought to be evaluated in the same manner as any other medical procedure.”⁴⁴

A different problem arises for patients who have never had decision-making capacity because they have never been in a condition in which they could meaningfully indicate what level of health care they would want if they were critically ill. Such patients include young children and individuals with severe mental retardation. Different states have dealt with this problem differently. Some have ruled that the right to refuse medical treatment must extend to incompetent patients because human dignity has value for them just as for patients who are competent, and that legal guardians or conservators have the right to make such decisions on behalf of their ward.⁴⁶ In such cases, some courts have opined, decisions about withholding treatment from patients who have never been competent should be based on an attempt to “ascertain the incompetent person's actual interests and preferences.”³⁹ In other words, the decision should be that which the patient would make if the patient were competent but able to take into account his or her actual incompetency. Other courts have ruled that it is unrealistic to try to determine what a patient who had never been competent would have wanted, and that, for legal purposes, such patients should be treated as children.⁴⁷ Some courts have specifically rejected the substituted judgment standard, finding that a third party should not have the power to make quality-of-life judgments on another's behalf.

Many legal issues regarding the termination of life-sustaining treatment remain unresolved. The courts have given essentially no guidance in the area of whether physicians have the authority to terminate life support for patients lacking decision-making capacity against the wishes of the patient's family. Generally, the courts have respected the physician's right to refuse to provide treatments that the physician considers to be medically inappropriate, but the applicability of this right to life support has yet to be established. In most cases involving attempts by hospitals or physicians to use a futility argument to justify foregoing life-sustaining treatment requested or demanded by patients or their family, the courts have ruled in favor of continuing treatment.⁴⁸

Advance Directives

Since the *Quinlan* decision,⁵ state legislatures and the federal government have passed laws designed to increase the authority of individuals to control the level of treatment they will receive

when they are incapable of participating in decision making. These laws set standards for several types of documents, but primarily living wills and medical powers of attorney. Collectively, these documents are known as written advance directives. These documents usually have legal standing only within the state where they are completed, and only if they conform to the state's statutory language, although some states grant some degree of validity to other states' advance directives. These documents can assist loved ones and health care professionals in determining what an individual would have wanted, especially if the patient has an irreversible condition such as a terminal illness or a persistent vegetative state. Health care providers can play a key role in encouraging patients to engage in advance care planning that culminates in completion of written advance directives.

Living Wills and Medical Powers of Attorney

Living wills indicate what level of life support and other medical care a patient would want under specified circumstances. The specific forms of treatment covered by living wills vary among states and are sometimes restricted to life-sustaining treatments. Some state laws specifically exclude medically supplied nutrition and hydration from the treatments that can be withheld or withdrawn. With the exception of Missouri, however, state courts have ruled that these exclusions refer only to nonmedical feedings.⁴⁹ The requirement that living wills provide for a wide range of unforeseeable eventualities forces the documents to be general in nature and limits their usefulness.⁶ In a study of 102 elderly individuals in Florida, Walker and colleagues⁵⁰ found that there was a wide range of resuscitation status preferences among patients who had completed living wills, and that the language of the living wills was too vague in most cases to determine their preferences.

Medical powers of attorney provide more flexibility than living wills because they name a surrogate decision maker who is authorized to make health care decisions on the patient's behalf if the patient loses decision-making capacity. The advantage of a medical power of attorney lies in the authority it grants the designated agent to make decisions on the basis of the specific details of the patient's circumstances and condition. Studies have found that spouses and other close family members are often inaccurate at predicting what their loved one would want.⁵¹ In addition, living wills and medical powers of attorney are limited by the well-documented fact that an individual's desire to receive aggressive medical care can change over time.⁵²⁻⁵⁴ What level of care a healthy individual imagines wanting during a hypothetical illness may be very different from what that individual wants when ill.⁵² On the one hand, as patients become increasingly ill, they may be willing to settle for a decreasing quality of life. On the other hand, when facing a long illness, patients may grow weary of hospitalization and invasive or otherwise unpleasant medical procedures or treatments and decline treatment that they previously thought they would have wanted.

Patient Self-Determination Act

The U.S. federal government encouraged the use of advance directives when it enacted the 1990 Patient Self-Determination Act (PSDA).⁵⁵ The law requires hospitals, nursing homes, and other health care institutions to (1) provide to patients written information regarding advance directives and the patient's right to accept or refuse treatment; (2) document in the patient's medical record whether an advance directive has been completed;

and (3) provide education about advance directives for patients, their families, and the facility's staff. Health care institutions failing to follow the PSDA may have their federal Medicare and Medicaid reimbursements withheld. Despite this legislation, studies in the 1990s reported that only a few hospitalized patients had their advance directives acknowledged, and that physicians were usually unaware when their patients with life-threatening illness preferred not to be resuscitated.^{56,57} A study of hospitalized patients with life-threatening diagnoses found that less than 50% of physicians knew when their patients did not want to receive cardiopulmonary resuscitation (CPR).⁵⁷ The proportion of elderly Americans who have completed advance directives is reported to have increased, however.⁵⁸

Deciding to Withhold or Withdraw Life Support

Physicians withhold or withdraw life support in two general circumstances: (1) when the patient or the patient's surrogate refuses further treatment, or (2) when the physician of record determines that further treatment is medically futile or inappropriate. In most cases in which life support is foregone, both criteria are met.⁵⁹ Ideally, such a momentous decision by physicians would be based on individual patient preferences and objective medical information. However, studies of ICU health care professionals found that personal characteristics of physicians are significantly associated with their decision making about withholding or withdrawing life support.⁶⁰⁻⁶³ These characteristics include age, religion, number of years since graduation, amount of time spent in clinical practice, level and type of specialization, type of hospital, and number of ICU beds where the physician works. In the study by Cook and colleagues,⁶¹ in which ICU health care professionals chose an appropriate level of care for 12 patient scenarios, there was extreme variability among individuals' decisions: only 1 of the 12 scenarios did more than half of the respondents make the same choice, and opposite extremes of care were chosen by more than 10% of the respondents in 8 of the 12 cases. Physicians have also been found to be much more willing to offer life support to patients with life-threatening cardiovascular or pulmonary disease than to patients with cancer, even when the prognosis is the same.⁶² That physicians' personal characteristics influence their decision making should not be surprising; rather, it should caution against intransigence and remind physicians of their own potential biases and of the likelihood that other equally competent professionals may disagree with their decisions. These findings re-emphasize the importance of ascertaining the patient's values and preferences; if life-support decisions can be significantly influenced by physicians' personal characteristics, leading to physicians disagreeing on appropriate levels of treatment, decision making should be based on the values and desires of the individual patient.

One challenge in end-of-life decisions is the uncertainty associated with predicting patient outcomes. The common use of the word *futility* implies that there exist accurate tools for identifying which patients are likely to improve or recover. Despite the existence of multiple prognostic and severity scoring systems useful in predicting aggregated group outcomes, foreseeing the outcome of individual patients remains an inexact science.⁶⁴ In most ICU cases, the concept of futility remains ephemeral and ill-defined, and physicians must depend on their clinical judgment to determine when further treatment has virtually no chance to return the patient to a reasonable quality of life

according to the patient's values. That such determinations are not completely accurate does not obviate their necessity, but does make caution and humility appropriate.

There is a broad consensus among medical societies, critical care physicians, and ethicists that withdrawing and withholding life support do not differ ethically from one another.^{6,9,11,65-67} Nonetheless, physician surveys have repeatedly found that many physicians feel differently about the two actions.⁶⁸⁻⁷⁰ Withdrawing a life-sustaining intervention, especially if the patient dies soon afterward, may feel more like causing death than withholding that same intervention. Because the two actions of withholding and withdrawing share the same justification, motivation, and end result, however, there is no moral basis for differentiating them. Physicians are in a stronger position to assert that they have "tried everything" to save the patient when withdrawing interventions than when declining to initiate a lifesaving intervention in the first place.

Finally, any decision to withhold or withdraw life support should be part of a coherent, comprehensive management plan. Decisions to continue or terminate specific treatments or tests should be related to clearly identified, patient-oriented goals. The decision to withdraw advanced life support represents a decision to allow a patient to die; continuing antibiotic therapy or ordering diagnostic tests makes no sense in such a context, unless they can be shown to contribute to patient comfort or an identified patient goal. In the same manner, failing to treat the infection of a patient who is being maintained on mechanical ventilation bespeaks confusion concerning the goals of treatment. In most cases, ICU physicians, patients, and family members should choose between providing palliative care and, alternatively, using all available means acceptable to the patient to prolong the patient's survival.

Withholding and Withdrawing Basic Life Support

Denying basic life support (e.g., medically supplied nutrition and hydration, oxygen) is a difficult step in medicine. Although more advanced life support may be viewed as "heroic" or "extraordinary," and other medical therapies such as antibiotics are aimed at treating infection, basic life support is simply that which everyone depends on to live; it may not seem to be part of medicine so much as part of normal human existence. Allowing a patient to die of malnutrition or dehydration may even seem like murder to some physicians. As noted previously, however, state courts have generally concluded that medically supplied nutrition and hydration are akin to other medical treatments. Ethicists⁷¹⁻⁷³ and medical societies have likewise generally denied an ethical distinction between terminating advanced and basic life support, although there has been some disagreement with this position.⁷⁴ Nonetheless, denying a patient without decision-making capacity medically supplied nutrition and hydration remains ethically and legally controversial.⁷⁵ Physicians should be familiar with their own state's laws and legal precedents; hospital attorneys can be of assistance in this regard. As always, the problem lies in identifying the patient's preferences when the patient cannot decide for himself.

Whatever a physician's personal views, thoughtful decision making about basic life support is essential in the ICU. Clinicians should consider four major points. First, any medical intervention should serve what the patient considers to be in his or her best interest as determined by open and forthright communication with the patient and the patient's family and loved

ones. Second, close family members and loved ones should be included in the decision-making process. This involvement not only serves to protect the best interests of the patient, but also helps prevent conflict regarding the course of treatment chosen. Third, physicians should anticipate the range of different medical courses that the patient is likely to follow and determine what the patient would want done for each predicted development. This anticipation makes possible a coherent medical plan that facilitates goal-centered decision making and that does not have to be reconceptualized with every change in the patient's condition. Fourth, physicians often find that withdrawing a life-sustaining intervention is psychologically more troubling than withholding it. Although this feeling can never serve as justification for withholding treatment, it emphasizes the desirability of not starting interventions without a thoughtful evaluation of whether they are consonant with the patient's best interests.

Terminally ill patients who are suffering are often best served by the withholding of antibiotics or steroids when infections or cerebral edema develop; these treatments frequently pull patients back from a peaceful death to live out a few more days or weeks in pain and indignity. Similarly, the placement of intravenous lines and the monitoring of blood chemistries and even vital signs should proceed only if they are part of a clearly defined, patient-oriented goal. If the patient or the patient's family want everything done to prolong the patient's life and these wishes seem inappropriate, a direct, logical challenge often fails, whereas a nonjudgmental and compassionate exploration of underlying feelings often results in more reasonable decisions. In the rare event that a family's decisions seem clearly at odds with the patient's best interests, physicians must remember that their first responsibility is to serve the patient.

Withholding Advanced Life Support

The major difference between withholding and withdrawing advanced life support (e.g., CPR, mechanical ventilation, inotropic and vasopressor agents) concerns the context in which the decision is made. The decision to withhold these treatments generally takes the form of a DNR order. In contrast to other medical treatments, patients are presumed to have consented to CPR unless they have specifically refused it. Because CPR must be initiated immediately to be effective, physicians and patients must make resuscitation status decisions before the need for CPR. The patient or surrogate is asked to make decisions about treatments that may or may not become necessary during the patient's hospital stay. Conversely, the decision to withdraw advanced life support involves treatments that the patient is experiencing; no hypothetical reasoning is necessary. This distinction bears on the nature of the communication that must occur between the physician and the patient and family.

In discussing resuscitation status with patients, physicians have a responsibility to convey an understanding of what is involved in CPR and mechanical ventilation, the probability of survival to hospital discharge if CPR is instituted, the near certainty of death if CPR is withheld, and why the physician does or does not recommend a DNR order. Physicians should stress that, regardless of resuscitation status, all other treatments and care will continue as previously planned; limits are being set, but a DNR order does not mean that the medical team is giving up on or abandoning the patient. Although determining a patient's resuscitation status represents an essential part of providing

responsible care to critically ill patients, studies continue to show that communication about this issue remains very poor, and most physicians do not know their patients' preferences.⁵⁷ Research has shown that physicians and family members cannot accurately predict patient preferences, so there is no substitute for talking with the patient.^{76,77} Historically, physicians often postponed making resuscitation status decisions until the patient no longer had decision-making capacity, but at least in some regions, there has been a shift toward establishing resuscitation status earlier in a patient's hospitalization.^{78,79}

Several major impetuses have focused increased attention on determining patients' preferences regarding resuscitation status, including studies showing poor post-CPR survival, an increased emphasis on patient autonomy and the right to refuse treatment, and growing concern about wasteful health care expenditures. Many studies have examined post-CPR survival, showing a range of 5% to 25% of patients surviving to discharge.⁸⁰⁻⁸⁴ For the CICU, patients resuscitated from ventricular arrhythmias, including ventricular fibrillation after myocardial infarction, have fared significantly better, with 50% surviving to discharge. In a 1995 study of CPR survival in ICU and non-ICU patients, Karetzky and colleagues⁸⁵ found that resuscitation was successful for only 3% of ICU patients receiving CPR compared with 14% of non-ICU patients.

These findings emphasize the dilemma posed by CPR, especially in the ICU. CPR represents an invasive and frequently brutal intervention, and can be justified only if it has a reasonable chance of benefiting the patient, and if it is in accord with patient wishes. Judgments of reasonableness must be informed by the patient's values because this is a subjective determination: A 5% chance of survival to discharge may be acceptable to some patients, but not to others. For patients to make informed decisions, they require clear and accurate information about the probability of survival.⁸⁶ Two surveys of more than 200 elderly patients each found that respondents consistently overestimated the likelihood of survival to discharge after CPR; in one of the studies, the overestimation was by 300% or more.^{87,88} Both studies found that patients' choices to accept or refuse CPR was strongly influenced by the probability of surviving to discharge. In the second study, Murphy and colleagues⁸⁸ found that the percentage of elderly patients who said they would opt for CPR after cardiac arrest during an acute illness decreased from 41% to 22% after they were informed of the probability of survival.

Because CPR is often a brutal and invasive procedure with a low likelihood of survival, and given the evidence that most elderly patients assert that they would not want CPR under many circumstances, there can be little ethical justification for not discussing CPR with this patient population. Patients should also be asked what they would want done following a successful resuscitation if, after 72 hours of aggressively sustaining their lives, the physician determines that they have little or no chance to regain a reasonable quality of life. To avoid conflict, physicians should include the patient's loved ones in these discussions and should ensure that there is consensus among the various members of the medical team.

For patient resuscitation status decisions to be respected, they must be documented in a readily accessible and legible manner in the medical record. Health care institutions using electronic medical records have immediate access to resuscitation status documentation if DNR orders are placed in a prominent place in the electronic medical record. Physicians who believe that they

cannot participate in resuscitation status decision making probably should not provide care for critically ill patients.

Many physicians find discussions about resuscitation status with patients difficult. Time limitations, stress, and the emotional difficulty of such discussions all contribute to this problem. These conversations become particularly challenging when terminally ill patients wish to have CPR attempted despite their physician's counsel that death is imminent or that CPR would be ineffective. When such conflicts arise, thoughtful and empathic communication can lead to a mutually acceptable resolution. Humans are endowed with a strong will to live, and even chronically and terminally ill patients find it difficult to accept death. When patients refuse to consent to a DNR order, they often agree to having life support withdrawn if, after a successful resuscitation, the physician determines that the patient has virtually no chance of regaining a reasonable quality of life as defined by the patient's values.

The most contentious DNR problem centers on the question of medical futility. Can physicians write a DNR order contrary to the wishes of the patient or the patient's surrogate when the physician judges that CPR would be medically futile? This is a complex dilemma in which ethical principles and duties are in conflict (e.g., patient autonomy, nonmaleficence, professional integrity). As noted previously, the term *futility* in medicine remains vague without a widely accepted definition.²⁶ In the literature regarding DNR orders written against patient wishes, two basic points of view emerge that are separated mainly by differing views of futility. Some authors have argued that determining what range of treatments to offer a patient must remain the physician's prerogative. When a physician determines that a certain therapy should be withheld because it is futile (i.e., because it has no reasonable likelihood of benefiting the patient), the patient's preferences become irrelevant. This position asserts that physicians have the professional responsibility to judge whether a specific medical intervention has what the physician considers to be a reasonable chance of benefiting the patient.⁸⁹

Opponents of this perspective argue that determinations of what is reasonable and what constitutes a benefit are subjective judgments that reflect the decision maker's underlying values.^{28,90} In this view, the value judgment of what constitutes an acceptable likelihood of offering a meaningful benefit is best made by the patient. This second perspective argues for a physiologic definition of futility, by which a treatment is futile only if it cannot achieve its immediate physiologic objective. Waisel and Truog⁹⁰ stated: "CPR is futile only if it is impossible to do cardiac massage and ventilations. As long as circulation and gas exchange are occurring, CPR is not futile, even if no one expects improvement in the patient's condition."

Hospitals have adopted different policies with regard to futility-based DNR orders, with some requiring physiologic futility and others allowing physicians greater leeway. The states of New York and Missouri have enacted statutes that specifically require a patient's consent or the consent of the patient's surrogate (when the patient lacks decision-making capacity) before a DNR order may be written. The issue of how to respond to patients who demand futile medical treatment is drawing increased attention in the context of rapidly increasing health care costs and the difficulty many Americans have with accessing care.

In resolving individual cases of conflict over appropriate levels of treatment, health care professionals should use clinical judgment and a clear consideration of the patient's values

and expressed goals. Assertions of medical futility must not be employed as a means of avoiding difficult discussions with patients and their loved ones. Before writing a DNR order contrary to a patient's wishes, a physician must communicate this intention to the patient and family and allow them the opportunity to transfer to a physician who would honor their wishes. It also is essential for physicians to be aware of their hospital's specific policy for handling such cases.

Withdrawing Advanced Life Support

The withdrawal of advanced life support is usually followed quickly by death and represents one of the most anguishing medical decisions for patients, loved ones, nurses, and physicians. When physicians have discussed life support and critical care preferences with their patients in advance and developed an appreciation of the patient's goals and quality-of-life values, the decision about whether to withdraw life support is often much clearer and less troubling. There are no strict guidelines for deciding how or when to withdraw advanced life support, although many position papers have been published.^{7,9,59,67} Generally, life support is withdrawn when the patient has virtually no chance of regaining a reasonable quality of life, or when the burdens of continued treatment outweigh the benefits.

Withdrawal is usually considered only for patients who have terminal and irreversible conditions, but there are exceptions. Each patient must be evaluated in terms of the specific clinical context and the patient's expressed values and wishes. Patients and their families have a right to know the best and most current data regarding the patient's condition and prognosis and the efficacy of the available treatments. Studies such as APACHE (Acute Physiology, Age, and Chronic Health Evaluation) III⁹¹ can be extremely valuable, but physicians should not exaggerate medicine's ability to make predictions about individual patients.

Patients on mechanical ventilators should not be presumed to lack decision-making capacity. To be judged as having decision-making capacity, patients must be able to appreciate their circumstances and their condition, understand the respective consequences of accepting or rejecting any proposed treatments, exhibit rational decision making, and articulate a choice.⁹² Psychiatric consultation may be useful when competency is questionable. For a patient to give informed consent for the withdrawal of life support, all narcotics must have been discontinued long enough for the patient to be clear-headed, and any treatable depression must have been clinically addressed.

Although most patients on advanced life support are determined to lack decision-making capacity, many are not. Physicians must make a rigorous effort to solicit the patient's wishes concerning the continuation or withdrawal of treatment. Patients with decision-making capacity who wish to have life support withdrawn must be carefully evaluated. They have an ethical and legal right, as noted previously, to control what is done to their bodies and to refuse medical treatments, even if these treatments are necessary to maintain life. Conversely, some patients on advanced life support often experience severe reactive depressions and, if they survive their critical illness, are grateful that their requests to discontinue life support were not honored. Evaluating patient requests and refusals can be extremely difficult. When patients with curable illnesses request that life support be withdrawn, physicians should vigorously re-evaluate the patient's decision-making capacity. When such

patients have dependent minors, legal guidance may be appropriate.

When considering the withdrawal of advanced life support, physicians should always seek unanimity among the members of the health care team and actively solicit different members' opinions. Nurses spend more time with ICU patients than anyone else, and their long hours at the bedside can give them valuable information and insights, especially regarding areas such as family dynamics and the range of the patient's alertness or discomfort over the course of the day. Problems can develop when any professional feels excluded from the decision-making process.

Withdrawing life support is a stressful proposition, and decision making by patients and family members cannot be rushed. The negotiations represent delicate processes that have their own timing, processes integrally involved with coming to accept the inevitability of death and loss.⁹³ As discussed previously, facilitators can assist in these situations. When the patient lacks decision-making capacity, the physician should engage the family and the patient's surrogate to work toward consensus on all life-support decisions.

When there is conflict between the family and medical team, establishing time-limited goals based on clinical judgment and outcome studies can facilitate resolution. Families often feel overwhelmed when advised that life support should be withdrawn. They frequently experience grief, guilt, anger, and confusion, and they may resist the physician's advice. Identification of concrete temporal milestones by which progress can be evaluated often helps facilitate the development of acceptance and coping. Family members might be told, "If we see no signs of improvement over the next 72 hours, then we believe you should consider withdrawing life support. We believe your loved one is suffering and has essentially no chance to regain any reasonable quality of life. To withdraw life support would allow your loved one a more peaceful and dignified death."

Time-limited goals serve the function of providing perspective. They remind the family to step back from day-to-day management concerns and consider the overall circumstances. The interlude also allows families and loved ones an opportunity to adjust what may have been unrealistic expectations of recovery and to express pent-up emotions. Physicians must be able to tolerate expressions of anger or hostility without becoming defensive or withdrawing. The anger usually subsides when the family understands that the physician is compassionate, supportive, and understanding.

When proposing that life support be discontinued, good communication skills assume central importance. One effective approach is to say, "It is my best judgment, and that of the other physicians and nurses, that your loved one has virtually no chance to regain a reasonable quality of life. We believe that life support should be withdrawn, which means your relative will probably die." This statement contains two important components: it is qualified in a way that acknowledges uncertainty and encourages shared decision making; it also clearly states that death is the anticipated result of withdrawing treatment. Without such information, true informed consent cannot be achieved.

At times of critical illness, grief-stricken or guilty family members may press for disproportionate treatment as a way to relieve their own distress. An open and understanding exploration of the underlying feelings usually resolves such difficulties.

Sometimes an honest disagreement persists: what seems disproportionate to the physician seems reasonable to the family. Several guidelines can help in such circumstances: (1) the physician's primary responsibility is to the patient; (2) in most cases, the family has the patient's best interests at heart and knows the patient better than the medical team; (3) ethicists, chaplains, social workers, and ethics committee members can assist in facilitating an agreement on the treatment plan; and (4) care can sometimes be transferred to a physician who agrees to comply with the family's wishes.

Health care professionals should avoid direct involvement in cases that conflict with their ethical values. Clinical judgment may be compromised by the tension and resentment that can arise in such circumstances. If possible, care should be transferred to another physician in these situations. When such involvement is unavoidable, the physician's disclosure of his or her own feelings to understanding colleagues or a psychotherapist make optimal care more likely.

Patients lacking decision-making capacity who have left no indication of quality-of-life values or life-support preferences can present a special challenge. In such circumstances, physicians must be familiar with their hospital's policy, state's laws, and legal precedents concerning substituted medical judgments. If a thorough discussion of the patient with family and loved ones fails to yield sufficient information about the patient's values, the hospital ethics committee should organize a multidisciplinary group composed of physicians, nurses, patient advocates (e.g., a social worker, chaplain, or ombudsman), and the patient's family or loved ones. The group can negotiate decisions based on the patient's best interests. Legal assistance rarely becomes necessary.

When implementing a decision to withdraw life support, the emphasis should be on maximizing patient comfort and minimizing emotional trauma to the family and loved ones. Although curtailing inotropic support may not result in distress, withdrawing mechanical ventilation can present the potential for extreme discomfort, especially if the patient is abruptly extubated and experiences airway obstruction. We advocate rapidly dialing down the supplemental oxygen, pressure support, and intermittent mandatory ventilation rate while maintaining a protected airway. Air hunger and anxiety should be controlled with intravenous morphine as necessary.⁹⁴

Euthanasia and Assisted Suicide

Euthanasia and assisted suicide received increased attention in the first half of the 1990s. From Dr. Jack Kevorkian and his suicide machine to various state ballot initiatives, the issue of whether physicians should be authorized to assist patients to die has become a significant social policy issue.⁹⁵ The term *euthanasia* literally means "good death"; traditionally, it has referred to putting terminally ill and suffering patients to death in a painless manner. Euthanasia in this sense is not usually directly relevant to critical care because ICUs are designed for patients who can be kept alive only with life-sustaining interventions; most ICU patients would die simply as a result of discontinuing all nonpalliative therapies.

The euthanasia debates touch on several important ICU issues, however. How does withdrawing life support differ from euthanasia? How does withholding antibiotics from a patient with bacterial pneumonia and advanced metastatic carcinoma differ from euthanasia? How does prescribing large doses of

narcotics, which in addition to relieving pain can cause respiratory depression and hasten death, differ from euthanasia?

The difference in these cases lies in causality and intentionality. When a physician withdraws life support from a terminally ill patient, it is the patient's disease that causes the death, not the withdrawal. Withdrawing treatment honors the patient's legal and ethical right to refuse treatment. Similarly, withholding antibiotics respects the patient's autonomy; it is the infection that kills the patient, not the withholding of medication. In the case of prescribing narcotics, the distinction becomes more subtle, but remains important; this is referred to as the *principle of double effect*.⁹⁶ Almost all medications and treatments in a physician's armamentarium have the potential for known side effects. Some side effects are desirable, and some are harmful, but the existence of side effects does not preclude treatment. When prescribing morphine and other narcotics to patients who are having mechanical ventilation withdrawn or who have terminal diseases and are in pain, the goal must be pain control, the reduction of anxiety, or even sedation; respiratory depression is a side effect, and it is tolerated in such cases, even to the point of hastening death, as long as the patient has been fully informed and has consented. Dosages must be titrated to achieve the intended goal. What is neither ethical nor legal is for physicians to prescribe medications or treatments in such a manner that the intended result is death. To some, these distinctions may seem purely semantic,⁹⁷ but they are legally valid and represent widely shared ethical thinking. Active euthanasia is a crime in the United States and is opposed by many leading physicians, philosophers, and biomedical ethicists; we oppose active euthanasia as well.

Cross-Cultural Conflicts

Patients' cultural values and beliefs must be understood to appreciate what their illness signifies to them and what they want from physicians.⁹⁸ Cultural patterns have great influence on how individuals and families view illness, medicine, dying, and death, and on their behavioral response during periods of critical illness. Individuals facing death tend to fall back on their traditional cultural or religious beliefs.⁹⁹ Health care providers in the United States increasingly find themselves in cross-cultural situations, confronted with the cultural dimensions of ethical decision making. Cross-cultural ethical issues in medicine have received increasing attention since the mid-1980s, and there has been growing acceptance within the medical community that bioethics is at least partly culturally determined.¹⁰⁰⁻¹⁰⁶ This means that ethical decision making in medicine depends on the specific cultural context in which the decision is being made, and that the ethical principles that Anglo-Americans consider important may seem unimportant to people from other societies.

Anglo-American biomedical ethics accords paramount status to the individual, underscoring the principles of individual rights, autonomy, and self-determination in decisions regarding health care. The fundamental ethical principle of patient autonomy has its basis in Western philosophy and in U.S. cultural values, which emphasize liberty, privacy, and individual rights. The central importance of individuals maintaining control over their body translates into the right to accept or refuse medical interventions. For individuals to be able to make medical decisions, they require an accurate understanding of their medical

condition and any proposed treatments; truth telling and informed consent are also stressed in Western medical ethics. Knowledge and understanding form the basis of informed consent and autonomous decision making.¹⁰⁷

Many other cultures view human identity in profoundly different ways, with much less emphasis on the individual. Many cultures have more relational understandings of human identity (i.e., individuals are defined by their relationships to others rather than by their characteristics as individuals), and the Western emphasis on individual rights and autonomy may not make sense to them.¹⁰⁸ Traditional Chinese society emphasizes the value of family bonds, community, harmony, and responsibility.¹⁰⁹ Respecting communal or familial hierarchies is more important than asserting individual autonomy. It is not that the interests of the family outweigh the interests of the individual; rather, the individual is conceived of primarily as a member of a family. Korean, Italian, and Mexican cultures show similar family-centered structures.^{110,111} The responsibility to show filial duty and protect the elderly may be what the family views as the most important factor in the care of terminally ill patients.¹¹²

The most common source of medical conflict resulting from these relational value systems concerns the disclosure of terminal diagnoses and negative prognostic information; many cultures object to informing patients of terminal diagnoses, especially diagnoses of cancer. A 1995 study of attitudes toward patient autonomy of different ethnic groups found that Korean-Americans and Mexican-Americans generally believed that patients should not be told about terminal diagnoses, and that the family, not the patient, should make life-support decisions. European-Americans and African-Americans were more likely to favor full disclosure and patient participation in decision making.^{113,114} The objection to disclosing distressing information stems from several different beliefs. Traditional Chinese and Southeast Asian cultures view the sick person as needing protection, similar to a child. From this perspective, telling patients upsetting diagnoses adds to their suffering, whereas healthy family members are in a stronger position to bear the bad news and make appropriate decisions. In addition, some cultures often view telling someone that they are dying as bad luck, similar to a curse. Traditional Navajo culture, which believes that "thought and language have the power to shape reality and to control events," also objects to discussing negative information as potentially harmful to the patient.¹¹⁵

When a family does not want a patient to know about a diagnosis, physicians face a difficult ethical dilemma because patient autonomy and the need for informed consent are central to American medical ethics and jurisprudence. From a legal standpoint, courts have ruled that physicians should not be liable for honoring a patient's specific request not to disclose information.^{115,116} Regarding issues of autonomy, Gostin¹⁰⁸ and Pellegrino¹⁰⁴ argue that patients have the right to use their autonomy to choose not to be informed. In the end, physicians must determine for themselves how to negotiate conflicts between their own value systems and the value systems of their patients. It is unreasonable to assert that physicians should strive to follow basic ethical principles and then claim that it is acceptable to toss these principles aside when they conflict with a patient's values. When conflict arises, open communication is essential, and a willingness to compromise serves all parties well. For such culturally conflictual situations, Freedman¹¹⁷ has proposed a strategy of "offering truth" to the patient, rather than "forcing

truth.” Using this strategy, a physician would ascertain directly from the patient how much he or she wants to know about diagnosis and prognosis, and the patient’s expressed wishes would be honored. At the very least, physicians should remain sensitive to cultural differences and maintain an open-minded and respectful attitude about other cultural beliefs and practices. Physicians should remember that a family’s cultural background can be a source of tremendous strength during the crisis of critical illness; violating a patient’s cultural mores should be avoided whenever possible.

In striving to understand a patient’s cultural background, the pitfall of stereotyping must be avoided; within a given culture, there can be great variation among individuals, and there is no substitute for talking directly to patients and their families to determine their cultural values and beliefs. Among patients who are immigrants, the patient and his or her family frequently span more than one generation, with different levels of retention of traditional cultural practices. It is important to note the contribution of various elements in the cultural fabric, such as socio-economics, education, and degree of acculturation. The role of culture must be seen in context with other factors that come into play in an individual’s decision making or behavior, such as economic considerations and individual attributes. Culture is only one component in a complex matrix of influences.

Medical decision-making for patients who lack decision-making capacity and who have no surrogate decision-maker

Medical decision-making for patients with neither decision-making capacity nor a surrogate decision-maker presents an ethical challenge for healthcare providers because there is no way to obtain informed consent for treatment. The challenge is particularly acute when these decisions involve the withholding or withdrawing of life-sustaining treatments but are also pertinent to any invasive or life-threatening procedures. Decision making for these patients should be guided by the best obtainable understanding of what the patient would have wanted using substituted judgment. Aggressive efforts to locate people who knew the patient well are encouraged. Where inadequate information is available to make a substituted judgment, the decision-making should be based on the patient’s best interest.

Although different medical organizations have recommended have recommended and different hospitals have adopted different specific policies for dealing with these scenarios, there is an emerging consensus that the medical team recommending invasive or life-threatening treatment or the withholding or withdrawing of life-sustaining treatments cannot also play the dual role of surrogate by consenting to their proposed actions.¹¹⁸⁻¹²³ Instead one of two approaches has been recommended by a number of hospitals and organizations when decisions involve limiting or withdrawing life support: either having a multidisciplinary review of the treatment plan by individuals not involved in the patient’s care (such as by the hospital ethics committee) or else involving the courts in order to have a guardian appointed to serve as a surrogate decision-maker. In cases involving invasive or high-risk procedures, an ethics consultant or other individual who is not involved in the patient’s care and who has expertise in patient rights and decision-making should participate in the decision-making process unless immediate treatment is needed

for a medical urgency or emergency. In all these cases, familiarity with and adherence to relevant state law is mandatory.

Conclusion

The two major goals of critical care physicians are to save salvageable patients and to facilitate a peaceful and dignified death for patients who are dying. The difficulty of achieving certainty and consensus regarding in which of these two categories an individual patient belongs leads to challenging ethical issues. These issues are best approached in an ordered and thoughtful manner. Whether the issue is a family insisting on treatment that the physician believes is futile or a ventilator-dependent patient requesting that life support be withdrawn, “thinking ethically” about these situations by being attentive to the four basic ethical principles (autonomy, beneficence, nonmaleficence, and distributive justice), by calculating consequences, and by using casuistry can facilitate a thorough analysis and help to resolve disagreements. In addition, four guidelines provide a procedural approach to ethical problems: (1) respect the role of patients as partners, (2) determine who has authority to make health care decisions for the patient, (3) establish effective communication with the patient and family, and (4) determine in an ongoing manner the patient’s quality-of-life values and desires.

Good communication skills are the most powerful tool in ethical conflicts. When questions about life and death are treated in a patient, nonjudgmental, and sensitive manner, ethical conflicts arise less often and tend not to become intractable. Physicians should encourage patients, families, and members of the health care team to express their thoughts and feelings about difficult cases. Whenever possible, decision making should occur by means of consensus.

From an ethical and legal perspective, patients with decision-making capacity have a clearly established right to refuse medical treatments. Providing treatment against a competent patient’s will can constitute battery. At the same time, patients do not have the right to demand specific treatments; only the physician can decide what therapies are appropriate to offer to a patient. The authority for decision making becomes less clear with legally incompetent patients; different states have different judicial precedents and laws concerning when treatment must be provided, and how life-sustaining treatment may be withdrawn from incompetent patients. Some states allow family members to provide substituted judgment for incompetent patients, whereas New York and Missouri require clear and convincing evidence that the patient, before becoming incompetent, had indicated that he or she would want life support to be withdrawn. Patients can protect their ability to help determine what types of medical care they receive by engaging in advance care planning and documenting their wishes via living wills or, preferably, medical powers of attorney.

Decisions about withholding or withdrawing life support occur frequently in ICUs and they represent a painful and difficult process for many physicians. The essential principle in these decisions is that end-of-life decision making must reflect the individual patient’s goals and quality-of-life values. At the same time, physicians are not obliged to provide futile treatments. How to communicate with patients and families and what words to use are probably the most important factors. Although some physicians may object to withholding or withdrawing life-sustaining treatment, patients have a clear and incontestable

right to refuse life support and other treatments, even when such refusal results in their death.

Some Asian, Hispanic, Native American, and European cultures do not share the Anglo-American prioritization of individual rights and autonomy. Patients from family-centered cultures may expect that medical decision making will be handled by the family and the physician with limited or no patient involvement. Many cultures believe that distressing diagnoses should be withheld from patients so they are not burdened with bad news. Physicians should be sensitive and tactful when treating patients from cultural backgrounds other than their own. Although physicians must remain true to their own personal ethics, they should also be cautious about imposing their own cultural values on patients who are guided by a different set of beliefs and customs. In many situations, cultural beliefs and practices can be accommodated without harm to the patient.

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Cardiac Intensive Care Unit Admission Criteria

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CHAPTER

3

History
Diagnoses
Periprocedure and Postprocedure Setting

Specific Populations
Conclusion

Cardiovascular disease (CVD) accounted for 36.3% of all deaths in the United States in 2004.¹ Nearly 2400 Americans die of CVD each day, an average of 1 death every 36 seconds. The United States leads the world in spending on health care, whether measured as a percentage of gross domestic product or as dollars per capita.² Despite this cost, cardiac intensive care unit (CICU) beds remain a limited resource. There is evidence that physicians can safely adapt to substantial reductions in the availability of CICU beds.³ Determining the appropriateness for admission to the CICU can be challenging, however, and has been the subject of study since the early 1980s.^{4,5}

Many disease processes typically lead to admission to the CICU (Table 3-1). This chapter discusses these conditions and the rationale for intensive care in their treatment.

History

The first description of the coronary care unit (CCU) was presented to the British Thoracic Society in July 1961.⁶ CCUs were initially established in the early 1960s in an attempt to reduce mortality from acute myocardial infarction (MI). The ability to abort sudden death from malignant ventricular arrhythmias in the post-MI setting led to the continuous monitoring of cardiac rhythm and an organized system of cardiopulmonary resuscitation, including external defibrillation.⁷ An early experience of patients with acute MI treated in the CCU published in 1967 showed that patients treated in the CCU had better survival rates compared with other patients with acute MI in the absence of cardiogenic shock.⁸ With creation of Myocardial Infarction Research Units in the United States by the National Heart, Lung and Blood Institute and evolving technologies, the foundation was in place for the CCU to expand into the modern-day CICU where comprehensive advanced care is provided for many cardiovascular conditions. The CICU has been called one of cardiology's 10 greatest discoveries of the 20th century.⁹

Diagnoses

Admissions to the CICU for chest pain and acute coronary syndromes (ACS), including acute MI, have been the most extensively studied. Algorithms exist to assist in the appropriate triage of chest pain patients to the CICU. These are reviewed in the next section. For other cardiovascular conditions, there is less developed efficacy and cost-effectiveness research, and the

decision to admit to the CICU is largely determined on clinical grounds depending on the individual patient care scenario. These other diagnoses are discussed separately.

Chest Pain and Acute Coronary Syndromes, and Acute Myocardial Infarction

Chest pain accounts for approximately 6 million annual visits to emergency departments in the United States, making chest pain the second most common complaint in the emergency department.¹⁰ ACS are life-threatening causes of chest pain seen in the emergency department and include unstable angina, non-ST segment elevation MI (NSTEMI), and acute MI or ST segment elevation MI. Less than 15% to 30% of patients who present to the emergency department with nontraumatic chest pain have ACS, however.^{11,12} An important challenge is to identify patients with ACS appropriately and admit them to the appropriate setting for further care. For the evaluation and management of patients with acute chest pain, prediction models have markedly improved our ability to estimate risk, and cost-effectiveness analyses have helped guide the development of new paradigms and the incorporation of new technologies.¹³

In addition to treating patients with ACS, the CICU has traditionally been considered appropriate for monitoring patients with acute chest pain until ACS is diagnosed or excluded. Increasing health care costs have created pressures, however, to increase the efficiency of CICUs. Possible strategies seek to decrease resource use by identifying low-risk patients for initial triage or early transfer to lower levels of care. The application of management algorithms and the development of intermediate care units are allowing for a distinction between intensive coronary care and careful coronary observation.¹⁴ The development of chest pain units located in the emergency department is another alternative to CICU admission. These units are safe, effective, and a cost-saving means of ensuring that patients with unstable angina who are considered to be at intermediate risk of cardiovascular events receive appropriate care.¹⁵ Patients at low clinical risk can receive immediate exercise testing in the chest pain unit if the appropriate diagnostic modalities are available. This approach is accurate for discriminating low-risk patients who require admission from patients who can be discharged to further outpatient evaluation.¹⁶

Several reports have detailed strategies to identify high-risk patients early. To achieve more appropriate triage to the CICU of patients presenting with acute chest pain, Goldman and

Table 3-1. Cardiovascular Conditions Requiring Admission to the Cardiac Intensive Care Unit

Chest pain, acute coronary syndromes, and acute myocardial infarction
Acute decompensated heart failure
Pulmonary hypertension
Arrhythmias
Sudden cardiac death
Cardiogenic shock
Conditions requiring IABP or other forms of mechanical circulatory support
Adult congenital heart disease (decompensated)
Valvular heart disease (with hemodynamic instability)
Aortic dissection
Hypertensive emergency
Cardiac tamponade
Pulmonary embolism (massive or submassive)
Postprocedure monitoring (percutaneous coronary intervention and electrophysiologic study)

IABP, intra-aortic balloon pump.

coworkers¹⁷ used clinical data on 1379 patients at two hospitals to construct a computer protocol to predict the presence of MI. This protocol was tested prospectively, and it had a significantly higher specificity (74% versus 71%) in predicting the absence of infarction than physicians deciding whether to admit patients to the CICU, and it had a similar sensitivity in detecting the presence of infarction (88% versus 87.8%). Decisions based solely on the computer protocol would have reduced the admission of patients without infarction to the CICU by 11.5% without adversely affecting the admission of patients in whom emergent complications developed that required intensive care.

In another study,¹⁸ the acute cardiac ischemia time-insensitive predictive instrument (ACI-TIPI) was used to triage patients with symptoms suggestive of acute cardiac ischemia to the CICU, telemetry unit, ward, or home. Use of ACI-TIPI was associated with reduced hospitalization among emergency department patients without acute cardiac ischemia. Appropriate admission for unstable angina or acute infarction was not affected. If ACI-TIPI is used widely in the United States, its potential incremental impact is estimated to be more than 200,000 fewer unnecessary hospitalizations and more than 100,000 fewer unnecessary CICU admissions.¹⁸

In a cost-effectiveness analysis, Fineberg and colleagues¹⁹ found that for patients with a 5% probability of infarction, admission to a CICU would cost \$2.04 million per life saved and \$139,000 per year of life saved compared with intermediate care. For the expected number of such patients annually in the United States, the cost would be \$297 million to save 145 lives.

In another study by Goldman and associates,²⁰ a set of clinical features was defined; if these features were present in the emergency department, they were associated with an increased risk of complications. These clinical features included ST segment elevation or Q waves on the electrocardiogram (ECG) thought

to indicate acute MI, other ECG changes indicating myocardial ischemia, low systolic blood pressure, pulmonary rales above the bases, or an exacerbation of known ischemic heart disease. The risk of major complications in patients with acute chest pain can be estimated on the basis of the clinical presentation and new clinical observations made during the hospital course. These estimates of risk help in making rational decisions about the appropriate level of medical care for patients with acute chest pain.

Despite these findings, the implementation of these algorithms in clinical practice by physicians without specific training in their use has been minimal.^{21,22} This situation may relate to physicians' reporting that they are too busy, are unsure of the value of the algorithms, and are concerned about the consequences of inappropriately discharging patients who are later found to have had MI.²³

A more recent analysis by Tosteson and colleagues²⁴ indicates that the CICU usually should be reserved for patients with a moderate ($\geq 21\%$, depending on the patient's age) probability of acute MI, unless patients need intensive care for other reasons. Clinical data suggest that only patients with ECG changes of ischemia or infarction not known to be old have a probability of acute MI this high. A summary has been developed that outlines the location to which chest pain patients should be admitted (Table 3-2).²⁵

Another important issue to consider is the length of stay in the CICU after patients are admitted. If patients are initially triaged to the CICU, the lack of cardiac enzyme abnormalities or recurrent chest pain during the first 12 hours of hospitalization are parameters that can be used to identify patients for whom a 12-hour period of CICU observation is sufficient to exclude acute MI.²⁶ In a study by Weingarten and colleagues,²⁷ physicians caring for patients with chest pain who were at low risk for complications received personalized written and verbal reminders regarding a guideline that recommended a 2-day hospital stay. Use of the practice guideline recommendation with concurrent reminders was associated with a decrease in length of stay from 3.54 ± 4.1 days to 2.63 ± 3 days and a total cost reduction of \$1397 per patient. No significant difference was noted in complications, patient health status, or patient satisfaction when measured 1 month after hospital discharge.

The European Society of Cardiology and American College of Cardiology restructured the definition of acute MI in 2000 (Table 3-3).²⁸ The principal revision compared with the previous World Health Organization definition²⁹ is the inclusion of biomarkers, specifically troponin, as a necessary component. There have been some attempts to assess the new definition and the widespread introduction of troponin measurement on CICU admitting practices. One study by Amit and colleagues³⁰ was a retrospective cohort study in which all admissions to the CICU the year before and after the introduction of troponin measurement and the updated MI definition were examined. There was a 20% increase in the number of CICU admissions, driven by a 141% increase in the number of NSTEMIs. Length of stay in the CICU decreased by 1 day for all ACS patients, and the 30-day mortality for acute MI did not change significantly. In another study by Zahger and associates,³¹ the number of NSTEMI patients increased by 33% after the definition change, whereas the number of patients with ST segment elevation MI remained the same. There was no change in the number of CICU beds at the participating institutions. The proportion of patients given

Table 3-2. Indications to Guide Where to Admit Patients with Acute Chest Pain**Intensive Care Unit**

One of the following:

- Substantial ischemic ECG changes in two or more leads that are not known to be old
 - ST segment elevation ≥ 1 mm or Q waves of ≥ 0.04 second
 - ST segment depression ≥ 1 mm or T wave inversion consistent with the presence of ischemia

Any two of the following, with or without substantial ECG changes:

- Coronary artery disease known to be unstable (in terms of frequency, duration, intensity, or failure to respond to usual measures)
- Systolic blood pressure < 100 mm Hg
- Serious new arrhythmias (new-onset atrial fibrillation, atrial flutter, sustained supraventricular tachycardia, second degree or complete heart block, or sustained or recurrent ventricular arrhythmias)
- Rales above the bases

Intermediate Care Unit

Any of the following conditions but meeting no criteria for intensive care:

- Coronary artery disease known to be unstable
- Systolic blood pressure < 110 mm Hg
- Rales above the bases
- Major arrhythmias (new-onset atrial fibrillation, atrial flutter, sustained supraventricular tachycardia, second-degree or complete heart block, or sustained or recurrent ventricular arrhythmias)
- New onset of typical ischemic criteria that meet the clinical criteria for unstable angina and that occur at rest or with minimal exertion

Evaluation or Observation Unit

New-onset symptoms that may be consistent with ischemic heart disease, but are not associated with ECG changes or a convincing diagnosis of unstable ischemic heart disease at rest or with minimal exertion

Known coronary artery disease whose presentation does not suggest a true worsening, but for which further observation is thought to be beneficial

Home with Office Follow-up in 7-10 Days to Determine Whether Further Testing Is Needed

Other conditions

Adapted from Lee TH, Goldman L: Evaluation of the patient with acute chest pain. *N Engl J Med* 2000;342:1187-1195.
ECG, electrocardiogram.

Table 3-3. European Society of Cardiology/American College of Cardiology Definition of Acute, Evolving, or Recent Myocardial Infarction

Typical increase and gradual decrease (troponin) or more rapid increase and decrease (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following:

- Ischemic symptoms
- Development of pathologic Q waves on the ECG
- ECG changes indicative of ischemia (ST segment elevation or depression)
- Coronary artery intervention (e.g., angioplasty)

Adapted from Antman E, Bassand J-P, Klein W, et al: Myocardial infarction redefined—a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol* 2000;36:959-969.

the diagnosis of NSTEMI increased significantly more in centers with high use of troponin. These changes have a significant impact on resource use.

Given this increased demand for a relatively fixed resource, the question of whether all NSTEMI patients need to be admitted to the CICU arises. The CRUSADE registry³² showed that patients with NSTEMI often receive excess doses of anti-thrombotic therapy, and that dosing errors occur more often in vulnerable populations and predict an increased risk of major bleeding. Some institutions have interpreted these data to indicate that all NSTEMI patients should be admitted to the CICU because a maximally observed setting may limit excess dosing and bleeding complications.

At our institution, it is practice for only NSTEMI patients who are high risk by the TIMI risk score³³ to be admitted to the

CICU. The lower risk NSTEMI patients are admitted to a telemetry unit with cardiac nurses. There is preliminary evidence that admission of patients with initially uncomplicated chest pain with a relatively low probability of acute MI to a stepdown unit does not place at increased risk those who eventually “rule in” for MI.³⁴ Regardless of specific setting, the adherence to clinical pathways offers the potential to improve the care of patients with ACS while reducing the cost of care.³⁵

Heart Failure

It is estimated that 5.2 million people in the United States are being treated for heart failure.¹ Hospital discharges for heart failure increased from 402,000 in 1979 to 1,101,000 in 2004.³⁶ Interventions to improve adherence, the control of hypertension, and the appropriate use of angiotensin-converting enzyme

Table 3-4. Events and Procedures for Congestive Heart Failure Patients during Hospital Stay

Event or Procedure	All Patients (N = 105,388) (%)	ICU/CICU Patients (n = 19,754) (%)
Death	4	11
Defibrillation or CPR	1	6
Mechanical ventilation	5	23
Intra-aortic balloon pump	<1	2
Pulmonary artery catheter	5	17
Dialysis	5	19
New-onset dialysis	1	3
Electrophysiologic study	4	5
Cardiac catheterization	10	20
With PCI	81	78

Adapted from Adams KF Jr, Fonarow GC, Emerman CL, et al; ADHERE Scientific Advisory Committee and Investigators: Characteristics and outcomes of patients hospitalized for heart failure in the United States: Rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). *Am Heart J* 2005;149:209-216.

CPR, cardiopulmonary resuscitation; PCI, percutaneous coronary intervention.

inhibitors may prevent many hospitalizations of heart failure patients.³⁷ Device therapy, including biventricular pacemakers and implantable cardioverter-defibrillators, has also led to significant improvements in outcomes for certain heart failure patient populations.^{38,39} Nonetheless, some patients admitted to the hospital with heart failure require advanced cardiac care in the CICU. Standard criteria for management of acute decompensated heart failure (ADHF) in the CICU are not clearly established. Management usually involves invasive hemodynamic monitoring and inotropic or vasopressor support that cannot be done outside the CICU in most institutions.

Admission for heart failure is a high-risk event for patients, particularly patients admitted to an intensive care unit (ICU) setting.⁴⁰ Table 3-4 shows the events and procedures that occurred during hospitalization of patients with congestive heart failure (CHF) in the ADHERE registry.

Weingarten and associates⁴¹ found that nearly one third of patients with CHF hospitalized in either the CICU or intermediate care unit are lower risk and potentially suitable for transfer 24 hours after admission. In this study, *low risk* is defined as patients without acute MI or ischemia, active or planned cardiac interventions, unstable comorbidity, worsening clinical status, or lack of response to diuretic therapy. A more common planned cardiac intervention for heart failure patients is the use of the pulmonary artery catheter. Although addition of the pulmonary artery catheter to careful clinical assessment increases anticipated adverse events, it does not affect overall mortality

and hospitalization in patients with severe symptomatic and recurrent heart failure.⁴²

In most hospitals, certain medical therapies used in the treatment for decompensated heart failure are delivered in the CICU setting. The need for pronounced afterload reduction is an indication for intravenous nitroprusside.⁴³ This therapy is commonly delivered in the CICU because it requires continuous blood pressure monitoring. The major limitation to the use of nitroprusside is its metabolism to cyanide, possibly leading to development of cyanide toxicity or rarely thiocyanate toxicity that may be fatal.⁴⁴

Patients with systolic dysfunction who remain volume-overloaded despite vasodilator and diuretic therapy may require intravenous inotropic support to improve systemic perfusion. The β agonist dobutamine is a useful inotropic agent for ADHF.⁴⁵ In patients with severe CHF, short-term administration of dobutamine selectively improves vascular endothelial function.⁴⁶ Another class of inotropic agents commonly used is the phosphodiesterase inhibitors. In addition to being given in the acute setting, prolonged outpatient therapy with milrinone, a phosphodiesterase inhibitor, has been employed.⁴⁷ The use of intravenous continuous infusion of inotropes, including dobutamine and milrinone, has not been shown to have a benefit in mortality.⁴⁸

Another treatment modality that has been used in the CICU or cardiac stepdown unit is the exogenous administration of nesiritide, recombinant human brain natriuretic peptide. In patients hospitalized with ADHF, nesiritide improves hemodynamic function.⁴⁹ More recent independent analyses have questioned the safety of nesiritide, however. Compared with non-inotrope-based control therapy, nesiritide may be associated with an increased risk of worsening renal function⁵⁰ and death⁵¹ after treatment for ADHF. If used, these treatments are best used in the CICU or cardiac stepdown unit to achieve hemodynamic targets.

Certain causes of heart failure require specific therapies. Patients with giant cell myocarditis have improved outcomes if they receive immunosuppressive treatment.⁵² Patients with a fulminant presentation from giant cell myocarditis, or more rarely from other etiologies such as lymphocytic or viral myocarditis, require an intensive level of hemodynamic support with inotropes and vasopressors in the CICU.⁵³

Patients receiving inotropic therapy can go on to have improved outcomes with the use of mechanical circulatory support, specifically left ventricular assist devices (LVADs), as destination therapy.⁵⁴ Although cellular recovery and improvement in ventricular function are observed, the degree of clinical recovery is insufficient for device explantation in most patients with chronic heart failure.⁵⁵ If not used as destination therapy, the LVAD may serve as a bridge to heart transplantation, and these patients are cared for in the cardiothoracic surgery ICU after surgery. Also, at cardiac transplantation centers, some advanced CHF patients require continuous infusion of a single high-dose intravenous inotrope (e.g., dobutamine, ≥ 7.5 $\mu\text{g/kg/min}$, or milrinone, ≥ 0.50 $\mu\text{g/kg/min}$), or multiple intravenous inotropes, in addition to continuous hemodynamic monitoring of left ventricle filling pressures, which satisfies criteria for listing as Status 1A by the United Network of Organ Sharing.⁵⁶ Additionally, patients undergoing new advanced cardiac care procedures, such as percutaneous mechanical devices,⁵⁷ require management in the CICU.

Multiorgan dysfunction in the setting of heart failure requires admission to the CICU. A reduced glomerular filtration rate is associated with an increased mortality in patients with heart failure.⁵⁸ Because many patients with ADHF and renal failure have compromised hemodynamics, a form of renal replacement therapy, such as continuous venovenous hemofiltration or hemodialysis, in the intensive care setting is commonly required. Other volume management techniques for heart failure treatment, such as ultrafiltration,⁵⁹ may necessitate care in the CICU or stepdown unit.

While the patient is hospitalized, careful attention to certain laboratory values such as serum sodium and blood urea nitrogen is reasonable because both values have been shown to be independent predictors of subsequent mortality.^{60,61} Treatment with tolvaptan, a vasopressin V2 receptor blocker, has been shown to increase serum sodium concentrations effectively in patients with euvolemic or hypervolemic hyponatremia,⁶² but has no effect on long-term mortality or heart failure–related morbidity.⁶³

Pulmonary Hypertension

Several treatments for pulmonary arterial hypertension are approved in the United States, including epoprostenol, treprostinil, bosentan, and sildenafil. Because limited data are available from head-to-head comparisons of approved therapies, the choice of treatment is dictated by clinical experience and by patients' preferences.⁶⁴ There are no evidence-based guidelines on when to admit patients with pulmonary hypertension to the CICU. Generally, patients with New York Heart Association or World Health Organization functional class IV may require an intensive care setting for management. Intravenous epoprostenol is an advanced pulmonary hypertension therapy that has been shown to improve functional capacity and survival in patients with idiopathic pulmonary arterial hypertension.⁶⁵ In addition to vasoreactivity testing in the cardiac catheterization laboratory, inhaled nitric oxide is sometimes used in acutely ill patients with severe pulmonary hypertension in the CICU.⁶⁶

Arrhythmias

Many arrhythmias require admission to the CICU. The decision to manage a patient with an arrhythmia in the CICU largely depends on the underlying rhythm disturbance, and whether it is associated with signs and symptoms of hemodynamic instability. Patients with arrhythmias needing management in the CICU include patients with tachyarrhythmias and bradyarrhythmias and survivors of sudden cardiac death. Length of stay in the CICU should be determined by the type of underlying rhythm, the clinical state of the patient, and whether measures have been taken to reduce the recurrence of an unstable arrhythmia. If the patient is deemed low risk, the patient can be transferred from the CICU.

Narrow-complex tachycardias can lead to unstable hemodynamics. In this situation, immediate synchronized cardioversion is indicated.⁶⁷ This is best done in the controlled setting of a CICU if possible. If a patient is out of the hospital or in a less monitored unit, admission or transfer to the CICU should be arranged for further management.

Wide-complex tachycardias may represent either supraventricular or ventricular arrhythmias. The mechanism of wide-complex tachycardias can be determined with clinical information and analysis of the 12-lead surface ECG.⁶⁸

Regardless of the cause, a wide-complex tachycardia that is unstable and associated with hemodynamic compromise must be treated promptly with electrical cardioversion. Pulseless ventricular tachycardia or ventricular fibrillation requires immediate defibrillation. Admission to the CICU may be required even in patients with implantable cardioverter-defibrillators. Electrical storm, or three or more appropriate shocks delivered because of repeated episodes of ventricular tachycardia or ventricular fibrillation occurring within a 24-hour period, often requires antiarrhythmic medical therapy to suppress arrhythmias and further shocks. In the AVID cohort, electrical storm was a significant independent risk factor for nonsudden cardiac death.⁶⁹

More recently, the American College of Cardiology/American Heart Association/European Society of Cardiology updated their guidelines for the management of ventricular arrhythmias and the prevention of sudden cardiac death.⁷⁰ For successfully resuscitated cardiac arrest victims, whether the event occurred in or out of the hospital, post–cardiac arrest care includes admission to an ICU and continuous monitoring for 48 to 72 hours.⁷¹ The outcome of patients experiencing sudden cardiac death remains poor. In the Seattle series, survival to hospital discharge for patients treated between 1998–2001 was not significantly better than for patients treated between 1977–1981.⁷² Protocols involving induction of hypothermia after return of spontaneous circulation phase in the ICU have been associated with improved functional recovery and reduced cerebral histologic deficits in various animal models of cardiac arrest. Additional promising preliminary human studies have been completed.⁷³

Bradyarrhythmias that require temporary transvenous pacing are an acceptable indication for admission to the CICU. Indications for temporary pacing are less clearly described than the indications for permanent pacing. Table 3-5 lists recommendations by class of evidence for transvenous pacing in the setting of acute MI, which includes several bradyarrhythmias.⁷⁴ Regardless of level of evidence, in practice patients who receive temporary transvenous pacemakers should be admitted to the CICU. Monitoring in the CICU should continue until the acute and reversible cause of the bradyarrhythmia is corrected, or a permanent pacemaker is placed.

Withdrawal of pacemaker or implantable cardioverter-defibrillator support at the end of life is becoming a more frequently encountered clinical scenario. Granting terminally ill patients' requests to remove unwanted medical support is legal and ethical.⁷⁵ An analysis by Lewis and coworkers⁷⁶ showed that only one third of terminally ill patients with ICDs actually had shock therapy withdrawn as part of a comfort care strategy.

Cardiogenic Shock

Cardiogenic shock is the most severe form of left ventricular failure. It can occur as a complication of acute MI or from other cardiovascular conditions (Table 3-6).⁷⁷ For the acute MI subgroup, the CICU is used for temporizing measures, such as intra-aortic balloon pump (IABP) counterpulsation and use of vasopressor support. These patients benefit from early revascularization with a mortality benefit at 6 months⁷⁸ that persists at 6 years of follow-up.⁷⁹ The use of early intravenous β blocker therapy in patients admitted to the CICU with acute MI complicated by unstable hemodynamics reduces the risk of reinfarction and ventricular fibrillation, but increases the risk of cardiogenic shock during the first day after admission.⁸⁰ Appropriately selected patients with acute cardiogenic shock in the

Table 3-5. Recommendations for Temporary Transvenous Pacing**Class I**

Asystole
 Symptomatic bradycardia (includes sinus bradycardia with hypotension and type I second-degree AV block with hypotension not responsive to atropine)
 Bilateral BBB, including alternating BBB, or right BBB with alternating LAFB/LPFB (any age)
 New or indeterminate age bifascicular block (right BBB with LAFB or LPFB, or left BBB)
 Mobitz type II second-degree AV block

Class IIa

Right BBB and LAFB or LPFB (new or indeterminate)
 Right BBB with first-degree AV block
 Left BBB, new or indeterminate
 Incessant VT, for atrial or ventricular overdrive pacing
 Recurrent sinus pauses (>3 seconds) not responsive to atropine

Class IIb

Bifascicular block of indeterminate age
 New or indeterminate age isolated right BBB

Class III

First-degree heart block
 Type I second-degree AV block with normal hemodynamics
 Accelerated idioventricular rhythm
 BBB known to exist before acute MI

Adapted from Ryan TJ, Anderson JL, Antman EM, et al: ACC/AHA guidelines for the management of patients with acute myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). *J Am Coll Cardiol* 1996;28:1328-1428.

AV, atrioventricular; BBB, bundle branch block; LAFB, left anterior fascicular block; LPFB, left posterior fascicular block; MI, myocardial infarction; VT, ventricular tachycardia.

setting of acute MI managed in the CICU have had encouraging initial experiences with use of ventricular assist devices.⁸¹

Other Indications for Intra-Aortic Balloon Pump

Other indications for IABP placement are clinical situations where admission to the CICU is necessary. IABP may be useful in a high-risk or complicated percutaneous coronary intervention (PCI),⁸² rescue PCI after failed thrombolysis,⁸³ and acute MI with mechanical complications such as acute ventricular septal defect and mitral regurgitation.⁸⁴ The prophylactic placement of an IABP before coronary artery bypass graft surgery has been performed in patients with left main coronary artery stenosis, severely depressed left ventricular systolic function, diffuse coronary artery disease, and redo surgery.^{85,86}

Adult Congenital Heart Disease

The total population of adult congenital heart disease patients in the United States in 2000 was 785,000.⁸⁷ This number, which exceeds the number of pediatric cases, reflects tremendous advances in pediatric cardiac care. Adult congenital heart disease patients may require management in the CICU. The need for CICU care is commonly due to the main consequences of

Table 3-6. Causes of Cardiogenic Shock

Complications of Acute Myocardial Infarction
Extensive left ventricular infarction
Extensive right ventricular infarction
Ventricular septal rupture
Acute severe mitral regurgitation
Cardiac tamponade with or without free wall rupture
Other Conditions
Aortic dissection
Myocarditis
Massive pulmonary embolism
Critical valvular stenosis
Acute mitral or aortic regurgitation
Calcium channel blocker or β blocker overdose

Adapted from Tschopp D, Mukherjee D: Complications of myocardial infarction. In Griffin BP, Topol EJ (eds): *Manual of Cardiovascular Medicine*, 2nd ed. Philadelphia, Lippincott Williams & Wilkins, 2004, pp 45-63.

congenital cardiac lesions: cyanosis, congestive heart failure, pulmonary hypertension, Eisenmenger syndrome, and cardiac arrhythmias. These patients are best cared for by a multidisciplinary team at designated adult congenital heart disease centers.⁸⁸

Valvular Heart Disease

There are many considerations in diagnosing and treating patients with valvular heart disease. Most center around the more common management decisions involving chronic valvular lesions. There are instances, however, of acute valvular pathology that require care in the CICU.

Patients with acute mitral regurgitation are often critically ill with significant hemodynamic abnormalities. In most cases, definitive treatment is surgery, but medical therapy in the CICU is needed to support the patient initially. Intravenous nitroprusside can reduce mitral regurgitation leading to increased forward cardiac output and diminished pulmonary congestion.⁸⁹ Nitroprusside should not be given as monotherapy in patients who are hypotensive at presentation. Some benefit may be achieved initially by concurrent administration of an inotropic agent such as dobutamine, but an IABP is often inserted.⁹⁰

Acute aortic insufficiency is a valvular condition that can require management in the CICU. The two most common causes of acute aortic insufficiency are endocarditis and aortic dissection.⁹¹ Treatment of acute severe aortic insufficiency is emergency aortic valve replacement. If there is any delay in surgery, stabilization may be attempted in the ICU using intravenous vasodilators, such as nitroprusside, and possibly inotropic agents, such as dopamine or dobutamine, in an attempt to enhance forward flow and lower left ventricular end-diastolic pressure.⁹⁰ An IABP is contraindicated because inflation of the balloon in diastole would worsen the severity of aortic insufficiency.

A special consideration is acute valvular disease in the setting of infective endocarditis. Surgery in native valve endocarditis is sometimes delayed to allow a longer duration of antibiotic

therapy; however, several studies support the use of early surgery in patients with acceptable indications.^{92,93} The decision as to when to operate is often difficult and requires close consultation with surgical colleagues for each case.

Patients with severe aortic stenosis and hemodynamic instability are managed in the CICU. If the patients are high risk for aortic valve replacement, percutaneous balloon valvuloplasty has been performed. This procedure has been shown to reduce aortic valve gradient, but morbidity and mortality remain high in this population.⁹⁴ The 2006 American College of Cardiology/American Heart Association guidelines for management of patients with valvular disease⁹⁰ concluded that balloon valvuloplasty is not a substitute for valve replacement in adults. The guidelines do recognize the above-mentioned situation as a setting in which balloon valvuloplasty may be reasonable. Its use for palliation in patients with serious comorbid conditions that prevent performance of aortic valve replacement is also a reasonable exception. These patients require intensive management in the CICU during the periprocedure time period. Two catheter-based techniques for replacing the aortic valve have also been investigated: percutaneous implantation via a retrograde femoral approach and direct apical puncture. These techniques are currently experimental, and more experience is required before either approach can be recommended for routine clinical practice.⁹⁵⁻⁹⁷

Aortic Disease

Patients with uncomplicated aortic dissections confined to the descending thoracic aorta (Stanford type B or DeBakey type III) are best treated with medical therapy in the ICU.⁹⁸ The acute management usually involves an intravenous β blocker, plus an intravenous vasodilator such as nitroprusside if further blood pressure lowering is needed to minimize aortic wall stress.⁹⁹ Pain control is also an important component of treatment. Patency or thrombosis of the false lumen has been found to have prognostic implications. Partial thrombosis of the false lumen, compared with complete patency, is a significant independent predictor of postdischarge mortality in patients with type B acute aortic dissection.¹⁰⁰

Patients with aortic intramural hematoma of the ascending aorta are at high risk for early progression to overt dissection and rupture and require undelayed surgical repair.¹⁰¹ Acute aortic dissection of the ascending aorta, or type A dissection, is highly lethal, with a mortality rate of 1% to 2% per hour after the onset of symptoms.¹⁰² Although the definitive treatment for type A dissections is emergent surgery, medical therapy including intravenous β blockade to reduce blood pressure and the force of left ventricular ejection is needed initially as the diagnosis is confirmed.⁹⁹

Hypertensive Emergency

Although there have been many advances in antihypertensive therapy, only 31% of patients with diagnosed hypertension have adequate blood pressure control.¹⁰³ Adherence to therapy remains a problem¹⁰⁴ and contributes to poor blood pressure control that can lead to hypertensive emergency. Nonadherence to medical therapy is the most common reason patients present to the emergency department with hypertensive crises.¹⁰⁵ Multiple classes of intravenous antihypertensive medications, including vasodilators, adrenergic inhibitors, and diuretics, are available for use in the CICU for the treatment of hypertensive emergency.¹⁰⁶ Intravenous infusion of nitroprusside is effective, reliable, and safe in this situation.¹⁰⁷ Labetalol is used

parenterally for rapid control of blood pressure in hypertensive emergencies.¹⁰⁸ Although useful as adjunctive therapy in hypertensive crises, diuretics should be used with caution if volume depletion is suspected.¹⁰⁹ The continuous infusion of parenteral antihypertensive agents is usually performed with concomitant invasive blood pressure monitoring by an arterial catheter. Patients can be transferred from the CICU after they are transitioned to oral therapy for blood pressure control and with improvement or stabilization of end-organ damage.

Cardiac Tamponade

A stable pericardial effusion without clinical signs of cardiac tamponade may not require admission to the CICU. In a patient with a known pericardial effusion, the clinical examination may help guide decisions about the appropriateness of expectant management or more urgent, invasive intervention.¹¹⁰ Cardiac tamponade with only mild hemodynamic compromise may be treated conservatively; this may require admission to the CICU for careful monitoring, serial echocardiographic studies, and therapy aimed at the underlying cause. Volume expansion is valuable in hypovolemic patients.¹¹¹ Tamponade with overt hemodynamic compromise requires urgent removal of pericardial fluid, which produces a rapid improvement in cardiac hemodynamics.¹¹² Removal of pericardial fluid can be performed by catheter pericardiocentesis or surgical pericardiectomy. Positive-pressure mechanical ventilation should be avoided if possible in patients with acute tamponade because it reduces cardiac filling further.¹¹³

Pulmonary Embolism

Thrombolysis can be lifesaving in patients with cardiogenic shock from massive pulmonary embolus.¹¹⁴ If performed in the emergency department, the patient should be admitted to the ICU for monitoring. Thrombolysis can minimize escalation of therapy—defined as the need for pressors, mechanical ventilation, cardiopulmonary resuscitation, or open-label thrombolysis—without an increase in major bleeding in patients with normal systemic blood pressure, but with right ventricular dysfunction or pulmonary hypertension.¹¹⁵

Periprocedure and Postprocedure Setting

The risk of producing a major complication (death, MI, or major embolization) during diagnostic cardiac catheterization is generally less than 1%.¹¹⁶ Rates of major complications after PCI are also low.¹¹⁷ If a coronary artery complication, myocardial ischemia, or vascular complication is suspected or detected, however, admission to the CICU after the procedure may be warranted. In particular, vascular access complications, including retroperitoneal bleeding, pseudoaneurysm formation, and arteriovenous fistula formation, may require postprocedure admission to the CICU. Patients with major bleeding after PCI have higher in-hospital and 1-year mortality compared with patients with minor or no bleeding.¹¹⁸ The need for transfusion of red blood cells for a bleeding complication after PCI is independently associated with in-hospital mortality.¹¹⁹

Complications of invasive cardiac electrophysiology studies are low. In one series, the complication rate was reported

at approximately 2%, and there was no mortality.¹²⁰ If a serious complication such as tricuspid valve damage, pulmonary embolism, cardiac chamber perforation, cardiac tamponade, or other vascular injury occurs, however, management in the CICU is appropriate in conjunction with cardiothoracic surgeons if needed.

Marenzi and coworkers¹²¹ have shown that periprocedural hemofiltration effectively prevents the deterioration of renal function resulting from contrast agent–induced nephropathy, and is associated with improved in-hospital and long-term outcomes. More frequent use of this treatment paradigm in patients with chronic kidney disease undergoing an invasive cardiac procedure requiring a contrast agent would result in a larger number of periprocedural admissions to the CICU.

Specific Populations

As CICUs are becoming more widespread, it is important to consider whether this valuable resource is being used appropriately for various patient populations. Emerging data investigating this topic are available for several patient populations.

Elderly

The elderly population, defined as individuals 65 years old or older, numbered 37.3 million in 2006, which represents 12.4% of the U.S. population, about one in every eight Americans.¹²² Patients 75 years old or older with acute MI were 2.5 times more likely not to be admitted to the CICU than younger patients with acute MI.¹²³ There is evidence that after cardiac surgery and intensive care admission, surviving elderly patients have experienced a favorable outcome in terms of quality of life, and mortality rates are acceptably low.¹²⁴ Efforts need to be directed toward narrowing this discrepancy in CICU admission rates. In a study of nonagenarians and centenarians with NSTEMI, increasing adherence to guideline-recommended therapies was associated with decreased mortality.¹²⁵ These findings reinforce the importance of optimizing care patterns for even the oldest patients with NSTEMI, while examining novel approaches to reduce the risk of bleeding in this rapidly expanding patient population.¹²⁵

Women

Attempts at making cardiovascular randomized controlled trials more inclusive of women seem to have had limited success. Women remain underrepresented in published trial literature relative to their disease prevalence¹²⁶; this has important implications because safety and efficacy can vary as a function of gender. In one cohort of patients with known coronary artery disease, less aggressive treatment of coronary artery disease and less use of aspirin among women than among men was found during 1 year of observation.¹²⁷ After controlling for baseline differences, women with coronary artery disease in this study experienced a more rapid decline in physical health status than did men. There is evidence that gender differences in the treatment of cardiac disease seem to be evident. There are no data reviewing gender differences in the CICU specifically, but some differences in the use of cardiac procedures have been observed. These gender differences may involve other factors, however. Mark and colleagues¹²⁸ reported that academic cardiologists made appropriately lower pretest predictions of categories of disease in women with possible coronary artery disease than in

men, and these assessments, along with women's lower rate of positive exercise tests, rather than bias based on sex, accounted for the lower rate of catheterization among women. Gender differences may also be augmented by varying practice patterns. Women with ACS experience more bleeding than men whether or not they are treated with glycoprotein IIb/IIIa inhibitors. Because of frequent excessive dosing in women, however, one fourth of this sex-related risk difference in bleeding is avoidable.¹²⁹ Gender differences in cardiac care is an issue that needs further exploration.

Minority Populations

After adjustment for sociodemographics, comorbidity, and illness severity, African Americans admitted to hospitals without revascularization services remain less likely to be transferred, and African Americans admitted to hospitals with revascularization are less likely to undergo revascularization compared with whites.¹³⁰ In a study by Johnson and associates,¹³¹ after adjustments were made for multiple clinical factors, a lower proportion of African Americans presenting with acute chest pain were admitted to the hospital, and, after being admitted, African Americans were less likely to be triaged to the CICU. It is imperative that all CICUs distribute resources to the patients in greatest medical need regardless of other factors.

Conclusion

The spectrum of patients managed in the CICU continues to evolve as advances in critical care and the diagnosis and treatment of cardiac disorders move forward. Remarkable progress has been made in the care of critically ill cardiac patients. Optimal use of the resources available in the CICU requires a successful integration with other hospital services, particularly the emergency department, cardiac catheterization laboratory, and cardiothoracic ICU and operating rooms. The CICU is a specialized unit with limited capacity that is commonly exceeded by its demand. Adherence to careful admission criteria would optimize potential benefits we can provide to our patients in the CICU.

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Physical Examination in the Cardiac Intensive Care Unit

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CHAPTER

4

General Assessment

Vital Signs

Head, Eyes, Ears, Nose, and Throat Examination

Jugular Venous Pulse and Abdominojugular Reflux

Chest and Lung Examination

Thorax and Heart Examination

Abdominal Examination

Neurologic Examination

Vascular Examination

Musculoskeletal and Integument Examination

Conclusion

The trouble with doctors is not that they don't know enough, but that they don't see enough.

Sir Dominic J. Corrigan (1802-80)

In the intensive care unit (ICU), the ubiquitous presence of advanced technology and "super-star" laboratory analyses has resulted in an over-reliance on imaging and testing and physicians less able to adequately examine critically ill patients. Yet particularly at the moments of initial patient contact, acute decompensation and after therapeutic interventions, when physicians may not have immediate access to these test results the ability to perform an outstanding physical evaluation remains critical. Since in the words of William Osler, "Medicine is the art of uncertainty and the science of probability," the physical examination should be used as a paramount tool, in concert with laboratory analysis and diagnostic imaging, to limit the uncertainty and increase the probability of accurate assessment.

The ideal physical examination requires time, patience a quiet room, and the ability to think and examine simultaneously. These elements are rarely present in an ICU setting. Yet through the tangle of electrocardiogram leads and intrusive sounds of intravenous pumps, cardiac monitors, ventilators, and conversations, it is the physician's responsibility to optimize the management of critically ill patients by focusing their senses and performing the physical examination to the best of their abilities.

General Assessment

The general assessment should include a broad evaluation of the patient's emotional status, appearance, and nonverbal cues. Although apprehension may be part of a patient's natural temperament, abrupt-onset or escalating anxiety should elicit serious diagnostic consideration until acute and life-threatening processes (e.g., escalating ventricular arrhythmias, impeding pulmonary edema, crescendo angina, extension of a myocardial infarction, aortic dissection) can be ruled out. Reassuring the patient may gain time for further investigation. A patient who needs to sit up to catch his or her breath suggests the presence

of pulmonary edema or a large pleural effusion, where a patient who finds relief of chest pain while sitting up and leaning forward may have acute pericarditis. The inability to get comfortable in any position often occurs with abdominal and genitourinary disorders, such as cholecystitis, penetrating ulcers, nephrolithiasis, ischemic bowel, and colonic obstruction. Cachexia, with decreased generalized muscle mass or temporal muscle wasting, suggests long-standing disease and is often seen with heart, renal, or hepatic failure, cancer, or nutritional disorders.

Vital Signs

When asked to examine a critically ill patient, careful consideration of the vital signs is often the difference between successful and unsuccessful outcomes. Being called on to evaluate a patient who is acutely decompensated necessitates that the physician obtain vital signs that are current and accurate. A "tachycardia" can occur when a cardiac monitor inadvertently counts the T wave. Similarly, "hypotension" may be urgently reported only to reveal an improperly situated or sized blood pressure cuff.

A critical aspect of vital sign assessment is the evaluation of trends. A patient whose heart rate has increased from a consistent baseline of 60 to 70 beats/min to 100 beats/min should be a cause for concern, similar to a patient who appears with an initial heart rate of 120 beats/min. Likewise, a patient with a respiratory rate that has gone from 12 to 22 breaths/min should be considered as seriously as one who presents with acute tachypnea.

Temperature

Because core body temperature is carefully controlled within a narrow range, the detection of hyperthermia or hypothermia offers important clinical clues. Normal oral body temperature is approximately 37° C (98.6° F) with early morning temperatures (approximately 1° C lower) compared with later in the afternoon. By convention, fever is defined as an oral temperature greater than 38° C (>100° F), although it is common practice to consider temperatures greater than 38.4° C (>101.1° F) in

hospitalized patients to be clinically significant (albeit without significant data to support this assumption).

Hyperthermia associated with infection (for patients not receiving negative chronotropic agents or with intrinsic cardiac conduction disease) should be accompanied by an increase in the pulse rate of approximately 8.5 beats/min for each 1° C increase in temperature (Liebermeister's rule).¹ The presence of a factitious fever is suggested by the lack of a similar temperature elevation in voided urine compared with the oral temperature. Although a hot drink can quickly increase oral temperature up to 2° C, 5 minutes later the increase is only 0.3° C.²

The pattern of the fever spikes should also be assessed; patterns include intermittent (returning to normal each day), sustained (with minor daily variation [i.e., <0.3° C] suggesting gram-negative infections or pneumonia), remittent (varying >0.3° C each day but not returning to normal), and relapsing (febrile and afebrile days suggesting the Pel-Ebstein fever of Hodgkin disease, *Borrelia* infections, or episodic cholangitis caused by a mobile common bile duct stone). Once-daily spikes (quotidian fever) occur with liver abscesses or acute cholangitis, whereas twice-daily spikes (double quotidian fever) suggest gonococcal endocarditis. Prolonged fever despite antibiotic therapy can also occur with connective tissue disorders, drug fever, neoplasm, abscess, or antibiotic-resistant organisms and superinfection.

The presence of hypothermia (oral temperature <35° C (<95° F)) requires confirmation. Drinking ice water reduces the oral temperature up to 0.6° C (1° F) for 5 minutes.² False-negative hypothermic readings can also occur with ear temperatures taken in the presence of cerumen and oral temperatures recorded in the presence of tachypnea. Confirmed hypothermia requires the assessment of a patient's temperature with a rectal thermometer (which averages approximately 0.6° C (1° F) higher than the oral temperature). The differential diagnosis of true hypothermia includes ambient cold exposure, submersion, hypothyroidism, hypoglycemia, sepsis, and adrenal insufficiency. With hypothermia from submersion or exposure, warming to room temperature is necessary for adequate assessment of end-organ and neurologic function.

Respiration

The respiratory effort, rate, and pattern should be assessed in ventilated and nonventilated patients. Accessory muscle use is common with pulmonary edema, chronic obstructive pulmonary disease (COPD), asthmatic exacerbations, and pneumonia. It may be detected visually or by palpation over the sternocleidomastoid or intercostal muscles. With acute tachypnea (a respiratory rate >25 breaths/min), an immediate assessment should be performed to distinguish peripheral cyanosis (dusky or bluish tinge to the fingers and toes without mucosal or buccal changes) from central hypoxemia (associated with a bluish tinge to the lips or mucosa under the tongue). Peripheral cyanosis may occur with or without hypoxemia, such as in the case of severe peripheral vasoconstriction. This condition is accompanied by cold extremities and compromised capillary refill.

Tachypnea (>25 breaths/min), when secondary to hypoxia, should nearly always be associated with a reflex tachycardia. Although resting tachypnea may occur with cardiopulmonary disease, it may also be present in response to fever, pain, anemia, hyperthyroidism, abdominal distention, respiratory muscle paralysis, obesity, or metabolic acidosis. When tachypnea accompanies chest pain or collapse, acute pulmonary embolism should be included in the differential diagnosis. When tachypnea is present with a history of orthopnea, it suggests the presence of pulmonary edema, pleural effusion or both. When tachypnea is present in a patient being weaned from a ventilator, tachypnea predicts weaning failure.³

Hypopnea is defined as less than 10 shallow or slow breaths per minute. It may be due to severe cardiopulmonary failure, sepsis, central nervous system (CNS) depressants (e.g., sedative-hypnotics, narcotics, and alcohol), or CNS disease (e.g., cerebrovascular accident, meningitis). Hypopnea may also occur secondary to factors that limit inspiration, such as pericarditis or pleuritis, or in the postoperative period.

Breathing patterns can reveal underlying pathology (Table 4-1). Exaggerated deep and rapid respirations were noted by Kussmaul to imply the presence of diabetic ketoacidosis because most causes of hypoxia usually result in *shallow* and rapid respirations. Apneic episodes with snoring suggest obstructive sleep apnea, a potentially treatable contributor to hypertension

Table 4-1. Breathing Patterns

Respiratory Pattern	Consider	Eponym/Classification
Deep and rapid	Diabetic ketoacidosis	Kussmaul respiration
Snoring with episodic apnea	Obstructive sleep apnea	
Waxing and waning tachypnea/hypopnea alternating with apnea	Oversedation Heart failure Severe CNS process Respiratory failure Renal disease (uremia)	Cheyne-Stokes breathing
Irregularly irregular (yet equal) breaths alternating with periods of apnea	Damage to the medulla oblongata (intracranial disease)	Biot breathing
Completely irregular breaths (pauses with escalating periods of apnea)	Severe damage to the medulla oblongata	Ataxic respiration
No breaths or occasional gasps	Severe cardiovascular or neurologic disease	Agonal breathing

CNS, central nervous system.

and right heart failure. Cheyne-Stokes breathing, in which periods of waxing and waning tachypnea and hyperpnea alternate with apnea, occurs in various cardiac, neurologic, and pulmonary disorders or with simple oversedation. When Cheyne-Stokes breathing occurs in the setting of uremia or heart failure, it portends a poor prognosis. Biot breathing is characterized by irregularly irregular breaths of equal depth that are associated with periods of apnea. It can be seen in patients with intracranial disease affecting the medulla oblongata. More severe damage to the medulla oblongata results in ataxic respiration, the complete irregularity of breathing, with irregular pauses and increasing periods of apnea. As this breathing pattern deteriorates further, it merges with agonal respiration.

Orthopnea (shortness of breath while supine) is most commonly present in patients with heart failure and pleural effusion, but also can occur with ascites, morbid obesity, and diaphragmatic paralysis. Alternatively, platypnea (shortness of breath when assuming the upright position) suggests the right-to-left shunting that occurs with an atrial septal defect or intrapulmonary shunt. Trepopnea (shortness of breath while lying on one side) occurs with a right pleural effusion or with unilateral lung or diaphragm disease when the healthy lung is down.^{4,5}

Pulse

The pulse should be assessed bilaterally for presence, rate, volume, contour, and regularity. An initial examination should always contain a description of the radial and carotid arteries, in addition to the brachial, femoral, popliteal, and pedal pulses. This examination is important for patients with hypotension, claudication, arterial insufficiency, or cerebrovascular accident, or after intra-aortic balloon pump insertion. Assessing the pulse for 30 seconds is more accurate than counting for only 15 seconds.⁶

A discrepancy in bilateral upper extremity pulses (especially with decreases in rate or volume on the left side) raises the possibility of aortic dissection, subclavian narrowing secondary to atherosclerosis or congenital webs. If such a discrepancy is present, the examiner should search for evidence of a subclavian steal phenomenon, detected as a decrease in pulse amplitude after raising or exercising the affected arm for approximately 45 seconds (the left side is affected 70% of the time; the reduction in systolic blood pressure is >20 mm Hg 94% of the time).⁷ Aortic dissection is suggested by the presence of a pulse deficit, focal neurologic signs, and mediastinal widening on the chest radiograph.⁸ Diminished lower extremity pulses are consistent with coarctation of the aorta or atherosclerotic disease of the abdominal aorta. Although the detection of low femoral pulse amplitude (or its absence) is crucial for assessing the risk-to-benefit ratio in patients who may require vascular access or device implantation, its diminution or absence after catheterization or intra-aortic balloon pump implantation requires urgent intervention.

When tachycardia (a heart rate >100 beats/min) is present, the regularity of the rhythm offers important diagnostic clues. Regular rhythm rates between 125 beats/min and 160 beats/min suggest sinus tachycardia, the presence of atrial flutter with 2:1 block, or ventricular tachycardia. The presence of intermittent cannon A waves in the neck veins is highly sensitive, whereas a changing intensity of the first heart sound (S_1) is highly specific for the detection of ventricular tachycardia.⁹ Atrial flutter may be accompanied by rapid undulations in the jugular venous pulse (flutter waves or F waves). Because sinus tachycardia may

be due to correctable causes, such as hypovolemia, hypoxia, infection, hyperthyroidism, anemia, or anxiety, or may be due to the pathologic adaptation occurring with chronic heart failure or myocardial ischemia, integration of these clinical suspicions with the nature of the underlying rhythm is important. The use of vagal maneuvers may help differentiate the causes of narrow-complex tachycardia.

The Valsalva maneuver, performed by asking the patient to bear down as if "having a bowel movement" or pushing up the abdomen against the examiner's hand placed on the middle of the abdomen, seems to be more effective than carotid sinus massage, performed by pressing on the neck at the bifurcation of the carotid artery just below the angle of the jaw, at terminating supraventricular tachycardia^{10,11} in 50% of cases. Paroxysmal supraventricular tachycardia (nodal re-entry and reciprocating tachycardias) may be interrupted with enhanced vagal tone. Sinus tachycardia, atrial flutter, and atrial fibrillation usually slow only transiently (but may reveal the underlying rhythm), although an abrupt halving of the rate may occur with atrial flutter. Detection of an irregular tachycardia on physical examination suggests atrial fibrillation, atrial premature beats, or ventricular premature contractions. In atrial fibrillation, assessment of the apical rate (counting heartbeats via auscultation) is more accurate than counting the radial pulse, accounting for a "pulse deficit."¹²

Bradycardia (heart rate <50 beats/min) may be appropriate in trained athletes, but should be asymptomatic and associated with a gradual increase in heart rate with exercise.¹³ Detection of a regular-rhythm bradycardia in a patient with fatigue, mental status changes, or evidence of impaired peripheral perfusion or pulmonary congestion raises the possibility of pharmacologic toxicity (digoxin, β blockers, or calcium channel blockers), hypothermia (owing to hypothyroidism or exposure), or an atrioventricular nodal or ventricular escape rhythm that occurs with complete heart block or sick sinus syndrome.

Appreciation of the pulse volume and contour is also informative (Table 4-2). Tachycardia with a bounding pulse is present with septic shock (owing to the acute reduction in afterload), hyperthyroidism, or the sudden collapse of the pulse with chronic aortic insufficiency (a water-hammer pulse). Consistent with the presence of chronic aortic insufficiency is the accentuation of the radial pulse when the examiner lifts the whole arm above the patient's head (Mayne's sign). A weak and thready pulse may be

Table 4-2. Pulse Characteristics

Pulse Description	Consider
Bounding	Septic shock, hyperthyroidism, chronic AI
Weak and thready	Severe LV dysfunction, hypovolemia, severe MR, complete heart block, pericardial effusion
Slow rising and weak	Severe AS
Alternating between strong and weak	LV dysfunction, pericardial tamponade
Double tap (pulsus bisferiens)	Hypertrophic cardiomyopathy, AS with AI

AI, aortic insufficiency; AS, aortic stenosis; LV, left ventricular; MR, mitral regurgitation.

present with severe left ventricular dysfunction, hypovolemia, severe mitral regurgitation, or complete heart block. A slow rising and weak carotid pulse (*pulsus parvus et tardus*) is consistent with a diagnosis of severe aortic stenosis, whereas a regular pulse that alternates between weak and strong (*pulsus alternans*) occurs with left ventricular dysfunction or pericardial tamponade. A “double tap” during systole (*pulsus bisferiens*) can occur with either hypertrophic cardiomyopathy or the combination of aortic stenosis and aortic insufficiency.^{14,15} In the presence of a *bisferiens* pulse, two soft and rapid sounds can be auscultated with each cardiac cycle as the brachial artery is compressed by a blood pressure cuff proximally.¹⁶

Irregular rhythms are classified as either *regularly irregular*, where the irregular beat can be anticipated at a fixed interval, or *irregularly irregular*, where the irregular beat occurs without predictability. A regularly irregular pulse commonly occurs with second-degree atrioventricular block (either Mobitz I or II, depending on whether the P–R interval is constant or lengthening before the dropped beat) or with interpolated ventricular premature beats. On the physical examination, the P–R interval can be visualized as the distance between the a wave and c wave on the jugular venous pulse (JVP). This distance, before and after the dropped beat, can be diagnostic when the electrocardiogram is unable to differentiate between Mobitz type I and II second-degree block. When an interpolated ventricular premature beat is present, it may be accompanied by a weakened pulse (owing to inadequate ventricular filling) that occurs at a fixed interval from the regular pulse.

An irregularly irregular pulse implies that the examiner cannot anticipate when the next beat will occur, and may be due to ventricular premature beats, atrial premature beats, multifocal atrial tachycardia, or atrial fibrillation. Although ventricular premature beats and atrial fibrillation are associated with a pulse deficit (where the auscultated apical rate is greater than the palpable radial pulse), the pulse that follows a ventricular premature beat should be stronger. It is clinically relevant to realize that significant numbers of ventricular premature beats can compromise cardiac output. Alternatively, if the beat following a ventricular premature beat is diminished (Brockenbrough sign), hypertrophic cardiomyopathy or severe left ventricular dysfunction should be considered. No pulse deficit (or compensatory pause) should be present with atrial premature beats or multifocal atrial tachycardia. The physician can differentiate atrial premature beats from ventricular premature beats by tapping out the rhythm with his or her hand. Atrial premature beats result in a beat that occurs while the physician's hand is “up.” Although a ventricular premature beat also occurs with the hand in the “up” position, the pulse resumes on the second down-beat after the compensatory pause.

Blood Pressure

In the ICU, there is no rule defining “normal blood pressure.” *Adequate* blood pressure varies by patient and clinical status, but is generally believed to consist of a mean perfusion pressure of at least 60 mm Hg and the absence of end-organ hypoperfusion. For accurate assessment, an adequately sized blood pressure cuff must be used (there are lines on all blood pressure cuffs to indicate adequate sizing) and should be correctly situated around the bicep (and not over clothing). A blood pressure obtained with a cuff that is too short or narrow, especially if the patient is obese or has an enlarged upper arm, may result in a factitiously elevated blood pressure.^{17,18}

Although palpation of pulses is commonly used in emergency situations to estimate systolic blood pressure (i.e., palpation of a radial pulse suggests a minimum systolic blood pressure of 80 mm Hg; a femoral pulse, a blood pressure of at least 70 mm Hg; and a carotid pulse, a blood pressure of at least 60 mm Hg), the overall accuracy of this estimation has been questioned.¹⁹ To obtain the palpable systolic blood pressure, the cuff should first be inflated until the radial pulse is no longer palpable (usually 150 to 200 mm Hg) and then slowly deflated (2 to 3 mm Hg per second) until the pulse returns.

For the auscultatory blood pressure, inflation should be repeated (inflate the cuff to 10 mm Hg above the palpable systolic blood pressure) and listen for the first and fifth (last audible) Korotkoff sounds during slow cuff deflation. The diastolic blood pressure may be difficult, if not impossible, to appreciate in the presence of fever, severe anemia, aortic insufficiency, thyrotoxicosis, vitamin B₁ deficiency, or Paget disease. For patients in atrial fibrillation or with significant ventricular arrhythmias, a relatively accurate blood pressure assessment is obtained by averaging three individual readings.

In patients with left ventricular systolic dysfunction, multiple etiologies of hypotension require assessment during the physical examination. Although hypotension may be caused by overly aggressive diuresis, it may also occur because of volume overload. The presence of a tachycardia with orthostatic hypotension (a blood pressure decrease of >20 mm Hg systolic or >10 mm Hg diastolic when the patient is assessed first in the supine position and then again after 2 minutes with the patient standing or sitting with legs dangling) is consistent with volume depletion. The differential diagnosis of hypotension includes factors that reduce systemic vascular resistance (e.g., infection, inflammation, adrenal insufficiency, anesthetic agents, atrioventricular malformations, and vascular insufficiency), stroke volume (e.g., hypovolemia, aortic stenosis, severe mitral regurgitation, ventricular arrhythmias, and left ventricular dysfunction owing to infarction, ischemia, or a cardiomyopathy), and heart rate (e.g., heart block or pharmacologic bradycardia).

Hypotension without a concomitant increase in the pulse rate (in the absence of medications that can blunt a heart rate response) raises the possibility of autonomic dysfunction. The presence of a *pulsus paradoxus* (a >10 mm Hg decrease in systolic blood pressure occurring at end-expiration with the patient breathing *normally*) can occur with cardiac tamponade (very sensitive when occurring with tachycardia, jugular venous distention, and an absent y descent),^{20,21} constrictive pericarditis (occurring with jugular venous distention that persistently augments with inspiration, a pericardial knock, hepatomegaly, and an exaggerated y descent),²² severe hypertension, pulmonary embolism, COPD, and severe obesity.

With appropriate clinical scenarios, blood pressure should also be assessed in both arms and one leg. Leg blood pressure can be assessed by placing the blood pressure cuff around the calf and using the dorsalis pedis pulse for auscultation or Doppler interrogation. A systolic blood pressure difference greater than 10 mm Hg between arms suggests aortic dissection, proximal aortic aneurysm, or subclavian artery stenosis. With coarctation of the aorta, arm blood pressures are greater than blood pressures in the legs (this may also be accompanied by underdeveloped lower extremity musculature compared with upper extremity musculature). Leg blood pressure that is more than 15 mm Hg higher than arm blood pressure suggests aortic

dissection, aortic insufficiency, or a proximal vasculitis (i.e., giant cell or Takayasu arteritis).

The pulse pressure ([systolic blood pressure – diastolic blood pressure] may also be informative. A low pulse pressure may be present with the decreased stroke volume of hypovolemia, tachycardia, severe aortic or mitral stenosis, pericardial constriction, or cardiac tamponade. With appropriate clinical suspicion, it has a high sensitivity and specificity to predict a cardiac index less than 2.2 L/min/m² when the pulse pressure divided by the systolic pressure is less than 0.25. A wide pulse pressure (>60 mm Hg) can be seen with hyperthermia, but may also suggest greater than moderate chronic aortic insufficiency or high output failure owing to severe anemia, thyrotoxicosis, atrioventricular malformation, sepsis, vitamin B₁ deficiency, or Paget disease. If the wide pulse pressure is present in just one arm, a search for an atrioventricular fistula distal to the site of blood pressure cuff should be undertaken.

Weight

The daily weight is an important vital sign. It often proves to be especially significant for patients in whom volume overload or hypovolemia subsequently complicates the clinical picture. When a weight appears inconsistent with prior weights or the clinical history, the clinician should not hesitate to have the patient reweighed. Noting an increase in weight may be crucial to discern the presence of volume overload in a patient with shortness of breath, whereas loss of weight should occur in patients being diuresed. A weight gain despite the presence of effective diuresis suggests increased fluid intake, either orally or via the intravenous route.

Head, Eyes, Ears, Nose, and Throat Examination

In the presence of an endotracheal or nasogastric tube, the physician first should ensure that the tube is not causing a pressure injury. If the patient has a neck or subclavian central line or Swan-Ganz catheter, the physician must ensure it is secured and uninfected. The head, eyes, ears, nose, and throat examination can also suggest the presence of several syndromes.

In adults, a large skull suggests Paget disease (with associated high output failure) or acromegaly (with frontal bossing and large features). A high arched palate, associated with a wide pulse pressure and pectus excavatum, is consistent with Marfan syndrome. Coarse hair texture or hair loss from the head, axilla, or pubic region suggests hypothyroidism. Temporal artery tenderness suggests the presence of temporal arteritis.

Eyelid xanthelasma or a corneal arcus or both may occur with either hypercholesterolemia or diabetes mellitus. Yellowed sclera are seen with hyperbilirubinemia, whereas blue sclera can be seen in Marfan and Ehlers-Danlos syndromes. Dry, puffy, and sunken (enophthalmic) eyes are consistent with hypothyroidism, whereas exophthalmic eyes with lid lag (white sclera visible between the margin of the upper eyelid and the corneal limbus with the patient looking downward) associated with a lid lag (an immobility or lagging of the upper eyelid on downward rotation of the eye) and lid retraction (widening of the palpebral fissure) are associated with hyperthyroidism. Periorbital edema is seen with the hypoalbuminemia of hepatic disease, a protein-losing nephropathy, or the superior vena cava syndrome.

The lack of periorbital edema with diffuse peripheral edema is a distinguishing feature of a cardiac versus hepatic or renal cause of peripheral edema; it is due to the inability of patients with heart failure and severe volume overload to elevate their upper torso to breathe more comfortably. Conjunctival pallor is a very specific sign of anemia, and this diagnosis is reinforced by the presence of concomitant palmar and palmar crease pallor.²³

When firmly palpating the patient's thyroid gland with the neck flexed (to relax the sternohyoid and sternocleidomastoid muscles), significant findings can include an enlarged thyroid (size appreciated larger than an inch) and the presence of nodules (4% prevalence; most are benign). It is important to note the size and site of these nodules for follow-up examinations.²⁴ During swallowing, the thyroid gland rises upward with the trachea to allow location of a neck mass either within or outside the thyroid gland.

Jugular Venous Pulse and Abdominojugular Reflux

The internal jugular venous pulse (JVP) is useful manometer for right atrial pressure. However, it is only accurate in indicating intravascular volume status and pulmonary capillary wedge pressure in the absence of tricuspid stenosis, right ventricular dysfunction, pulmonary hypertension, and a restrictive or constrictive cardiomyopathy. The JVP should be sought by first asking the patient to lift their chin up and turn to the left against the resistance of the examiner's right hand. Within the triangle formed by the visible heads of the sternocleidomastoid muscle and the clavicle, the examiner should then search with the neck muscles relaxed, for the weak impulses of the jugular vein along a line from the jaw to the clavicle. Shining a tangential light from slightly behind the neck can accentuate the visibility of the transmitted venous impulses. Simultaneous palpation of the radial pulse, assuming the patient is in sinus rhythm, allows detection of a neck pulsation (a wave) immediately preceding the peripheral pulse (Fig. 4-1). Alternatively, one can visualize the x descent as an inward movement along the line of the jugular vein that occurs simultaneously with the peripheral pulse.

In patients with presumed volume overload, jugular venous distention may be best assessed with the patient sitting upright

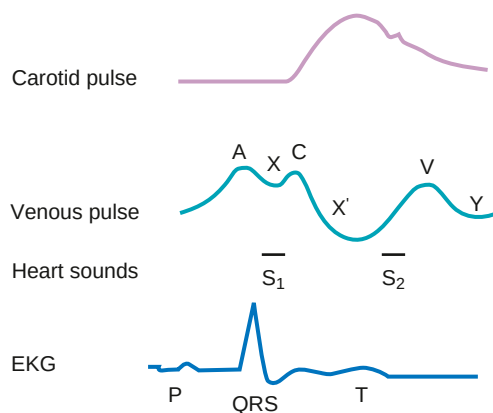


Figure 4-1. Timing of jugular venous pressure. ECG, electrocardiogram.

at 90 degrees, a position in which the clavicle is approximately 7 to 8 cm above the right atrium (equivalent to the upper limit of normal for right atrial pressure, 5 to 7 mm Hg). The 7 to 8 cm is added to the maximal vertical distance at which any venous pulsations are seen above the clavicle to estimate the right atrial pressure. If the JVP cannot be appreciated in the upright position, an attempt can be made to visualize it sequentially with the upper body at a 45-degree angle (where only 4 to 5 cm is needed to the distance above the clavicle where the venous pulsations were seen). If venous pulsations are still difficult to discern, either of two extremes may be present: either the lack of elevation of the right atrial pressure or jugular venous distention above the angle of the jaw, even in the upright position.

A low right atrial pressure may be investigated further by increasing right atrial filling (i.e., with deep inspiration or passive leg elevation). The left internal jugular vein is less useful than the right internal jugular vein for estimation of the JVP because of the presence of valves impeding venous return or compression of the innominate vein. When it must be used, right atrial pressure should be considered approximately 1 cm lower than the visualized left internal jugular pulse.^{25,26} Likewise, the external jugular veins should be avoided in assessing the JVP because of the extreme angle with which they contact the superior vena cava, and their occasional absence or diminution in the presence of elevated catecholamine levels.²⁷

Although the value of sequential assessment of the JVP has been confirmed by studies of patients with left ventricular dysfunction,²⁸ patients undergoing cardiac catheterization for dyspnea or chest pain,²⁹ and patients with suspected chronic heart failure,³⁰⁻³² it is important to confirm these findings with additional signs of volume overload in the acute setting.^{33,34} When an increasing creatinine value is seen despite the presence of an elevated JVP (with or without diuresis), the differential diagnosis includes refractory left ventricular dysfunction requiring inotropic support, severe right ventricular dysfunction, restrictive or constrictive cardiomyopathy or right heart failure, or underlying renal dysfunction or renovascular disease. With right ventricular dysfunction, the assessment of JVP as a measure of pulmonary capillary wedge pressure becomes progressively less accurate.

Abdominojugular reflux is deemed present when the height of the neck vein distention, visualized with the patient's neck at a 45-degree angle, is increased by at least 3 cm (and maintained for approximately 15 seconds) during a steady pressure of approximately 20 to 35 mm Hg applied over the right upper quadrant or midabdomen (you can learn what exerting 20 to 35 mm Hg of pressure feels like by compressing an inflated blood pressure cuff against a flat surface until the sphygmomanometer reads 30 mm Hg). It is important to instruct patients not to hold their breath because the Valsalva maneuver negates the effect of abdominal pressure. The increased abdominal pressure on the mesenteric or splanchnic veins increases venous return to the right ventricle. With right or biventricular heart failure (and the limited ability to increase right and left ventricular output), distention of the internal jugular vein occurs. A positive abdominojugular reflux effect may also occur with tricuspid stenosis, tricuspid insufficiency, constrictive pericarditis, restrictive cardiomyopathy, pulmonary hypertension, and mitral stenosis. Although limited data are available in the ICU setting, abdominojugular reflux in patients presenting to the emergency department had a low sensitivity (33%) but a high specificity (94%; $P = .028$) for the diagnosis of heart failure. However,

its sensitivity significantly increases in patients with known chronic congestive heart failure,³² when abdominojugular reflux is absent it cannot be taken as evidence *against* the diagnosis of heart failure.³⁵

Chest and Lung Examination

The thorax should first be examined for the presence of an old sternotomy (suggesting prior coronary artery bypass grafting, valve replacement, or congenital heart disease) or thoracotomy scars (suggesting prior pulmonary pathology). If the patient is intubated, the physician needs to ensure that both sides of the chest are expanding evenly.

Although Laënnec's invention of the stethoscope rendered obsolete the need for the physician to place the ear directly against the chest wall to appreciate heart and lung sounds, modern technology has yet to replace the need for daily auscultation of the lungs via the stethoscope (Table 4-3). The waning ability of physicians to appreciate reliably abnormalities in the lung examination undoubtedly limits the information available for patient management, however.³⁶ The lung bases should be auscultated in an alternating fashion, beginning at the lateral posterior aspects of the lung fields and following a side-by-side trek up the lung fields. Although the diaphragm of the stethoscope is used to detect most normal and pathologic lung sounds, the bell is more advantageous for detecting the rhonchi associated with primary tuberculosis or fungal disease in the apices.

Crackles (or rales) are discontinuous lung sounds (that sound like Velcro being pulled apart) generated when an abnormally closed airway snaps open, usually at the end of inspiration.³⁷ "Clear lungs" may be present in 25% of patients presenting with heart failure.³¹ The Boston Criteria for Heart Failure gives 1 point if the crackles are basilar and 2 points if they extend further.³⁸ Crackles have a low sensitivity but high specificity to predict the presence of left ventricular dysfunction or an elevated pulmonary capillary wedge pressure.^{29,30,32} Crackles may also be caused by interstitial lung disease, amiodarone toxicity, pulmonary fibrosis, or COPD.³⁹

Table 4-3. Auscultation of the Lungs

Breath Sound	Consider
Rhonchi	
Diffuse	COPD
Localized	Pneumonia, tumor, foreign body
Stridorous	Large airway obstruction
Wheezes	
Expiratory	Reactive small airway obstruction (asthma, allergies, β blockers)
De novo	Nonasthmatic causes (mass, pulmonary embolism, pulmonary edema, aspiration, foreign body)
Crackles or rales	Pulmonary edema, interstitial lung disease, COPD, amiodarone toxicity

COPD, chronic obstructive pulmonary disease.

Rhonchi (coarse, dry, leathery sounds) are present in the setting of large airway (bronchial) turbulent flow caused by inflammation and congestion, and occur in the ICU most commonly with pneumonia or COPD. When detected, it should be noted whether they occur during inspiration or expiration, and if they are generalized or localized. Stridor refers to loud, audible, and inspiratory rhonchi that suggest extrathoracic large airway obstruction. Diffuse rhonchi suggest generalized airway obstruction that occurs with COPD. Localized rhonchi suggest pneumonia or obstruction owing to tumor or a foreign body. Generally, rhonchi caused by mucous secretions subside or altogether disappear with coughing.

The presence of expiratory wheezes (continuous and high-pitched musical sounds) often denotes reactive small airway obstruction. Because airway size is reduced in the recumbent position, wheezing should worsen when lying down. When accompanied by a prolonged expiratory phase, wheezes signify the presence of airflow through a narrowed tract that is often seen with asthma, allergies, or the toxic effects associated with β blockade. In some patients, the presence of pulmonary edema may result in musical breath sounds similar to wheezes, giving rise to the term *cardiac asthma*. When wheezing is detected de novo in an older patient, a search for nonasthmatic causes, including obstructing masses, pulmonary embolism, pulmonary edema, aspiration pneumonitis, and foreign-body obstruction, is warranted.⁴⁰ Decreased or absent breath sounds in a lung field are consistent with atelectasis, pneumothorax, pleural effusions, COPD, acute respiratory distress syndrome, or pleural thickening.

Egophony (when a verbalized “E” is appreciated via auscultation as an “A”) occurs in the presence of a pleural effusion, but can also be heard with lung consolidation and pneumonia. Although not sensitive, egophony is specific for a parapneumonic process.⁴¹ Lung consolidation can be confirmed further by the presence of bronchophony (when “clearer” voice sounds are heard over consolidated lung tissue). Bronchial breath sounds (breath sounds that are louder than normal) are also heard when consolidation of lung tissue is present because solid tissue transmits sound better than tissue filled with air. When bronchial breath sounds are heard and accompany a dull area to percussion at the base of the left scapula, it suggests the presence of a large pericardial effusion (Ewart sign).

Dullness to percussion at the lung base suggests the presence of pleural effusion and rarely lung consolidation. If the percussive dullness responds to postural changes (i.e., diminution in the left lateral decubitus position), a pleural effusion is likely present.⁴² Although left-sided pleural effusions are common after chest surgery (e.g., post-coronary artery bypass graft surgery after left internal mammary artery dissection) and with pancreatitis or pancreatic cancer, bilateral or right-sided effusions are more consistent with heart failure. Pleural effusions may also occur with pneumonia, hypoalbuminemia (seen with nephrotic syndrome or cirrhosis), and nearly all types of malignancy.

Thorax and Heart Examination

The thorax should be appreciated by looking upward at the chest from the foot of the bed. This view may reveal a pectus excavatum (a congenital anterior chest wall deformity producing a concave, or caved-in, appearance that suggests Marfan or Ehlers-Danlos syndrome or right heart failure), pectus carinatum (an outward “pigeon chest,” protrusion of the anterior chest wall associated

with decreased lung compliance, progressive emphysema, and a predisposition to respiratory tract infections), and barrel chest deformities (with increased anteroposterior chest diameters that may be observed with obstructive forms of chronic pulmonary disease such as cystic fibrosis and severe asthma).

When the examiner is positioned on the right side of the patient, visible or palpable precordial pulsations may be appreciated owing to a thin body habitus or secondary to cardiac disease. Pulsations in the second intercostal space to the left of the sternal border suggest an elevated pulmonary artery pressure, whereas pulsations seen in the fourth intercostal space at the left sternal border are consistent with right ventricular dysfunction or an acute ventricular septal defect. Apical pulsations may be secondary to systemic hypertension, left ventricular hypertrophy, hemodynamically significant aortic stenosis, or a left ventricular aneurysm. With the examiner standing on the right side of the patient, the left ventricular apex is palpated by placing the right hand transversely across the precordium under the nipple, and is perceived as an upward pulsation during systole against the examiner's hand. An enlarged apical impulse is variously described as an impulse detected more than 2 cm to the left of the midclavicular line in the fifth intercostal space or as greater than the size of a quarter and palpable in at least two interspaces. Recognition may be enhanced with the patient in the left lateral decubitus position or when sitting up and leaning slightly forward.

Detection of left ventricular enlargement is a function of age (it increases steadily for men and women, occurring in 66% of men and 58% of women in the 65- to 69-year age range and 82% of men and 79% of women >85 years).⁴³ It has a sensitivity of approximately 65% and a specificity of 95%, with a negative predictive value of 94% for predicting left ventricular systolic dysfunction.³⁰ Although obesity may limit the detection of the left ventricular apical impulse, a displaced impulse is effective in suggesting the diagnosis of heart failure, even in patients with COPD.⁴⁴ Fluid or air in the right pleural cavity, a depressed sternum, and secondary retraction of the left lung and pleura all can result in an apparent augmentation of the left ventricular impulse, however.⁴⁵ Left ventricular enlargement is suggested further by the presence of a sustained apical impulse (persisting more than halfway between S1 and S2 during simultaneous auscultation and palpation). If the left ventricular apical impulse is detectable at end-systole, a dyskinetic ventricle is most likely. If the apical impulse seems to retract during systole, the presence of constrictive pericarditis or tricuspid regurgitation should be considered.

All auscultatory fields should be palpated with the fingertips to detect a thrill (establishing the presence of a grade IV/VI murmur). In addition, the presence of a palpable P2 (an upward pulsation during diastole in the pulmonic position) suggests the presence of either secondary (acute pulmonary embolism, chronic mitral regurgitation or stenosis) or primary pulmonary hypertension. When a pulsation is palpable in the aortic position during systole, it suggests either hypertrophic cardiomyopathy or severe aortic stenosis, whereas its presence over the left sternal border in the fourth intercostal space, especially in the setting of an acute myocardial infarction, raises the possibility of a ventricular septal defect. A presystolic impulse (correlating with the a wave and equivalent to an audible S₄) suggests ventricular noncompliance, and may be present with myocardial ischemia or infarction or with left ventricular hypertrophy secondary

to hypertension, aortic stenosis, acute mitral regurgitation, or hypertrophic cardiomyopathy.

Auscultation of the Heart

Cardiac auscultation in the acute care setting allows for the detection of common holosystolic (mitral regurgitation and ventricular septal defect), systolic ejection (aortic stenosis or hypertrophic cardiomyopathy), and diastolic (aortic insufficiency and mitral stenosis) murmurs that can precipitate or exacerbate a decompensation in the ICU or the presence of abnormal heart sounds indicating underlying pathology (Table 4-4). Rapid assessment can often be lifesaving, but it should not replace a more systematic investigation when acute stabilization has occurred.

S_1 , best appreciated as a high-pitched and split sound at the cardiac apex, is produced at the time of mitral (M_1) and tricuspid (T_1) valve closure, and occurs before the upstroke of the peripheral pulse. An accentuated S_1 is present when the mitral or tricuspid valves are widely separated in diastole (i.e., with atrial fibrillation, with a shortened P–R interval, or in the presence of an obstructing myxoma) or with mitral or tricuspid valves that are difficult to open (i.e., mitral or tricuspid stenosis when the valves have become calcified). When a stenotic valve becomes nearly immobile, however, the intensity of S_1 decreases. A soft S_1 may be present when the valves are already nearly closed at the onset of systole, as occurs with moderate to severe aortic insufficiency, with advanced heart failure, with a prolonged P–R interval, or when the mitral valves are incompetent (owing to

papillary muscle dysfunction, ventricular dilation, or myxomatous degeneration).

S_2 , which occurs at the time of closure of the semilunar aortic (A_2) and pulmonary (P_2) valves, is probably caused by the deceleration of blood in the root of the pulmonary artery and aorta at end-systole. It is best appreciated in the second intercostal space, midclavicular line (pulmonic position) using the diaphragm of the stethoscope. Normally, the intensity of A_2 exceeds the intensity of P_2 . A soft A_2 can occur in the setting of incompetent aortic valves (e.g., aortic insufficiency), a decrease in the distance that the valves have to traverse (e.g., severe aortic stenosis), or a decreased diastolic pressure closing the aortic valve (e.g., with sepsis or an atrioventricular fistula), or secondary to physical muffling of heart sounds that occur with the air trapping of COPD. An accentuated S_2 may be caused by a loud A_2 (e.g., severe systemic hypertension or aortic dilation) or a loud P_2 (e.g., pulmonary hypertension). During auscultation, an accentuated P_2 is said to occur when the pulmonary component of S_2 is louder than S_1 in the fourth to sixth intercostal spaces. Associated findings may include a prominent a wave, an early systolic click (caused by the sudden opening of the pulmonary valve against a high pressure), and a left parasternal lift signaling the presence of right ventricular hypertrophy.

The timing of S_2 splitting into A_2 and P_2 components should be described. Normally, A_2 precedes P_2 . *Wide splitting* of S_2 (when P_2 is delayed relative to A_2) occurs with early aortic valve closure (e.g., severe mitral regurgitation) or delayed pulmonic valve closure (e.g., right bundle branch block, with a secundum atrial septal defect or with pulmonary hypertension). *Paradoxical splitting*, when A_2 occurs after P_2 , may occur because of early pulmonary valve closure (e.g., severe tricuspid insufficiency or with pre-excitation with early right ventricular contraction); delayed activation of the left ventricle (e.g., left bundle branch block); or the prolongation of left ventricular contraction that occurs with hypertension, aortic stenosis, or severe systolic dysfunction. *Fixed splitting*, when the time interval between A_2 and P_2 is not increased during inspiration, may be due to a large atrial septal defect and severe right ventricular failure. Currently, no evidence-based assessments of these findings in the critical care setting are available.

S_3 , which occurs early in diastole, is best appreciated at end-expiration with the bell near the apex and with the patient in the left lateral decubitus position. This low-pitched sound occurs approximately 0.16 second after S_2 . Although often normal when detected in children and young adults, S_3 in patients older than age 40 implies an increase in the passive diastolic filling of either the right (RVS_3) or the left (LVS_3) ventricle. LVS_3 may be detected in patients with heart failure; hypertrophic cardiomyopathy, left ventricular aneurysm; or with hyperdynamic states (e.g. thyrotoxicosis, arteriovenous fistula, hyperthermia, and sepsis). A retrospective analysis of the SOLVD database noted that the presence of LVS_3 in patients with symptomatic chronic left ventricular dysfunction was associated with an increased risk of hospitalization for heart failure and death from pump failure.²⁸ The presence of S_3 in patients with advanced heart failure had 68% sensitivity and 73% specificity for detecting a pulmonary capillary wedge pressure greater than 18 mm Hg.³² RVS_3 is best appreciated with the patient in the supine position, while listening over the third intercostal space at the left sternal border. It is accentuated during inspiration because of rapid

Table 4-4. Clinical Auscultation of S_1 , S_2 , S_3 , and S_4

Heart Sound	Consider
S_1	
Accentuated	Atrial fibrillation, mitral stenosis
Soft	Immobile mitral valves, MR or severe AI
S_2	
Accentuated	(P_2) Pulmonary hypertension; (A_2) Systemic hypertension; Aortic dilation
Soft	(A_2) AI, sepsis, AV fistula
A_2-P_2 splitting	
Wide	Severe MR, RBBB, atrial septal defect (secondary), pulmonary hypertension
Paradoxical	Severe TR, WPW, LBBB, severe hypertension or AS
Fixed	Large atrial septal defect, severe RV failure
S_3	
Present	Heart failure, HOCM, thyrotoxicosis, AV fistula, sepsis, hyperthermia
S_4	
Present	Ischemic or infarcted LV, hypertrophic, dilated or restrictive cardiomyopathy

AI, aortic insufficiency; AS, aortic stenosis; AV, atrioventricular; HOCM, hypertrophic obstructive cardiomyopathy; LBBB, left bundle branch block; MR, mitral regurgitation; RBBB, right bundle branch block; TR, tricuspid regurgitation; WPW, Wolff-Parkinson-White.

right ventricular filling, and occurs with severe tricuspid insufficiency or right ventricular failure.

S_4 is a low-pitched sound best heard with the bell of the stethoscope at the apex in the left lateral decubitus position. It occurs just before S_1 and can be readily distinguished from a split S_1 by its ability to be extinguished by firm pressure on the bell. S_4 is believed to be due to the vigorous atrial contraction necessary to propel blood into a stiffened left ventricle (and is absent in atrial fibrillation). The stiffened left ventricle may be present with an ischemic or infarcted left ventricle or with hypertrophic, dilated, or restrictive cardiomyopathy. Because diastolic and systolic defects can result in S_4 , its presence does not contribute to their differentiation.⁴⁶ Similar to RVS_3 , RVS_4 increases in intensity with inspiration. When LVS_3 and LVS_4 are appreciated, usually in the setting of tachycardia with systolic dysfunction, a summation gallop is said to be present.

Three additional diastolic sounds should be sought during routine evaluation. (1) A high-pitched early diastolic click is caused by abnormal semilunar valves (bicuspid aortic valve or pulmonic stenosis), dilation of the great vessels (aortic aneurysm or pulmonary hypertension), or augmented flow states (truncus arteriosus or hemodynamically significant pulmonic stenosis). (2) A mid-diastolic opening snap, occurring approximately 0.08 second after S_2 and best appreciated in the fourth intercostal space at the left sternal border or apex, is caused by the opening of a stenotic (although pliable) mitral valve. The opening snap disappears when the valve becomes severely calcified. Shortening of the interval from S_2 to the opening snap occurs as the left atrial pressure increases, and indicates progressive disease severity. The opening snap of a stenotic mitral valve can be differentiated from a split S_2 by a widening of the S_2 –opening snap interval that occurs when a patient with mitral stenosis stands up. (3) A dull-sounding early diastolic to mid-diastolic knock suggests the abrupt cessation of ventricular filling that occurs secondary to a noncompliant and constrictive pericardium.

Heart Murmurs: Static and Dynamic Auscultation

Heart murmurs are appreciated as systolic, diastolic, or continuous, and should be described further according to their location, timing, duration, pitch, intensity, and response to dynamic maneuvers (Table 4-5). Although the gradations I–III are arbitrary (grade I, very faint, difficult to hear; grade II, faint, but readily identified; and grade III, moderately loud), the presence of a grade IV murmur always denotes the presence of an associated palpable thrill. Grade V is a louder murmur with a thrill, whereas grade VI occurs when the murmur is heard with the stethoscope physically off the chest wall.

Holosystolic murmurs, with a soft or obliterated S_2 , occur with tricuspid regurgitation, ventricular septal defects, and mitral regurgitation. Tricuspid regurgitation is suggested when the holosystolic murmur is best appreciated in the fourth intercostal space along the left sternal border and augments on inspiration, with passive leg elevation, and with isometric handgrip. The presence of pulsations in the fourth intercostal space at the left sternal border suggests either a ventricular septal defect or concomitant right ventricular dilation or dysfunction. In the setting of an acute inferior wall or extensive anterior wall myocardial infarction, the presence of a new holosystolic murmur occurring with a palpable right ventricular lift requires that an acute ventricular septal defect be excluded. The holosystolic murmur of mitral regurgitation is best appreciated at the apex during end-expiration in the left lateral decubitus position, and is associated with a soft S_1 . With severe mitral regurgitation, it may be associated with a slowly increasing peripheral pulse owing to partial runoff of the left ventricular volume into the left atrium.

With acute mitral regurgitation, the murmur may be absent or may appear earlier or later in systole. When mitral regurgitation is severe, evidence of pulmonary hypertension may also be present. Posterior mitral leaflet involvement results in a murmur that radiates anteriorly, whereas posterior radiation into the axilla suggests anterior mitral valve leaflet dysfunction. In more stable patients in whom positional changes are possible,

Table 4-5. Dynamic Cardiac Auscultation

Maneuver	Physiology	TR	PS	VSD	MR	AS	HOCM	AI
Inspiration	Increased venous return and ventricular volume	↑	↑		nc*/↑			
Expiration	Brings heart closer to the chest wall	↑			nc/↑			
Leg elevation	Increased SVR; increased venous return						↓	
Mueller maneuver	Decrease CVP/BP/SNA (10 sec), then increase in BP/SNA (5 sec) and surge in BP/decrease SNA with release	↑						
Valsalva maneuver	Decreased venous return and ventricular volumes (phase 2)		↓		↓	↓	↑	↓
Squatting to standing	Decreased venous return and volume	↓	↓	↓	↓	↓	↑	
Standing to squatting	Increased venous return; increased SVR			↑	↑	↑	↓	↑
Handgrip	Increased SVR; increased CO; increased LV filling pressures			↑	↑	↓	↓	↑

Note: Inspiration also increases the murmur of tricuspid stenosis and pulmonary regurgitation.

*nc, no changes.

AI, aortic insufficiency; AS, aortic stenosis; BP, blood pressure; CO, cardiac output; CVP, central venous pressure; HOCM, hypertrophic obstructive cardiomyopathy; LV, left ventricular; MR, mitral regurgitation; PS, pulmonary stenosis; TR, tricuspid regurgitation; SNA, sympathetic nerve activity; SVR, systemic vascular resistance; VSD, ventricular septal defect.

prompt squatting from a standing position results in a rapid increase in venous return and peripheral resistance that causes the murmur of mitral regurgitation (and aortic insufficiency) to grow louder. A similar phenomenon occurs with isometric handgrip, although the exact mechanism is unknown.

The harsh systolic ejection murmur of aortic stenosis begins shortly after S_1 , peaks toward midsystole, and ends before S_2 (crescendo-decrescendo). It is best appreciated in the second intercostal space to the right of the sternal border and radiates into the right neck. The absence of this radiation should bring the diagnosis into question. A systolic thrill may be palpable at the base of the heart, in the jugular notch and along the carotid arteries. Associated findings include an ejection click (occurring with a bicuspid valve, which disappears as the stenosis becomes more severe) and, with increasing severity, a slow increase and plateau of a weak carotid pulse (pulsus parvus et tardus).⁴⁷ The severity of the obstruction is related to the duration of the murmur to its peak and not its intensity. An early-peaking murmur is usually associated with a less stenotic valve, whereas a late-peaking murmur, suggesting a longer time for the ventricular pressure to overcome the stenosis, suggests a more severe stenosis. A nearly immobile and stenotic aortic valve can result in a muted or absent S_2 . The high-pitched, diastolic blowing murmur of aortic regurgitation frequently occurs with aortic stenosis.

Hypertrophic cardiomyopathy is also associated with a crescendo-decrescendo systolic murmur. It is best appreciated *between* the apex and left sternal border, however, and although it radiates to the suprasternal notch, it does *not* radiate to the carotid arteries or neck. The murmur of hypertrophic cardiomyopathy can also be distinguished from aortic stenosis by an increase in murmur intensity (when the outflow tract gradient is increased) that occurs during the active phase of the Valsalva maneuver, when changing from sitting to standing (the left ventricular volume abruptly decreases) and with the use of vasodilators. Hypertrophic cardiomyopathy may also be accompanied by the holosystolic murmur of mitral regurgitation owing to the anterior motion of the mitral valve during systole.

Although S_3 and S_4 are common with hypertrophic cardiomyopathy, they lack prognostic significance. Additional findings include a laterally displaced double apical impulse (resulting from the forceful contraction of the left atrium against a non-compliant left ventricle) or a triple apical impulse (resulting from the late systolic impulse that occurs when the nearly empty left ventricle undergoes near-isometric contraction). Similarly, a double carotid arterial pulse (pulsus bisferiens) is common because of the initial rapid increase of blood flow through the left ventricular outflow tract into the aorta, which declines in midsystole as the gradient develops, only to manifest a secondary increase during end-systole. The jugular venous pulse reveals a prominent a wave owing to the diminished right ventricular compliance associated with septal hypertrophy.

Diastolic murmurs are caused by insufficiency of the aortic or pulmonary valves or stenosis of the mitral or tricuspid valves. Chronic aortic insufficiency is heralded by a high-frequency, early diastolic decrescendo murmur, best appreciated in the second to fourth left intercostal space with the patient sitting up and leaning forward. As aortic insufficiency becomes more severe, the murmur takes up more of diastole. When left ventricular dysfunction results in restrictive filling, the murmur of aortic regurgitation may shorten and become softer.

Moderate to severe aortic insufficiency may also be accompanied by an Austin Flint murmur, a low-frequency, mid-diastolic to late diastolic murmur best appreciated at the apex caused by left atrial flow into an “overexpanded” left ventricle.⁴⁸ As Austin Flint reported, “In some cases in which free aortic regurgitation exists, the left ventricle becoming filled before the auricles contract, the mitral curtains are floated out, and the valve closed when the mitral current takes place, and, under these circumstances, this murmur may be produced by the current just named, although no mitral lesion exists.” Aortic insufficiency may be accompanied by a soft S_1 , prominent S_3 , and diastolic rumble. The apical impulse in chronic aortic insufficiency, which is frequently hyperdynamic and diffuse, is also often displaced inferiorly and leftward.

Severe aortic insufficiency is associated with wide pulse (i.e., systole >100 mm Hg and diastole <60 mm Hg) pressure and a multitude of eponym-rich clinical findings, including a Corrigan or water-hammer pulse, de Musset sign (a head bob with each systole), Müller sign (systolic pulsations of the uvula), Traube sign (“pistol-shot” systolic and diastolic sounds heard over the femoral artery), Hill sign (when the popliteal cuff systolic pressure exceeds the brachial cuff pressure by >60 mm Hg), and Quincke sign (capillary pulsations seen when a light is transmitted through a patient’s fingernail). Duroziez sign is elicited as an audible systolic murmur heard over the femoral artery when the artery is compressed proximally along with a diastolic murmur when the femoral artery is compressed distally.

Other diastolic murmurs include the following. (1) Pulmonary regurgitation is a diastolic decrescendo murmur that is localized over the second intercostal space. When it is due to dilation of the pulmonary valve annulus, it produces the characteristic Graham-Steele murmur. (2) Mitral stenosis is a mid-diastolic rumble that is appreciated with the bell as a low-pitched sound at the apex, immediately after an opening snap, which increases in intensity with exercise. (3) Anatomic or functional tricuspid stenosis (the latter with the delayed opening of the tricuspid valve seen with large atrial or ventricular septal defects) is associated with a mid-diastolic rumble or with the aforementioned Austin Flint murmur of aortic insufficiency. Mitral stenosis can be differentiated from tricuspid stenosis by the localization of the latter to the left sternal border and its augmentation with inspiration.

Finally, the superficial, high-pitched or scratchy sound of a pericardial friction rub is best heard with the patient in the sitting position while leaning forward at end-expiration. This murmur may be systolic, systolic and diastolic, or triphasic, and should be suspected in the postinfarction or acute pericarditis setting with pleuritic chest pain and diffuse ST segment elevations on electrocardiogram.

Abdominal Examination

Examining the abdomen on admission and daily during hospitalization can unify diagnoses and potentially identify common in-hospital abdominal complications. Pancreatitis, cholecystitis, and ischemic bowel all can manifest *de novo* in a patient days after admission to the ICU. If a wound or dressing is present, the physician should put on gloves and carefully take the dressing down (or request to be present at the time of dressing change) to examine the site. The abdomen should be inspected for obesity, cachexia, and distended or bulging flanks (the last-mentioned

may be due to ascites, organomegaly, colonic dilation, ileus, or a pneumoperitoneum). A search for the stigmata of liver disease (i.e., spider angiomas and caput medusae), signs of intra-abdominal hemorrhage such as flank (Grey Turner sign) or periumbilical (Cullen sign) ecchymosis, hernias, and surgical scars should also be performed. Abdominal striae and bruises, in addition to moon facies and central obesity, may be caused by excess glucocorticoids owing to exogenous administration or endogenous overproduction (e.g., Cushing syndrome secondary to pituitary, lung, adrenal, or carcinoid tumors). Visible peristalsis and a distended abdomen argue for bowel obstruction as the cause of abdominal pain and should complement the finding of hyperactive bowel sounds.⁴⁹

Auscultation with the diaphragm of the stethoscope should be performed over each major vascular territory in the abdomen for high-pitched systolic bruits suggesting renal artery stenosis, aortic aneurysm, hepatic or splenic vascular lesions, or the potential cause of mesenteric ischemia. An abdominal bruit may be present in 80% to 85% of patients with renal artery stenosis. Venous (continuous) hums, associated with portal venous hypertension, are best appreciated with the bell of the stethoscope, usually in the right upper quadrant.

In the ICU, it is important to assess the change in bowel sounds over time. Bowel sounds should be sought with the diaphragm of the stethoscope; although loud, high-pitched, and hyperactive bowel sounds may herald the presence of an obstructed bowel, they may also be present with gastroenteritis, inflammatory bowel disease, or gastrointestinal bleeding. Bowel sounds are considered absent only after listening for at least 3 minutes in each quadrant. Absent or decreased bowel sounds suggest the presence of a paralytic ileus (common after surgery or in the presence of hypokalemia, opiates, constipation, and hypothyroidism) or mesenteric thrombosis. Special attention should be paid to “crampy” and diffuse or periumbilical abdominal pain that progressively increases. If pain is accompanied by decreased or absent bowel sounds, distention, guarding, or rebound, the probability that ischemic or obstructive bowel disease is present is significantly increased. A succussion splash, defined as a palpable or audible “splash” elicited by applying a firm push to the abdomen, occurs when a hollow portion of the intestine or an organ/body cavity contains a combination of free fluid, air, or gas. A succussion splash is commonly caused by intestinal or pyloric obstruction (e.g., pyloric stenosis or gastric carcinoma) or a hydropneumothorax over a normal stomach. In critically ill patients, catastrophic intestinal rupture, bowel strangulation, or infarct must also be considered.

Palpation may reveal the presence of peritoneal signs (rebound or involuntary guarding) that are best assessed by watching the patient’s facial expression during light, followed by progressively deeper, palpation. Voluntary guarding is the defensive posture patients use to avoid palpation by contracting their abdominal musculature. This is not considered a peritoneal sign and may be avoided either by distracting the patient or performing repeated examinations of the abdomen to acclimate the patient to touch. Involuntary guarding is the reflex contraction of abdominal muscles, often owing to peritoneal inflammation. Rebound tenderness occurs when the patient reports augmentation in abdominal pain after abrupt release of pressure exerted with deep palpation at the site of abdominal tenderness. Although additive to the examination, this sign is neither specific nor sensitive for peritonitis, and may cause undue patient discomfort

without cause. Peritoneal signs in a critically ill patient should provoke an immediate search for evidence of organ perforation, an ischemic bowel, or peritonitis.

Envisioning the underlying structures is also helpful in determining potential causes of pain on palpation. Right upper quadrant tenderness is commonly associated with hepatic (e.g., hepatitis, hepatic congestion from heart failure) or gallbladder (e.g., acute cholecystitis, biliary colic) disease, a duodenal ulcer, or right lower lobe pneumonia. A positive Murphy sign (an inspiratory pause during palpation of the right upper quadrant) is a specific, but not sensitive, indicator of gallbladder disease. Right lower quadrant pain on palpation shifts the focus to the ascending colon (e.g., appendicitis or cecal diverticulitis) and tubulo-ovarian structures (e.g., ectopic pregnancy, tubo-ovarian abscess, ruptured ovarian cyst, and ovarian torsion). Appendicitis is also suggested by the presence of McBurney sign, tenderness located two thirds the distance from the anterior iliac spine to the umbilicus on the right side.

Left upper quadrant pain suggests pancreatic (e.g., acute pancreatitis or pancreatic tumor) or splenic (e.g., splenic congestion, splenomegaly, or infarction) disease or left lower lobe pneumonia. Left lower quadrant pain occurs with sigmoid and descending colon disease (e.g., diverticulitis) or left-sided tubulo-ovarian pathology. Midline or periumbilical discomfort on palpation occurs during early appendicitis, gastroenteritis, or pancreatitis. Pancreatitis may be associated with epigastric tenderness, guarding, hypoactive bowel sounds, fever, and hypotension. Flank pain should also raise the possibility of an abdominal aortic aneurysm, pyelonephritis, and renal colic. Lower abdominal or suprapubic pain occurs with nephrolithiasis, cystitis, ectopic pregnancy, and pelvic inflammatory disease.

The discovery of an abdominal mass during palpation should include a complete description of its size, consistency (hard, soft, or nodular), and pulsatility. Not all abdominal masses indicate tumors; bowel obstruction, inflammatory bowel disease, an enlarged left lobe of the liver, and abdominal aortic aneurysm are some examples of nontumorous masses. A pancreatic mass is rarely palpable.

Percussion may reveal localized abdominal dullness suggesting organomegaly, stool, or the presence of an abdominal mass, whereas generalized abdominal dullness is often associated with ascites. With a suspicion of ascites, noting whether dull areas shift with changes in patient position can be informative. This shift can be detected most easily by the presence of dullness in areas of prior tympany when the patient’s abdomen is percussed in the recumbent position and after the patient has been rolled approximately 30 degrees away from the examiner.

Percussion can be used to detect hepatomegaly. The lower edge of the liver can be detected by placing the right hand in the right lower quadrant of the abdomen and gently moving toward the lower rib margin, approximately 2 cm with each gentle breath of the patient. If the edge is not felt, no further examination is required. If the edge is appreciated, the superior border of the liver should be determined by percussion, starting in the third intercostal space and moving down one interspace at a time until the note changes from resonant to dull. In obese patients, “scratching” with auscultation for the change from tympany to dull on superior and inferior aspects of the liver may be performed. Hepatomegaly is said to be present if the liver span is appreciated for greater than 12 cm (although the actual mean liver span along the midclavicular line is apparently 7 cm

in women and 10.5 cm in men). Splenomegaly may be present if the spleen is detected while advancing the examining hand upward toward the left upper quadrant during exhalation with palpating for the spleen edge during inspiration. Percussive dullness over the spleen in the midaxillary line during inspiration also suggests splenomegaly. Finally, a rectal examination should be performed to search for potential causes of urinary tract obstruction (e.g., benign prostatic hypertrophy) or infection (e.g., prostatitis), and to evaluate the stool for gross or occult blood.

Neurologic Examination

One third of patients admitted to the ICU have neurologic complications that may double the length of a hospital stay and increase the likelihood of death.⁵⁰ Depressed consciousness is a major contributor to prolonged ventilation. Careful attention and notation should be made on the initial examination and with changes in neurologic state.

The neurologic examination should begin with an assessment of sensorium (dementia or delirium) and the level of consciousness. Level of consciousness has been described as alert, lethargic (easily aroused with mild stimulus), somnolent (easily aroused, but requires stimulation to maintain arousal), obtunded/stuporous (arousable only with repeated and painful stimuli), and comatose (unarousable despite vigorous stimulation with no purposeful movements). If comatose, the depth of the coma can be assessed by the degree of corneal reflex loss. A continuous performance test (asking the patient to raise a hand) can be used to evaluate alertness in noncomatose patients, but a formal Glasgow Coma Scale score should be routinely monitored, along with brainstem reflex assessment, in all unresponsive or minimally responsive patients.

Frontal release signs (forced grasping) and perioral primitive reflexes (snout and pout) are found in diffuse structural and metabolic disease. Flexor and extensor postures can occur in traumatic and metabolic coma (e.g., secondary to hypoxia, ischemia, hypoglycemia, or uremia). Upper motor neuron disease (destructive, pharmacologic, infectious, or metabolic) can be implied by the coexistence of a positive Babinski response, indicated by an upward movement of the great toe (instead of a normal downward turn) in response to a forceful stroke along the lateral plantar surface of the foot from the heel toward the toes. "Fanning" of the toes is a normal phenomenon.

Delirium is an acute and reversible confusional state, occurring in 20% of all hospitalized elderly patients.⁵¹ It can be assessed by formal screening tools that focus, at any altered level of consciousness, on an acute change in mental status from a patient's baseline that is fluctuating, with difficulty focusing attention or disorganized thinking or both.⁵² Assessment of dementia is impossible in a patient who is delirious.

Pupil asymmetry, alterations in size, or poor reactivity (i.e., dilated and fixed) suggests a history of cerebral anoxia, intracranial vascular events, masses, or metabolic or drug abnormalities. Although patients in a coma usually have closed eyelids, tonic lid retraction or reopening after forced closure may be present with pontine disease. The brainstem can also be examined more formally using oculocephalic maneuvers or oculovestibular testing. The presence of hand tremors can suggest thyrotoxicosis or parkinsonism (associated with a pill-rolling phenomenon); hand tremors that occur with purposeful

movement suggest cerebellar pathology (e.g., alcoholism or cerebrovascular accident). In patients with evidence of diabetic neuropathy or parkinsonism, autonomic dysfunction should be suspected. Myoclonus (brief, often asymmetric, generalized body jerks lasting <0.25 second) may appear as a result of cerebral hypoxia or ischemia.

Cranial nerves should be assessed grossly or more intently with active neurologic insults. The optic nerve (CN II) is assessed by confirming visual acuity. Pupillary reactions to light (CN III) are examined by shining a bright light obliquely into each pupil in turn, looking for papillary constriction in the ipsilateral (direct) and contralateral (consensual) eye. A decreased direct response (or dilation) indicates an afferent pathway defect (Marcus Gunn pupil) such as occurs with optic neuritis, ischemic optic neuropathy, or severe retinal disease. Fixed and dilated pupils are associated with brainstem injury, but may also be due to a recent dose of atropine. A pupil that is capable of accommodation but does not respond to light (Argyll-Robertson pupil) is associated with tertiary syphilis (and should be considered if the differential diagnoses include aortic dissection or aortic insufficiency), neurosarcoidosis, and Lyme disease.⁵³ Anisocoria (pupil inequality = 1 mm) suggests a CNS mass or bleed, and may explain the precordial T wave inversions seen in a comatose patient without evidence of cardiomyopathy, myocarditis, or electrolyte abnormalities. Simple anisocoria (>0.4 mm difference between eyes) is present in nearly 40% of healthy individuals, however.⁵⁴

Pupillary accommodation may be tested by holding a finger approximately 10 cm from the patient's nose and, while observing the pupillary response in each eye, asking the patient to alternate looking into the distance and at the finger. Narrowing should occur with focus on the near finger, whereas dilation should occur when focusing afar. The presence of eyelid ptosis may also suggest a defect in the third cranial nerve or the presence of a posterior communicating artery aneurysm. Old age, trauma, chronic inflammation, neoplasms, and thyroid abnormalities are more commonly the cause, however.

Extraocular movements should be assessed by asking the patient to follow the examiner's finger with the eyes (without moving the head) and checking gaze in the six cardinal directions using a cross or "H" pattern (CN III, IV, and VI). The examiner should pause during upward and lateral gaze to check for nystagmus.

Trigeminal nerve (CN V) motor function can be assessed by palpating for temporal or masseter muscle strength while asking the patient first to open the mouth and then to clench the teeth. The three sensory components of the trigeminal nerve can be tested by assessing the response on both sides of the face to a sharp and blunt object lightly placed against the forehead, cheeks, and jaw. An intact corneal reflex (eye blink when the cornea is touched by a cotton wisp) tests the sensory component of the fifth cranial nerve and the motor component of the seventh cranial nerve. Facial asymmetry or droop is also present with seventh cranial nerve injury (e.g., secondary to Bell palsy, cerebrovascular accident, or trauma). Bell palsy can be differentiated from stroke by the ability of a patient with Bell palsy to close his or her eye or wrinkle the forehead. Less common causes of seventh cranial nerve injury include sarcoidosis and Lyme disease.

The eighth cranial nerve can be coarsely assessed by having the patient, with the eyes closed, detect the sound of fingers lightly rubbing together alternatively next to each ear. Sensorineural hearing loss can be associated with a genetic form

of dilated cardiomyopathy.⁵⁵ A hoarse voice may be caused by tenth cranial nerve abnormalities, such as compression of the recurrent laryngeal nerve motor branch by the marked left atrial enlargement that can occur with severe mitral stenosis. The motor strength of the eleventh cranial nerve is assessed by asking the patient to shrug the shoulders against resistance. Finally, the hypoglossal nerve (CN XII) is assessed by asking the patient to protrude the tongue and move it side to side.

Assessment for sensory deficits, abnormal peripheral reflexes, and muscle strength may help guide the evaluation of patients with possible systemic neurologic or myopathic disease. The sensory examination requires the attention, participation, and understanding of the patient. Light touch is tested by touching the skin with a wisp of cotton or a tissue and asking the patient to acknowledge the feeling while not looking. Pain sensation can be elicited using a sharp object; temperature sensation can be grossly ascertained using cold and warm objects. Vibration is tested with a tuning fork and needs to be compared bilaterally. Sensory deficits can offer important clues regarding the systemic, central, or peripheral location of underlying lesions. Diabetes mellitus is suggested by a “stocking-glove” distribution of sensory defects; focal hyperesthesia or anesthesia can occur with the dry beriberi of vitamin B₁ deficiency (high output cardiac failure occurs in wet beriberi). The presence of hand tremors can suggest thyrotoxicosis or parkinsonism (associated with a pill-rolling phenomenon), whereas hand tremors that occur only with purposeful movements suggest cerebellar pathology (e.g., alcoholism or cerebrovascular accident). Delayed ankle reflexes in a patient with cool, dry, and coarse skin with bradycardia is highly suggestive of hypothyroidism.^{56,57}

Motor deficits may be difficult to evaluate in the ICU, but should be initially sought in all major muscle groups by having the patient move each muscle group against resistance. Motor strength is reported as 5/5 (normal strength), 4/5 (movement against resistance, but less than normal), 3/5 (movement against gravity, but not against added resistance), 2 (movement at the joint, but not against gravity), 1/5 (visible muscle movement, but no movement at the joint), and 0/5 (no muscle movement). Motor deficits may be present with a cardiomyopathy in patients with Duchenne or Becker muscular dystrophy, whereas the presence of motor and conduction defects can occur with myotonic dystrophy. Focal muscle weakness raises the possibility of a new or old upper motor neuron lesion (e.g., multiple sclerosis, intracranial mass, or cerebrovascular accident) or mononeuropathy. Symmetric proximal weakness can occur with numerous myopathies, whereas symmetric distal weakness can occur with polyneuropathy, amyotrophic lateral sclerosis, and Guillain-Barré syndrome. Statins and alcohol can affect either distal or proximal muscle groups.

Vascular Examination

The vascular examination may begin with the auscultation of both flanks for the presence of a bruit suggestive of renal artery stenosis. Angiographically significant renal artery stenosis may be present in nearly 60% of patients with peripheral arterial disease. The aorta can often be assessed on deep palpation of the central abdomen. A pulsatile pulse immediately above the level of the umbilicus is a nonsensitive sign of an abdominal aortic aneurysm and is most readily detected in men older than 60 years. Auscultation of both abdominal flanks may detect

the presence of renal artery stenosis. In patients complaining of exertional or positional leg pain, the absence of a pulse or the presence of arterial ulcers is often diagnostic for vascular insufficiency. In the setting of an intra-aortic balloon pump or after a catheter-based coronary artery assessment or intervention, particular attention has to be paid to following the pulses sequentially on the investigated limb.

Musculoskeletal and Integument Examination

The musculoskeletal examination should begin with a general assessment for global or focal muscle wasting or atrophy. During lung auscultation, one can simultaneously inspect the spine for scoliosis, lordosis, or kyphosis. Each spinous process should be inspected for focal areas of tenderness. Holt-Oram syndrome, associated with atrial and ventricular septal defects, usually manifests with upper limb skeletal deformities, including unequal arm lengths; anomalous development of the radial, carpal, and thenar bones of the hand; triphalangeal or absent thumbs; or phocomelia. Arachnodactyly (long spidery fingers) may be found in patients with Marfan syndrome. Capillary pulsations under the fingernails may be evident with aortic regurgitation, sepsis, or thyrotoxicosis whereas splinter hemorrhages also raise the possibility of bacterial endocarditis. The presence of Osler nodes (painful reddish papules approximately 1 cm on the fingertips, palms, toes, or soles of the feet) also suggests endocarditis.

The joints should be felt for crepitus during passive motion, and in the setting of fever or focal neurologic symptoms, the neck should be assessed for evidence of nuchal rigidity. The extremities should be assessed for unilateral or bilateral edema (suggestive of heart failure, hypoproteinemia, or vein thrombosis), cellulitis, phlebitis, or ischemic extremities. While evaluating the legs, the clinician should check if subcutaneous anticoagulation or compression boots are necessary.

Skin erythema and warmth suggest inflammation, including soft tissue swelling or focal areas of tenderness. Specific skin patterns may suggest particular diseases and may prove critical to the care of patients in the ICU. A rash typically found on the palms, soles, dorsum of the hands, and extensor surfaces that begins as macules that develop into papules, vesicles, bullae, urticarial plaques, or confluent erythema is consistent with Stevens-Johnson syndrome. Other skin findings associated with disease include the malar flush (mitral facies) of mitral stenosis, brick-red coloring seen with polycythemia, bronze coloring associated with hemochromatosis, oral hyperpigmentation and brown coloring with Addison disease, “moon facies” of Cushing disease, and a butterfly rash across the nose consistent with systemic lupus erythematosus.

Approximately 4 to 5 g/dL of unoxygenated hemoglobin in the capillaries generates the blue color appreciated clinically as central cyanosis.⁵⁸ For this reason, patients who are anemic may be hypoxemic without showing any cyanosis. Central cyanosis (involving the mucous membranes of the lips, tongue, and earlobes) with warm extremities strongly suggests right-to-left shunting (usually the shunt is >25% of the total cardiac output), severe anemia (hematocrit <15%), severe hypoxia, or concomitant lung disease. Cyanosis may also occur in the presence of increased amounts of methemoglobin (e.g., with use of dapsone,

nitroglycerin, or topical benzocaine) or sulfhemoglobin. Pseudocyanosis, a blue color to the skin without deoxygenated hemoglobin, may occur with the use of amiodarone, phenothiazines, and some metals (especially silver and lead). Central cyanosis often improves with supplemental oxygen. Clubbing suggests central cyanosis, right-to-left shunting with or without congenital heart disease, or bacterial endocarditis. Cyanosis in the presence of normal oximetry suggests anemia, poor cardiac output, or hypercapnia. If the lower limbs are cyanosed, but the upper limbs are not, a patent ductus arteriosus should be expected. Peripheral cyanosis with cool extremities suggests the presence of low cardiac output, hypovolemia, or peripheral vasoconstriction. Warming the extremity often improves cyanosis.

Jaundice, which may be present with hepatitis, alcoholic liver disease, choledocholithiasis, pancreatic cancer, or metastatic liver disease, can be differentiated from other causes of yellow skin by the concomitant “yellowing” of mucous membranes under the tongue or in the conjunctiva of the eye. The presence of spider angiomas, palmar erythema, dilated abdominal veins, and ascites increases the likelihood of a hepatocellular cause of the jaundice.⁵⁹ The finding of a palpable gallbladder (Courvoisier sign) is highly suggestive of extrahepatic obstruction.

Conclusion

The physical examination offers much to help hone and optimize diagnostic and therapeutic paradigms. In the hands of the astute clinician, the physical examination offers timely keys for the successful management of critically ill patients in the ICU.

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Scientific Foundation of Cardiac Intensive Care

SECTION



Role of the Cardiovascular System in Coupling the External Environment to Cellular Respiration

CHAPTER



Peter D. Wagner

**Cardiovascular Function and Pulmonary
Gas Exchange**

**Cardiovascular Function and Systemic
Gas Exchange**

THE CARDIOVASCULAR system exists primarily to transport O_2 and nutrients to the various body tissues and to transport CO_2 and other waste products from the tissues to the lungs, kidneys, or liver for disposal. This system is a component of the O_2 transport pathway, linking the environment, via the lungs and chest wall, to tissue cells, via the heart and the vascular network.

This chapter focuses on cardiovascular function as it affects O_2 transport between the environment and the tissue cells. Total cardiac output and its distribution among and within organs are crucial aspects of O_2 transport efficiency in health and disease. Although the principles of O_2 exchange and transport in the lungs and tissues are fundamentally similar, it is worthwhile to discuss pulmonary and tissue O_2 transport separately. Normal physiologic processes are described first, followed by pathophysiologic consequences of disease, from the point of view of cardiac function.

Cardiovascular Function and Pulmonary Gas Exchange

Cardiac function is important to O_2 exchange in the lungs in many ways. First, total pulmonary blood flow, which is normally equal to cardiac output, affects PO_2 of venous blood entering the lungs. Although in health this is of little significance, it is of

major importance in disease. Second, the relationship between total pulmonary blood flow and the volume of blood in the pulmonary capillaries determines red blood cell exposure (or transit) time in the lungs. In resting normal humans, transit time is much greater than what is needed; this may not be the case during exercise or in disease. Third, the distribution of pulmonary blood flow among the 300 million alveoli cannot be perfectly matched to the ventilation of the alveoli. This causes ventilation-perfusion ($\dot{V}_A/\dot{Q}$) mismatch, which interferes with arterial oxygenation. This $\dot{V}_A/\dot{Q}$ mismatch is of little consequence in health, but is of major importance in disease of the cardiopulmonary system. Fourth, any dysfunction of the left ventricle that increases diastolic filling pressure has the potential for causing pulmonary edema, especially if pulmonary capillaries have been damaged by disease. Pressures are sufficiently low in health that edema does not occur at rest. With heavy exercise, mild interstitial edema can occur, but the effects are subtle. The importance of left ventricular dysfunction increases dramatically when filling pressures exceed 20 to 25 mm Hg.¹ Pulmonary microvessels may undergo a degree of physical disruption at very high vascular pressures.² Fifth, right ventricular hypertrophy from pulmonary diseases can impair left ventricular function, effectively decreasing left ventricular compliance through mechanical interdependence of the heart chambers. These five concepts are now discussed.

Total Pulmonary Blood Flow and Oxygen Exchange

Pulmonary O_2 exchange under steady-state conditions obeys mass balance principles. Corresponding equations can be written to describe O_2 uptake from respired air and into the pulmonary circulation.³ These equations are:

$$\dot{V}O_2 = \dot{V}_I \cdot F_{IO_2} - \dot{V}_A \cdot F_{AO_2} \quad [1]$$

$$\dot{V}O_2 = \dot{Q}[CaO_2 - C\bar{v}O_2] \quad [2]$$

where $\dot{V}O_2$ is whole-body O_2 consumption, $\dot{V}_I$ and $\dot{V}_A$ are inspired and expired alveolar ventilation, F_{IO_2} and F_{AO_2} are inspired and expired alveolar O_2 fractional concentrations, $\dot{Q}$ is total pulmonary blood flow, and CaO_2 and $C\bar{v}O_2$ are arterial and pulmonary arterial (mixed venous) O_2 concentrations. These two equations embody the principle of taking the difference between the O_2 flow rate into and out of the lungs, expressed for ventilation (Equation 1) or blood flow (Equation 2). Although not completely correct, it is reasonable for clinical purposes to assume that $\dot{V}_I$ equals $\dot{V}_A$ to simplify Equation 1. Strictly, $\dot{V}_A = \dot{V}_I - \dot{V}O_2 + \dot{V}CO_2$, where $\dot{V}CO_2$ is CO_2 output by the lungs. If the respiratory quotient (R) equals 1, $\dot{V}O_2 = \dot{V}CO_2$, and $\dot{V}_A = \dot{V}_I$. Normally, $\dot{V}O_2$ exceeds $\dot{V}CO_2$ so that R is, on average, 0.8. Under these conditions, $\dot{V}_A$ is about 1% less than $\dot{V}_I$, an unimportant difference.

In healthy lungs, alveolar PO_2 , which is proportional to F_{AO_2} in Equation 1, is tightly related to CaO_2 in Equation 2 by the O_2 -hemoglobin (Hb) dissociation curve. CaO_2 can be directly computed using alveolar PO_2 and the O_2 -Hb dissociation curve.⁴ This is not true in lung disease, where for Equation 1, F_{AO_2} is mean alveolar $[O_2]$ averaged over the 300 million alveoli, weighted by the ventilation of each, and CaO_2 is arterial $[O_2]$, similarly averaged but weighted by blood flow to each of the alveoli. When ventilation or blood flow is distributed in a nonhomogeneous manner in lung disease, the PO_2 corresponding to mean alveolar gas is often much higher than that of arterial blood corresponding to CaO_2 . CaO_2 cannot be accurately calculated from F_{AO_2} and the O_2 -Hb dissociation curve.

In the normal lung, it is clear from Equation 1 that alveolar $[O_2]$, F_{AO_2} , is a direct function of $\dot{V}O_2$, F_{IO_2} , and alveolar ventilation only; so too is arterial $[O_2]$, CaO_2 . The important conclusion is that changes in cardiac output ($\dot{Q}$) have no influence on arterial $[O_2]$ or PO_2 in normal lungs, so long as CaO_2 is a direct function of F_{AO_2} . An increase in cardiac output per se with anxiety or fever would not affect arterial PO_2 in a normal lung if $\dot{V}O_2$, F_{IO_2} , and ventilation remained unchanged. A decrease in cardiac output from dehydration, blood loss, or myocardial infarction also would not affect arterial PO_2 under the same assumptions in a normal lung.

Equation 2 shows that the sole influence of cardiac output on gas exchange in a normal lung is to affect mixed venous $[O_2]$ and PO_2 . As cardiac output decreases, so too does $C\bar{v}O_2$, and as cardiac output increases, so too does $C\bar{v}O_2$. Although, as stated, this does *not* affect arterial $[O_2]$ or PO_2 in the normal lung, this is not the case in lungs with diseases associated with ventilation–blood flow mismatch or right-to-left shunting. In such diseases, it is still true that $C\bar{v}O_2$ must increase and decrease with cardiac output just as in health, if other influences are constant; however, because arterial blood is the mixture of blood from all lung regions, a shunt or areas of low $\dot{V}_A/\dot{Q}$ ratio mix in blood from such regions having lower $[O_2]$ than normal, reducing mixed arterial $[O_2]$ and PO_2 . As cardiac output decreases, the $[O_2]$ and PO_2 of such shunts or low $\dot{V}_A/\dot{Q}$ regions decrease because

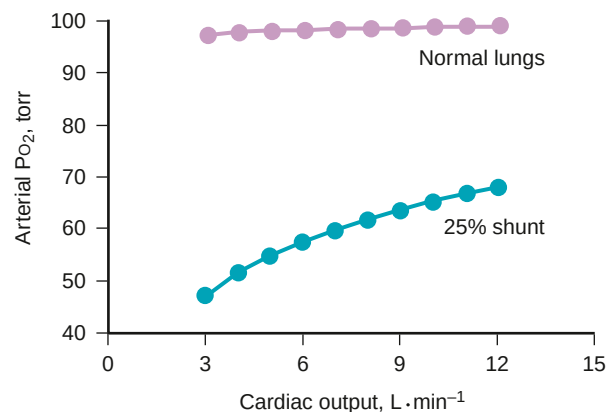


Figure 5-1. Effect of changes in cardiac output on arterial PO_2 in normal and diseased lungs. In this example, the diseased lung contains a 25% right-to-left shunt. Arterial PO_2 is essentially independent of cardiac output in health, but depends significantly on cardiac output in disease.

such pathways essentially fail to oxygenate flowing blood above mixed venous levels.

The contribution of such regions to arterial blood, being tightly coupled to mixed venous $[O_2]$, is closely dependent on cardiac output. The end result is more severe arterial hypoxemia as cardiac output decreases, and less severe hypoxemia as cardiac output increases. This situation is illustrated in Figure 5-1, in which a normal lung and a lung containing as an example of disease a 25% right-to-left shunt are compared as cardiac output changes. Arterial O_2 saturation, a better reflection of the O_2 concentration of the blood, follows changes in PO_2 (Fig. 5-2). Mixed venous PO_2 (Fig. 5-3) changes similarly in both cases according to Equation 2, but arterial PO_2 and O_2 saturation vary with cardiac output only in the abnormal lung. The clinical message is clear—the degree of arterial hypoxemia in a given patient depends not only on how much shunt or $\dot{V}_A/\dot{Q}$ mismatch is present, but also on cardiac output. If arterial PO_2 were to decrease in such a patient, changes in cardiac output should be excluded if the arterial PO_2 change is to be interpreted as a change in health of the lung. Application of the classic shunt or venous admixture equation^{5,6} illustrates this principle dramatically:

$$\dot{Q}_{VA}/\dot{Q}_T = 100 \cdot [C_{IO_2} - CaO_2]/[C_{IO_2} - C\bar{v}O_2] \quad [3]$$

where $\dot{Q}_{VA}/\dot{Q}_T$ is venous admixture as a percentage of the cardiac output and C_{IO_2} is essentially the $[O_2]$ of normal end-capillary blood in nonshunted, normal $\dot{V}_A/\dot{Q}$ regions of the lung.

When $\dot{Q}_{VA}/\dot{Q}_T$ is computed over the range of cardiac output values and for the examples in Figure 5-1, assuming $C\bar{v}O_2$ stays constant ($P\bar{v}O_2$ constant at the normal value of 40 mm Hg for $\dot{Q}_T = 6 \text{ L} \cdot \text{min}^{-1}$ in each case, rather than the *actual* $C\bar{v}O_2$ associated with each cardiac output), it can be seen (Fig. 5-4) how badly $\dot{Q}_{VA}/\dot{Q}_T$ is overestimated when actual cardiac output is low, and underestimated when cardiac output is high. Neither of the extremes of cardiac output in Figure 5-4 (i.e., $3 \text{ L} \cdot \text{min}^{-1}$ and $12 \text{ L} \cdot \text{min}^{-1}$) is beyond the range of common experience in the intensive care unit. Apparent shunt ($\dot{Q}_{VA}/\dot{Q}_T$) would be about twice the actual value when cardiac output is reduced by 50%, and half the real value when cardiac output is doubled if venous $[O_2]$ is assumed to be at normal levels.

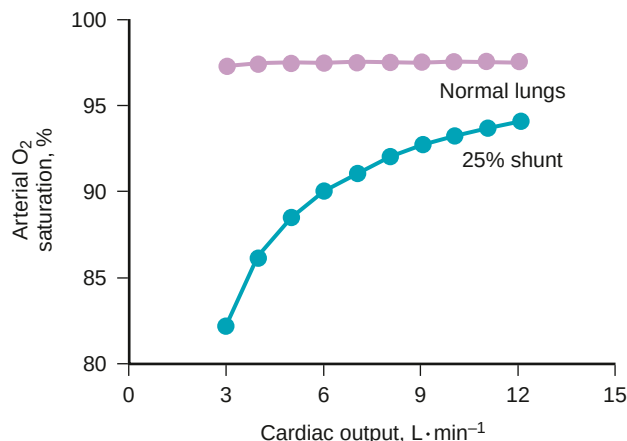


Figure 5-2. Effect of cardiac output on arterial oxygen saturation, from the same calculations as used in Figure 5-1. Saturation varies considerably with cardiac output in diseased, but not in normal, lungs.

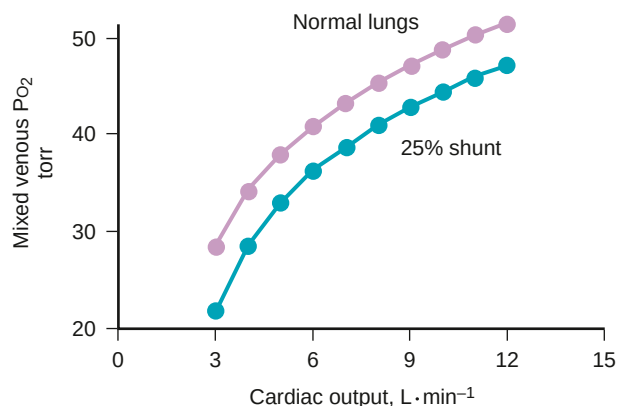


Figure 5-3. Change in mixed venous PO_2 with cardiac output for the conditions of Figures 5-1 and 5-2. Mixed venous PO_2 changes similarly with cardiac output in health and disease. Absolute PO_2 is slightly higher in health at a given cardiac output.

Pulmonary Transit Time

The preceding section assumes sufficient time for O_2 to equilibrate fully across the blood gas barrier; that is, PO_2 in the capillary blood has increased from mixed venous levels all the way to alveolar PO_2 within the available red blood cell contact time. Average red blood cell contact time normally appears to be about 0.75 second. This estimate is the ratio of resting capillary blood volume (75 mL, measured by the carbon monoxide technique⁷) to the corresponding cardiac output (6 $L \cdot min^{-1}$). Figure 5-5 indicates the normal PO_2 profile calculated along the pulmonary capillary and shows full equilibration in about 0.25 second, leaving 0.5 second in reserve.⁸ Although transit times in different alveoli are not uniform,⁹ the variance in such times is still small enough that full equilibration occurs at rest, even in channels with the shortest transit and even during moderate exercise. Only during heavy exercise does failure of equilibration occur in healthy individuals.¹⁰ At high altitudes, diffusion limitation is seen with even light to moderate exercise and becomes a major factor reducing arterial $[O_2]$ under such conditions.¹¹

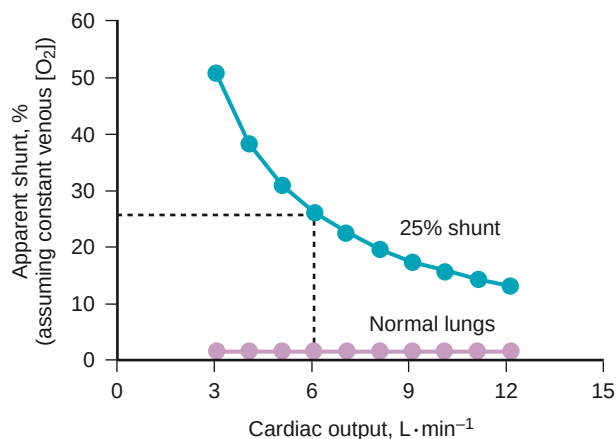


Figure 5-4. Calculated or apparent shunt as a percentage of cardiac output, when the assumption is made that oxygen concentration in mixed venous blood is constant, equaling that seen when cardiac output is 6 $L \cdot min^{-1}$. This assumption leads to large errors in calculated shunt when cardiac output is reduced or increased. The dashed lines indicate conditions under which the assumption is correct, so that calculated shunt is also accurate, but only at that point.

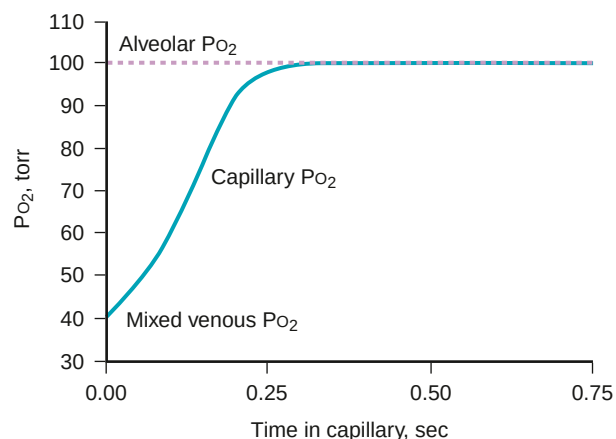


Figure 5-5. Time course of PO_2 change along the pulmonary capillary as oxygen moves from alveolar gas into the flowing capillary blood. Starting at a mixed venous PO_2 of 40 mm Hg, full equilibration with alveolar gas is reached in about 0.25 second, leaving a large reserve in transit time under normal conditions.

In cardiopulmonary diseases, diffusion limitation in the lung rarely occurs, even when patients are well enough to exercise. The exception is interstitial pulmonary fibrosis. Here, diffusion limitation is usually seen during exercise, which aggravates hypoxemia.¹² Diffusion limitation can also occur at rest in such patients.¹³ Pulmonary diffusing capacity must be less than about 60% of normal, however, before diffusion limitation is seen because of previously described reserves in red blood cell transit time.¹³ Hypoxemia in cirrhosis of the liver seems to have a small component of diffusion limitation as well.

In severe cardiopulmonary diseases, such as acute pulmonary edema from left ventricular failure or acute respiratory distress syndrome, conditions develop that reduce O_2 diffusing capacity. In particular, the normally thin (0.5- μm) blood-gas barrier separating alveolar gas from capillary blood can become edematous; however, it is thought that this does not produce

measurable O_2 diffusion limitation. In more advanced disease, there is alveolar filling with edema fluid, cellular debris, or both, which abolishes all ventilation of affected alveoli and produces what is more commonly termed *shunt* (i.e., perfusion of unventilated alveoli). It could be argued that such alveoli are completely diffusion-limited because no O_2 exchange occurs at all. This becomes a semantic issue and should not detract from the more important problem of understanding the pathologic and physiologic changes that occur with these diseases.

Distribution of Blood Flow within the Lungs

In normal lungs, output from the right ventricle is not equally distributed among the 300 million alveoli. Gravity affects blood flow distribution; more blood flows through dependent than nondependent alveoli because of the weight of the blood.¹⁴ There are nongravitational influences on blood flow distribution as well. The fractal branching nature of the vascular tree produces nonuniform distribution,¹⁵ and the lack of perfect anatomic symmetry perturbs flow patterns further.¹⁶ There may also be greater perfusion of central (proximal) than peripheral (distal) lung regions,¹⁷ although this has not been resolved. As a result of all of these independent sources of nonuniformity, a substantial degree of nonhomogeneous blood flow distribution exists. It seems, however, that the distribution of ventilation is largely matched to that of blood flow, so that ventilation and blood flow are each greatest and least in the same areas.¹⁸ This matching is imperfect, but interferes only trivially with O_2 transport in the normal lung. If the ideal lung produces an arterial PO_2 of 100 mm Hg, the real lung in young healthy subjects produces an arterial PO_2 of 90 to 95 mm Hg. Because of the flat O_2 -Hb dissociation curve at this PO_2 , the effect on arterial $[O_2]$ of this 5- to 10-mm Hg decrease is negligible.

Equations 1 and 2, although used previously for considering the whole lung, can be applied at the local alveolar level, where the terms now reflect local alveolar and end-capillary O_2 levels and local $\dot{V}O_2$. Still assuming equality of $\dot{V}_I$ and $\dot{V}_A$ at this level and setting Equations 1 and 2 equal to one another yields a new relation:

$$\dot{V}_A [FIO_2 - FAO_2] = \dot{Q} [C\bar{c}O_2 - C\bar{v}O_2]$$

or

$$\dot{V}_A / \dot{Q} = [C\bar{c}O_2 - C\bar{v}O_2] / [FIO_2 - FAO_2] \quad [4]$$

where $C\bar{c}O_2$ is the standard term for end-capillary $[O_2]$ in a local lung region.

Equation 4 shows that within such a local lung region, alveolar (and end-capillary) $[O_2]$ is a unique function of the $\dot{V}_A / \dot{Q}$ ratio and the so-called boundary conditions (i.e., the inspired and mixed venous O_2 levels). A third factor implicit to Equation 4 is the PO_2 - $[O_2]$ relation defined by the O_2 -Hb dissociation curve.

Equation 4 points out how changes in the local $\dot{V}_A / \dot{Q}$ ratio are key factors affecting local gas exchange and arterial PO_2 and $[O_2]$.^{3,5,6} Figure 5-6 shows how local PO_2 depends on the $\dot{V}_A / \dot{Q}$ ratio for room-air breathing and a range of three mixed venous PO_2 levels. At $\dot{V}_A / \dot{Q}$ ratios in the normal range (about 0.3 to 3),¹⁹ local PO_2 varies considerably with $\dot{V}_A / \dot{Q}$ and PvO_2 . At lower $\dot{V}_A / \dot{Q}$ ratios typical of most cardiopulmonary diseases (i.e., below the normal range), local PO_2 is tied to PvO_2 , and is virtually independent of the $\dot{V}_A / \dot{Q}$ ratio. As cardiac output and PvO_2 change, low $\dot{V}_A / \dot{Q}$ regions closely reflect these changes, affecting arterial PO_2 as mentioned previously. The quantitative

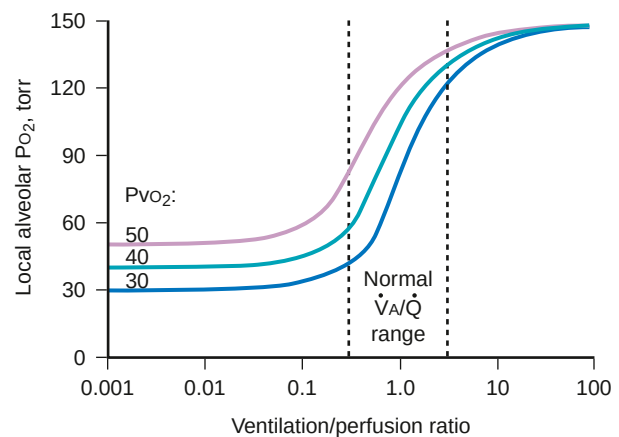


Figure 5-6. Alveolar PO_2 in small lung regions as a function of local $\dot{V}_A / \dot{Q}$ ratio. The normal $\dot{V}_A / \dot{Q}$ range is shown. The most important observation to be made is that when $\dot{V}_A / \dot{Q}$ ratio is reduced below normal, alveolar PO_2 is tied closely to PO_2 in the mixed venous blood.

manner in which blood flow is distributed within the lungs, and how this relates to the distribution of ventilation and of $\dot{V}_A / \dot{Q}$ ratios are major factors in gas exchange and in arterial oxygenation.

In cardiopulmonary disease, areas of low or zero $\dot{V}_A / \dot{Q}$ ratio are commonly seen and are responsible for hypoxemia.²⁰ In most cases, areas of low or zero $\dot{V}_A / \dot{Q}$ ratio are generated by abnormalities in local ventilation, not blood flow, although the alveolar edema underlying such effects may have its origins in primary cardiac disease. Local reduction in ventilation from airway obstruction or alveolar filling with cell debris or fluid is the usual mechanism. There are some specific situations in which hypoxemia seems to be the result of primary vascular changes. The hypoxemia of chronic liver disease is the result of pulmonary vascular malformations that mostly act as right-to-left shunts; the blood in these malformations does not participate in gas exchange.²¹⁻²³ Pulmonary thromboembolic disease, by obstructing some pulmonary arteries, results in overperfusion of nonembolized areas. This overperfusion reduces the local $\dot{V}_A / \dot{Q}$ ratio of nonembolized alveoli and is a primary reason for hypoxemia when it occurs in such patients.²⁴

Of particular relevance to cardiovascular state in the context of pulmonary gas exchange is a curious, poorly understood, but reproducible phenomenon whereby, as total blood flow through the lung (usually cardiac output) increases or decreases, so too does fractional shunt or venous admixture.²⁵ Figure 5-7 is a dramatic example of this phenomenon in a patient with lung disease on variable right heart bypass.²⁶ As pulmonary blood was mechanically varied from 1 to 5 L/(min · m²), percentage of shunt increased from 15% to 40% of the cardiac output. To underline the magnitude of this effect, absolute shunt perfusion increased from 0.15 L/(min · m²) to greater than 2 L/(min · m²), a more than 10-fold increase. Because these changes are rapidly reversible within minutes, it seems unlikely that the greater blood flow is actually causing more damage and shunt on this basis.

There is probably some systematic change in blood flow distribution between ventilated, normal regions and the unventilated alveoli causing the shunt to change with total blood flow.²⁷ This change generally occurs regardless of the anatomic distribution

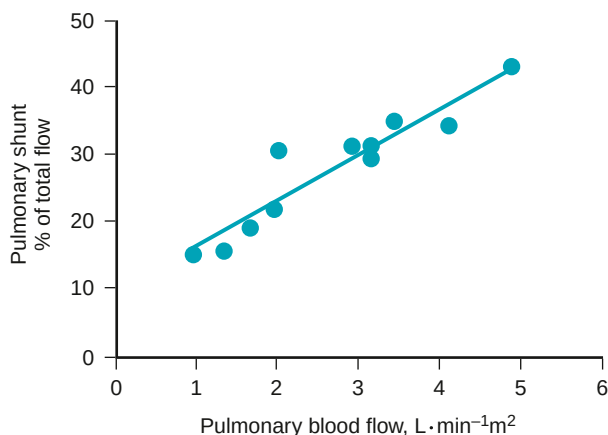


Figure 5-7. Dependence of percentage shunt through the lungs on pulmonary blood flow in a single patient with acute respiratory distress syndrome. In this patient on partial right heart bypass, pulmonary blood flow varied between $1 \text{ L} \cdot (\text{min} \cdot \text{m}^2)^{-1}$ and $5 \text{ L} \cdot (\text{min} \cdot \text{m}^2)^{-1}$. Shunt varied between 15% and 40% in a linear manner.

of disease and seems to be unrelated to lung structure in any systematic way. Numerous animal studies done under many circumstances mirror the human experience, regardless of whether the cardiac output is manipulated mechanically or pharmacologically.²⁸ The finding that the increase in percent of shunt with cardiac output is far greater in animals breathing pure O_2 than room air, and greater than in animals breathing a hypoxic gas mixture points to an interaction between hypoxic pulmonary vasoconstriction and blood flow as the basic mechanism.²⁹

At low blood flow rates while breathing 100% O_2 , unventilated alveoli are greatly vasoconstricted by hypoxia, whereas ventilated units have little or no vascular tone. Any increase in total blood flow is directed mostly to the unventilated units because the higher pressure of high blood flow can overcome hypoxic vasomotor tone, whereas little additional blood flow can be accommodated by already relaxed, well-ventilated regions. From the clinical standpoint, it is important to be aware of the shunt–total blood flow relationship when interpreting pulmonary gas exchange as cardiac output varies.

Closely related to the previously described phenomenon is the effect of systemic vasodilators, which are sometimes given to patients in left heart failure to reduce afterload. When such patients have pulmonary gas exchange abnormalities, often as a result of pulmonary edema from the heart failure itself, there are areas of low or zero $\dot{V}_A/\dot{Q}$ ratio as a result of edema of the alveolar wall, alveolar gas space, or both.²⁰ Consequently, these regions are subject to hypoxic pulmonary vasoconstriction. Administration of a systemic vasodilator (e.g., nitroprusside) dilates not only the systemic vasculature, but also the pulmonary vasculature. The latter is particularly evident in the most vasoconstricted areas having a low $\dot{V}_A/\dot{Q}$ ratio. The result is increased blood flow through these areas (i.e., an increase in shunt or venous admixture).²⁰ Such changes act to worsen arterial hypoxemia. A reduction in arterial PO_2 is not often seen, however, because the simultaneous increase in cardiac output seen with vasodilators increases mixed venous PO_2 . As described in previous arguments (see Figs. 5-1 and 5-6), arterial PO_2 would be increased by this mechanism. The two opposing influences tend to balance, with no net change in arterial oxygenation.²⁰

Despite no change in arterial $[\text{O}_2]$, if cardiac output increases, total O_2 transport (the product of cardiac output and arterial $[\text{O}_2]$) also increases. This increase may be beneficial to cellular O_2 metabolism because it may increase O_2 availability to cells.

Left Ventricular Dysfunction and Lung Fluid Exchange

Another point of interaction among the heart, the lungs, and O_2 transport occurs when left ventricular filling pressures increase for any reason (e.g., myocardial or valvular disease). The potential problem is pulmonary edema. The lungs normally allow a steady flux of water and proteins from the capillaries to the interstitial space. This lymph finds its way in peribronchial lymphatic channels from peripheral to central lung regions and exits the hilum of the lungs in lymph ducts that drain into the superior vena cava. Transcapillary fluid flux is described by the Starling equation:

$$J = K[(P_{MV} - P_{INT}) - \sigma(\Pi_{MV} - \Pi_{INT})] \quad [5]$$

where J is fluid flux across the capillary wall, K is an overall filtration coefficient proportional to permeability and surface area of the microvascular network, and σ is a reflection coefficient for proteins. The latter is 0 when the wall is freely permeable to proteins and 1 when completely impermeable; σ must be low because albumin levels in pulmonary lymph are approximately 70% to 90% of those in capillary plasma.^{30,31} P_{MV} and P_{INT} are intracapillary microvascular and extracapillary interstitial hydrostatic pressures. Π_{MV} and Π_{INT} are the protein osmotic pressures in the same regions.

The equation sums the intracapillary and extracapillary hydrostatic and osmotic forces. The net result is positive¹ so that normally about 0.25 to 1 mL of lymph is transported across the capillary each minute. The lymphatic drainage system can easily handle this load. Its drainage efficiency is increased by one-way valves that make use of the respiratory excursions in intrathoracic pressure to pump lymph from alveoli centrally to the lymph ducts for return to the venous system.

For a structurally normal capillary, microvascular pressures must exceed 25 mm Hg before the rate of fluid movement out of the capillaries exceeds drainage capacity, and edema develops.¹ Normal microvascular pressures are 5 to 10 mm Hg. If capillary permeability is increased by capillary damage in disease, or if plasma protein levels are very low, alveolar edema occurs at pressures much lower than the expected 25 mm Hg.

When left ventricular dysfunction from any cause elevates pulmonary microvascular pressures sufficiently, the stage is set for clinical pulmonary edema, which causes reduced local ventilation, sometimes to the point of abolition of local gas exchange, resulting in areas of low $\dot{V}_A/\dot{Q}$ ratio and shunt. The mechanisms involved may include alveolar wall interstitial edema that reduces alveolar compliance and ventilation; compression of conducting airways, blood vessels, or both by fluid moving centrally as lymph, increasing resistance and decreasing gas or blood flow; or alveolar flooding with edema, abolishing ventilation and gas exchange in these alveoli completely. Left ventricular dysfunction is discussed further elsewhere in this text.

Ventricular Function and Lung Disease

Increasing evidence suggests that primary lung disease causing chronic pulmonary hypertension and resulting in right ventricular hypertrophy impedes left ventricular filling^{32,33}; this is functionally equivalent to increased diastolic stiffness

of the left ventricular wall. Left ventricular filling pressures are increased, and this increase is transmitted back through the pulmonary microvascular bed. As pressure in that bed is increased, transcapillary fluid flux tends to increase, increasing the risk of edema discussed previously. Further retrograde pressure transmission elevates pulmonary artery pressure, worsens the load on the right ventricle, and sets up a potential vicious cycle of events impeding cardiac and pulmonary function.

Although the importance of this mechanism in clinical disease states remains to be determined, there is some evidence of its pertinence to a specific human disorder: high-altitude pulmonary edema.³⁴ Susceptible individuals develop patchy pulmonary edema after rapid ascent and vigorous effort at altitudes of 9000 feet above sea level and higher. Although such individuals are known to have an exaggerated pulmonary vasoconstrictor response to hypoxia,³⁵ they also have higher left ventricular filling pressures (as estimated by pulmonary artery occlusion pressures) during exercise than do subjects resistant to high-altitude pulmonary edema.³⁴ Although this observation may reflect intrinsic variance in left ventricular stiffness per se, it is also compatible with the interdependent ventricular effects described previously, whereby right ventricular hypertension reduces effective left ventricular compliance.

Another type of cardiac complication of lung disease comes from ventilator strategies used in patients on assisted ventilation in the intensive care unit. High respiratory inflation pressures are commonplace to overcome loss of pulmonary compliance as a result of fluid and cell buildup in the alveolar region. Positive airway pressure is also commonly maintained at end-expiration to prevent alveolar collapse. When these strategies overinflate less affected alveoli, their capillaries are stretched and compressed, which increases pulmonary vascular resistance. This increased pulmonary vascular resistance combined with the positive intrathoracic pressures as a result of positive end-expiratory pressure impairs venous return and right and left ventricular function, and cardiac output is reduced, often by surprisingly large amounts.³⁶

Balancing ventilatory strategies to maintain alveolar gas exchange while minimizing undesirable cardiovascular consequences is a classic and difficult problem in management of acutely ill patients, and guidelines are continually being revised for optimal ventilatory care.³⁷ Until the consequences of such strategies on O₂ transport to critical organs including the heart can be assessed accurately, it will be difficult to rationalize the use of a particular approach. As positive end-expiratory pressure is increased, arterial [O₂] may improve as a result of alveolar re-expansion of previously atelectatic regions, but at the cost of diminished cardiac output and organ blood flow.³⁸ O₂ transport, the product of arterial [O₂] and blood flow to each organ, may increase, remain the same, or decrease in ways that are difficult to measure, let alone understand in terms of metabolic consequences. Optimal ventilatory care remains a critical area of clinical and basic research.

Cardiovascular Function and Systemic Gas Exchange

After O₂ exchange between alveolar gas and capillary blood has occurred, oxygenated arterial blood must be transported to the various organs and tissue beds of the body. After reaching the

microvasculature of each bed, O₂ is moved from its intraerythrocytic location bound to Hb through a series of steps to reach intracellular mitochondria.³⁹ Most O₂ taken in at the lungs is used at the mitochondrial level to produce adenosine triphosphate (ATP) for energy and heat needs of the organs.

The O₂ unloading pathway in a typical tissue traverses the following sequential steps.³⁹ First, O₂ must chemically dissociate from the Hb molecule. In vitro studies of this reaction suggest that when a person is at rest, there is sufficient unloading time for this dissociation to proceed to completion, but during intense exercise, this may not be the case. Next, O₂ molecules in solution must diffuse out of the red blood cell, into the microvascular plasma, and through the capillary endothelial wall. The amount of capillary surface area available within an organ is thought to be a critical variable, which under some conditions (e.g., in muscle during exercise, possibly in multiple organ failure in several capillary beds) is a limiting component to the movement of O₂ from red blood cell to mitochondria.^{40,41} The final step for O₂ is intracellular movement to reach mitochondria.

All of these transport steps rely on passive diffusion; there are no active (i.e., energy-requiring) O₂ transport processes. In muscle, intracellular O₂ movement is considered to be uniquely accelerated, however, by the binding of O₂ to myoglobin.^{42,43} This binding of O₂ to myoglobin reduces intracellular Po₂, maintaining a large Po₂ difference between the red blood cell and the muscle cytoplasm, which facilitates O₂ diffusion by Fick's law of diffusion. Myoglobin molecules can move freely in cytoplasm, and this aids O₂ transport further. Because of the great metabolic need for O₂ during exercise, this mechanism is considered important. Without myoglobin, aerobic ATP production might be significantly reduced by the lower O₂ transport rate. Finally, in muscle and other tissues, there may be a high concentration of mitochondria close to the cell wall, particularly near capillaries.³⁹ Whether this association facilitates O₂ movement directly to mitochondria or serves some other purpose, such as to facilitate metabolic clearance of waste products, is unknown.

This basic process of tissue O₂ transport is common to all tissues. Quantitative features depend on individual anatomic factors that determine microvascular richness and diffusion distances. Just as in the lungs, this diffusive system is generally adequate in all organs in normal humans at rest; however, during exercise in healthy states and possibly also in disease states, diffusive conductance may be limited to the point of constraining O₂ flux to the mitochondria and local metabolic rate. Maximal O₂ consumption is determined in part by the finite nature of the overall muscle diffusive conductance between the red blood cells and the mitochondria.⁴⁴ The decrease in maximal $\dot{V}O_2$ with hypoxia and increase in hyperoxia are further compatible with this notion. Behavior of O₂ consumption as O₂ transport to tissues is varied at rest or in disease is also compatible with a limited, finite O₂-diffusing conductance and pathway, although other factors may be responsible (discussed later).

Another important concept in O₂ transport to different organs and within organs is heterogeneity. In an ideal organism, blood flow and O₂ transport to each tissue would be precisely matched to local metabolic need. The organs with more O₂ would generally receive correspondingly more blood flow. Organs with a need for high blood flow based on other functions (e.g., kidney, liver) disrupt this ideal. Consequently, [O₂]

of venous blood from various organs differs in accord with the relationship between O_2 and blood flow ($\dot{Q}$), as Equation 2 would dictate. Even within organs, local heterogeneity may exist such that some regions are overperfused, whereas others are underperfused. Underperfused regions may be unable to achieve their normal metabolic rate because of lack of O_2 , and cellular dysfunction may result.

There is blood flow heterogeneity within all organs. This has been repeatedly shown using tracer (washout or microsphere) studies.^{45,46} This technique and the related method of radioactive tracer washout can measure only the distribution of blood flow, however, *per unit mass of tissue*. No technology is available that can measure regional blood flow in relation to O_2 consumption ($\dot{V}O_2$). Unless local O_2 consumption and local tissue mass are tightly correlated, tracer techniques cannot give us the desired information: how uniform (or nonuniform) is the local $\dot{V}O_2$ -blood flow relation? It is by no means necessary that tissue mass and $\dot{V}O_2$ are closely related. If local $\dot{V}O_2$ depends on O_2 delivery to the region, a close relationship cannot exist; local $\dot{V}O_2$ changes with blood flow, regardless of tissue mass. This is a serious technologic limitation on the understanding of O_2 transport-metabolism heterogeneity. This technologic limitation is partly why clinical application of principles of O_2 transport in the intensive care unit has been frustrating and has not produced improvement in patient care. Only when techniques are developed that assess patients' heterogeneity of $\dot{V}O_2$, blood flow, and cellular metabolism in the critical organs (e.g., brain, heart, kidney, gut) can proper use be made of the theoretical understanding of O_2 transport.

In addition to finite diffusive conductance and heterogeneity, a third physiologic phenomenon may interfere with O_2 transport within organs: the diffusive shunt for O_2 .^{47,48} To the extent that thin-walled precapillary and postcapillary blood vessels containing arterial and venous blood are physically juxtaposed in a tissue bed, there may be some direct diffusive escape of O_2 from the precapillary vessel into the postcapillary vessel. Although the existence of this phenomenon has been shown, its quantitative importance is probably small. Frozen tissue spectroscopy (measuring red blood cell Hb- O_2 saturation) in cross sections of such vessel pairs fails to yield evidence of this, at least in myocardium.⁴⁸

Another factor that can also interfere with O_2 transport out of the microcirculation is anatomic, non-nutritive, vascular arteriovenous connections or shunts.⁴⁹ Although anatomic studies show the existence of such pathways, their functional significance in health, let alone in disease, remains to be firmly established. Mathematical models of O_2 transport⁵⁰ suggest that experimental data are compatible with such shunts, but the key question of whether the same data can also be explained *without* invoking such shunts has not been answered.

With this introduction, the relationship between O_2 transport and O_2 consumption can be discussed. As recently as 1985, in a 600-page book devoted to acute respiratory failure in acute respiratory distress syndrome, less than one paragraph was devoted to this critical topic.⁵¹ In a more recent book on the subject, the area merited an entire chapter⁵²; at more recent international critical care meetings, symposia have regularly addressed the problem, and attempts have been made to tailor clinical care to maximizing O_2 transport.

In the healthy state, variations in total-body O_2 transport ($\dot{Q}O_2$) can be produced by varying cardiac output ($\dot{Q}T$),

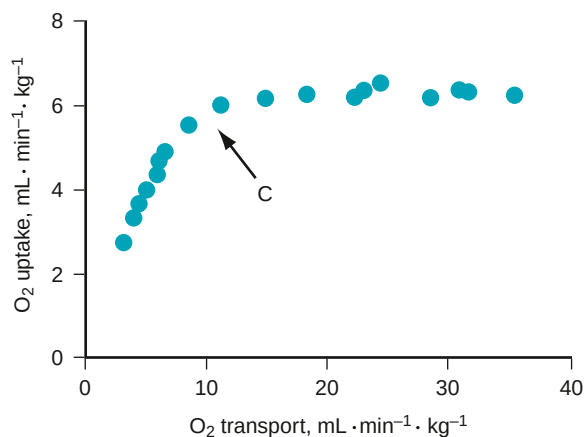


Figure 5-8. Effect of total oxygen transport (cardiac output $\times$ arterial oxygen concentration) on total body oxygen uptake in the anesthetized dog. Above point C, at about $10 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ O_2 transport, oxygen uptake is essentially independent of oxygen transport. To the left of point C, oxygen uptake falls toward the origin almost in proportion to reduced O_2 transport.

Hb concentration ($[Hb]$), or arterial O_2 saturation (SaO_2). $\dot{Q}O_2$ is essentially the product of these three variables:

$$\dot{Q}O_2 = k \cdot \dot{Q}T \cdot [Hb] \cdot SaO_2 \quad [6]$$

where k is the stoichiometric binding constant for O_2 and Hb; it is the number of milliliters of O_2 that can be bound by 1 g of Hb. Theoretically, k is 1.39, but it may be only 1.34 in practice because of small amounts of methemoglobin or carboxyhemoglobin. Equation 6 ignores the normally insignificant amounts of physically dissolved O_2 in the blood, which amount to only 1.5% of total arterial $[O_2]$ in healthy individuals.

When in normal animals $\dot{Q}O_2$ is varied over a reasonable range by manipulating $\dot{Q}T$, $[Hb]$, or SaO_2 , total-body O_2 consumption ($\dot{V}O_2$) is usually found to be constant (i.e., independent of $\dot{Q}O_2$). As $\dot{Q}O_2$ is reduced further, however, $\dot{V}O_2$ begins to decrease, and when $\dot{V}O_2$ is plotted against $\dot{Q}O_2$, the decreasing relation is essentially linear and heads toward the origin. Figure 5-8 shows an example of this pattern in a normal dog.⁵³ The biphasic $\dot{V}O_2$ - $\dot{Q}O_2$ relation shown in Figure 5-8 exemplifies the flat region of the curve where $\dot{V}O_2$ is not dependent on $\dot{Q}O_2$, and the portion at low $\dot{Q}O_2$ where, as $\dot{Q}O_2$ decreases, so does whole-body $\dot{Q}O_2$.

Figure 5-8 is from well-controlled studies in which, as a result of constant body temperature, muscle paralysis, and mechanical ventilation, overall cellular metabolic need for O_2 can reasonably be assumed to be constant. Under such conditions, the approximate (and difficult to identify precisely) junction (see point C in Fig. 5-8) of the independent and dependent portions of the curve is termed the *critical point*, and the associated $\dot{Q}O_2$ is termed the *critical O_2 transport (or delivery) value*. In the literature, DO_2 is often used instead of O_2 . The accepted interpretation of the dependent region (below point C in Fig. 5-8) is that mitochondrial O_2 supply has been reduced sufficiently by the severe reduction in $\dot{Q}O_2$ that mitochondrial O_2 needs cannot be fully met. As a result, $\dot{V}O_2$ decreases. A key observation is that at and below the critical point, mixed venous PO_2 has *not* fallen to zero. An apparent paradox exists: a decrease in $\dot{V}O_2$, yet failure to extract all of the O_2 out of the blood, which, had that been

possible, would have at least maintained $\dot{V}O_2$ down to a lower value of $\dot{Q}O_2$. It is therefore concluded that there is a physical limit to O_2 transport between blood and mitochondria.

Two competing but not mutually exclusive hypotheses based on reduced O_2 supply have been advanced to explain $\dot{V}O_2$ dependency on $\dot{Q}O_2$.⁵⁴ The first is heterogeneity. As the transport of O_2 molecules into the arterial tree is progressively reduced, but above the critical point C (see Fig. 5.8), sufficient O_2 flux to every organ exists. The system simply extracts the same amount of O_2 per unit time from a diminishing arterial supply, in concert with mass balance principles (see Equation 2), resulting in a mixed venous $[O_2]$ that decreases progressively with $\dot{Q}O_2$. Below the critical point, O_2 extraction no longer can be maintained because as a result of complex regulatory processes controlling blood flow between and within organs, some organs or cells within organs are deprived of flow and O_2 , to ensure survival of more critical organs and cells.

The second possibility is that tissue O_2 diffusive conductance, in excess above the critical point, is insufficient to move O_2 molecules from the tissue microvascular red blood cells to the mitochondria.⁵⁵ This is not because O_2 diffusive conductance suddenly decreases when $\dot{Q}O_2$ is reduced below the critical value, but because O_2 flux from red blood cells to mitochondria by diffusion depends on the product of the diffusive conductance, DO_2 , and the PO_2 difference between the red blood cells (P_{RBC}) and the mitochondria (P_{MITO}) according to Fick's law of diffusion:

$$\dot{V}O_2 = DO_2 [P_{RBC} - P_{MITO}] \quad [7]$$

Above the critical point, P_{RBC} and P_{MITO} are much greater than zero, or the minimal mitochondrial PO_2 necessary to sustain mitochondrial respiration (about 0.5 mm Hg according to in vitro studies). At the critical point, with no change in DO_2 implied, P_{RBC} and P_{MITO} have decreased as $\dot{Q}O_2$ is reduced and venous PO_2 decreases (discussed previously), and P_{MITO} has reached the critical mitochondrial value (0.5 mm Hg) for sustaining mitochondrial O_2 . As $\dot{Q}O_2$ is reduced below the critical value, P_{RBC} decreases even further; P_{MITO} cannot be sustained, and $\dot{V}O_2$ must decrease as a result of mitochondrial O_2 supply limitation. Both hypotheses could be simultaneously correct and interactive; more research is needed to clarify these and any other possibilities.

A third possible factor should be mentioned. Rather than $\dot{V}O_2$ passively decreasing as a result of limited O_2 supply from either heterogeneity or diffusion limitation, intracellular sensors of O_2 could mediate a protective reduction in metabolic O_2 requirements. An example is the behavior of renal $\dot{V}O_2$ as renal blood flow is reduced.⁵⁶ Because most of renal O_2 consumption goes into active Na^+Cl^- reabsorption from tubular fluid, and the salt load depends on glomerular filtration and on blood flow, renal $\dot{V}O_2$ decreases with renal blood flow and with renal $\dot{Q}O_2$ because the metabolic demands on the kidney decrease. This is a special case and mechanism, and is not thought to reflect behavior of the other organ systems.

The preceding has not differentiated among the three possible means of reducing $\dot{Q}O_2$ mentioned at the outset: manipulating blood flow, [Hb], or SaO_2 . Classic studies comparing these strategies have revealed that reducing SaO_2 or [Hb] produces the same critical point C (see Fig. 5-8) when expressed as the value of $\dot{Q}O_2$ at which $\dot{V}O_2$ begins to decrease.⁵⁷ $\dot{V}O_2$ begins to decline at a higher venous PO_2 , however, when O_2 transport is reduced

by anemia rather than by hypoxia. This action is consistent with an effect of anemia reducing the O_2 diffusional conductance, much as is the case for O_2 diffusing capacity and [Hb] in the lungs, requiring a higher driving pressure (see Equation 7) to maintain $\dot{V}O_2$. Support for this idea comes from exercise studies of maximal $\dot{V}O_2$ as [Hb] is changed, showing [Hb] dependence of muscle O_2 diffusional conductance.^{58,59}

To this point, only whole-organism data have been described, but it is important to explore the $\dot{V}O_2 - \dot{Q}O_2$ relationship in individual organ systems. Similar biphasic $\dot{V}O_2 - \dot{Q}O_2$ curves have been found in several organ systems: skeletal muscle,⁶⁰ liver,⁶¹ and intestine.⁶² Although critical values of organ $\dot{Q}O_2$ may be different, the research conditions under which they have been measured are difficult to compare, and to a rough approximation, the whole-body data seem to reflect these individual organ results reasonably. The implication is that to the extent that heterogeneity of O_2 transport is important to the $\dot{V}O_2 - \dot{Q}O_2$ relationship, this is likely to be based more on intraorgan than interorgan differences in O_2 flow; however, this area needs more investigation.

It seems that when $\dot{V}O_2$ is O_2 supply-dependent (below point C; see Fig. 5-8), cellular metabolism and integrity are threatened. The physician's natural therapeutic reaction would be to increase $\dot{Q}O_2$ by manipulating blood flow or [Hb] or arterial O_2 saturation, and this reaction has found its way into the critical care arena. This is not a trivial undertaking; of the three components of $\dot{Q}O_2$ potentially subject to manipulation, arterial O_2 saturation is of limited availability in most critically ill patients because of their lung disease. Hyperoxia provides only a small improvement in O_2 saturation, and renders the lungs vulnerable to O_2 toxicity. Shunt reduction by ventilating the lungs with high pressures reduces cardiac output and may offset the gains in O_2 saturation. Increasing [Hb] may produce viral contamination of blood; as [Hb] is increased, cardiac output may decline, also offsetting the gains in overall $\dot{Q}O_2$. This leaves enhancing cardiac output as the remaining major possibility. The hearts in such patients are usually already under stress and pumping two to three times the usual resting volume per minute in response to the high tissue metabolic needs associated with tissue repair and fever.⁶³

Cardiac function may be impaired by high respiratory pressures (discussed previously); the myocardium may be damaged by the systemic disease processes of critically ill patients (e.g., patients with acute respiratory distress syndrome); and coronary blood flow may be compromised as a result of prior coronary artery disease or aggressive ventilator strategies. Encouraging greater cardiac function with various inotropic or sympathomimetic agents (e.g., dopamine, dobutamine) carries significant risk under these circumstances and cannot be universally recommended until the physicochemical basis of O_2 supply dependency of $\dot{V}O_2$ in these patients is fully understood.

There are two additional significant caveats to the entire $\dot{V}O_2 - \dot{Q}O_2$ issue. The first is delineating signal from noise. $\dot{V}O_2$ is the product of blood flow and arteriovenous $[O_2]$ difference, whereas $\dot{Q}O_2$ is the product of blood flow and arterial $[O_2]$. Unless $\dot{V}O_2$ and $\dot{Q}O_2$ are measured by technically independent techniques, there is major covariance between $\dot{Q}O_2$ and $\dot{V}O_2$ as a result of the use of blood flow and arterial $[O_2]$ in $\dot{V}O_2$ and $\dot{Q}O_2$. Measurement errors in blood flow and arterial $[O_2]$ must give an apparent correlation between $\dot{V}O_2$ and $\dot{Q}O_2$ (i.e., data compatible with O_2 supply dependency)⁶⁴; however, this

would be clearly a false-positive outcome. This issue is particularly a problem for sequential measurements in a given individual. This problem also occurs in comparing patients of different size or $\dot{V}O_2$ on a plot of $\dot{V}O_2$ versus $\dot{Q}O_2$; a small patient generally shows lower values for both variables than a large patient. Normalization for body size must be performed before interpretation. Cross-sectional surveys of single datum points from many subjects may not be particularly useful in understanding the phenomenon further. Before accepting data supporting a dependency of $\dot{V}O_2$ on $\dot{Q}O_2$, it is essential to ensure that appropriate methods and statistical treatment of the data have excluded false-positive correlations between $\dot{V}O_2$ and $\dot{Q}O_2$.^{40,41}

The second difficulty in understanding the $\dot{V}O_2 - \dot{Q}O_2$ relationship is a physiologic one. In the preceding discussion, it is assumed that cellular O_2 requirements are constant as $\dot{Q}O_2$ is manipulated by the investigator. This requirement is obvious; if a patient is studied first while skeletal muscles are active and then again when paralyzed by a muscle relaxant and on a ventilator, total-body O_2 requirements would be reduced. Just as during normal exercise, O_2 transport, cardiac output in particular, is regulated by O_2 requirements. In the previous comparison, $\dot{V}O_2$ and $\dot{Q}O_2$ would be greater before paralysis, and a $\dot{V}O_2 - \dot{Q}O_2$ plot would suggest O_2 supply dependence of $\dot{V}O_2$. It is critical to understand the difference; a change in $\dot{V}O_2$ caused by a change in $\dot{Q}O_2$ constitutes true O_2 supply dependence of $\dot{V}O_2$, whereas a change in activity of cells or tissues requiring more O_2 is generally reflected by an increase in $\dot{Q}O_2$ to meet these needs.⁵⁶ This is an appropriate response that should not be regarded as O_2 supply dependence of $\dot{V}O_2$ in the previous context; yet, on a diagram relating $\dot{V}O_2$ and $\dot{Q}O_2$, both scenarios look the same.

In critically ill patients, $\dot{V}O_2$ is sometimes found to vary with O_2 transport ($\dot{Q}O_2$) under conditions and at $\dot{Q}O_2$ levels that would not produce changes in $\dot{V}O_2$ in health. The physician must first ensure these changes are real and not the result of covariance and errors. The physician must ascertain, if possible, whether the relationship is driven by a change in O_2 requirement (i.e., false O_2 supply-dependent relationship) or a change in O_2 availability (i.e., true O_2 supply-dependent relationship). Only if the latter is established can the physician begin to consider the pros and cons of manipulating O_2 transport variables; however, even then, options are limited, as previously explained. Because the various intraorgan relationships between cellular metabolic normalcy and O_2 supply in critically ill patients is poorly understood, it is likely to be some time before the necessary technologies are developed to allow physicians to make rational use of these undoubtedly important concepts.

Mixed venous O_2 saturation ($S\bar{v}O_2$) may be used in assessing cardiovascular sufficiency in critically ill patients.⁶⁵ The attractiveness of continuous, accurate, real-time measurements of $S\bar{v}O_2$ using a Swan-Ganz catheter with fiberoptics allowing external spectrophotometric determination of Hb saturation has brought this issue into prominence. A rearrangement of Equation 2 and the previous discussion provide a rational basis for interpretation of $S\bar{v}O_2$. Because

$$\dot{V}O_2 = \dot{Q}T[CaO_2 - C\bar{v}O_2] \quad [2]$$

the right side can be re-expressed so that:

$$\dot{V}O_2 = 1.34 \cdot \dot{Q} \cdot [Hb] \cdot [SaO_2 - S\bar{v}O_2] \quad [8]$$

This transformation assumes negligible contribution of dissolved O_2 (see Equation 6). By rearrangement of Equation 8:

$$S\bar{v}O_2 = SaO_2 - \dot{V}O_2 / [1.34 \cdot [Hb] \cdot \dot{Q}T] \quad [9]$$

Provided that arterial saturation (SaO_2), $\dot{V}O_2$, and $[Hb]$ remain constant, a decrease in $S\bar{v}O_2$ indicates a decrease in $\dot{Q}T$, and this can be useful as a cardiac output monitor. A decrease in SaO_2 or $[Hb]$ or an increase in $\dot{V}O_2$ also reduces $S\bar{v}O_2$; these variables must be assessed independently to interpret $S\bar{v}O_2$. An increase in $S\bar{v}O_2$ can occur from an increase in cardiac output, but is also seen if, as a result of peripheral tissue heterogeneity, O_2 diffusion limitation, or both, $\dot{V}O_2$ was reduced. Therapeutically beneficial and harmful phenomena can move $S\bar{v}O_2$ in the same direction, obscuring interpretation of $S\bar{v}O_2$. A further transformation of Equation 9 yields:

$$S\bar{v}O_2 = SaO_2 [1 - \dot{V}O_2 / \dot{Q}O_2] \quad [10]$$

Looking at Figure 5-8, it would be expected that along the flat portion of the relation, above the critical point C, $S\bar{v}O_2$ must decrease as $\dot{V}O_2$ stays constant while $\dot{Q}O_2$ is reduced; this is clear from Equation 10. Below the critical point C, if the $\dot{V}O_2 - \dot{Q}O_2$ relation is truly a straight line passing through or near the origin, the ratio $\dot{V}O_2 / \dot{Q}O_2$ may be essentially constant while $\dot{V}O_2$ and $\dot{Q}O_2$ are decreasing. If SaO_2 is constant under such conditions, $S\bar{v}O_2$ also is constant. It is possible that under the very conditions the physician wants to identify (i.e., O_2 supply dependency of $\dot{V}O_2$), $S\bar{v}O_2$ could be essentially constant and obscure the presence of the presumed cellular metabolic derangement.

Monitoring of $S\bar{v}O_2$ alone yields data that are open to many interpretations that could have either beneficial or deleterious implications.⁶⁵ Without measures of all the determinants of $S\bar{v}O_2$ (i.e., SaO_2 , $\dot{V}O_2$, $[Hb]$, and cardiac output), unique interpretation is impossible. This conclusion is clouded further by the obvious fact that $S\bar{v}O_2$ is mixed venous O_2 saturation, and its relationship to oxygenation of individual critical organs is, as discussed previously, a major unknown in critically ill patients. $S\bar{v}O_2$ reflects PO_2 of the venous blood, not of the intracellular environment. When O_2 transport between blood and mitochondria is compromised in disease, venous PO_2 is likely to exceed PO_2 at the mitochondria considerably. This situation is analogous to lung disease, in which alveolar PO_2 can greatly exceed arterial PO_2 ; the alveolar value is not used as an index of arterial PO_2 in this setting because they move in opposite directions as disease worsens.

The medical community has a long way to go before a clear understanding of the role of the cardiovascular system in O_2 transport in critically ill patients can be obtained. Technologic advances in assessing cellular metabolic function in critical organs in the context of O_2 supply and at a level that can assess functional heterogeneity within and between organs are the key to success in this regard.

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Regulation of Cardiac Output

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CHAPTER

6

Arteriovenous Oxygen Difference
Reflex Control of Cardiac Output
Left Ventricular Performance
End-Systolic Pressure-Volume Relationship

Application of the Pressure-Volume Approach
to Pathologic Conditions
Limitation of the Pressure-Volume Approach
Conclusion

THE CARDIOVASCULAR system supplies the tissues with oxygen and metabolic substrates and removes carbon dioxide and other waste products. The integration of all its components (venous circulation, right heart, lungs and pulmonary vascular system, and left heart and arterial circulation) results in the cardiac output.

The cardiac output is readily measured in the clinical setting using indicator dilution techniques. A common approach is to inject a cold solution into the right atrium, and measure the resulting blood temperature transient by using a thermistor on the tip of a catheter positioned in the pulmonary artery. An alternative approach is to measure cardiac output using the Fick principle. The rate of oxygen consumption of the patient is measured by collection of expired gases or, less accurately, assumed using a standard nomogram based on the patient's height, weight, and age. The difference in arterial and pulmonary venous oxygen content (A-VO₂ difference) is measured. Cardiac output is calculated as:

$$\text{Cardiac output} = \text{O}_2 \text{ consumption} / \text{A-VO}_2 \text{ difference} \quad [1]$$

Cardiac output is usually normalized for body surface area and expressed as the cardiac index. The normal range for the cardiac index at rest is wide, 2.5 to 4.2 L/min/m², and cardiac output can decline by almost 40% without deviating from normal limits. A low cardiac index of less than 2.5 L/min/m² usually indicates a marked disturbance in cardiovascular performance and is almost always clinically apparent. Although the resting cardiac output or index is an insensitive measure of cardiovascular performance, it is clinically valuable in critically ill patients.

Arteriovenous Oxygen Difference

The provision of adequate tissue oxygenation depends on the integrated function of the heart, peripheral and pulmonary vasculature, lungs, blood, and peripheral metabolism.¹ According to the Fick principle, the oxygen consumed by the body is equal to the product of the cardiac output and the A-VO₂ difference. Under normal circumstances at rest, oxygen delivery exceeds consumption, so that adequate tissue oxygenation is provided with an A-VO₂ difference of 40 ± 10 mL/L. If arterial oxygen tension and serum hemoglobin are normal, this results

in a mixed venous oxygen saturation of 70% or more. If cardiac output decreases, the tissues extract a greater fraction of oxygen from the arterial blood, and mixed venous oxygen saturation decreases. A mixed venous oxygen saturation of 70% or more indicates that oxygen delivery and cardiac output are sufficient to meet the needs of the body.²

A wide A-VO₂ difference and reduced mixed venous oxygen saturation may result from an abnormality of cardiovascular function that has resulted in a reduced cardiac output, a defect in blood oxygen-carrying capacity, or pulmonary disease. When the ability of the tissue to increase its extraction of oxygen is exhausted, tissue hypoxia results. In these conditions, anaerobic metabolism is heralded by a precipitous increase in venous lactate levels.³

During exercise, oxygen consumption can increase 18-fold. This increase in O₂ demand is met partly by an increase in cardiac output up to sixfold (from 3 to 18 L/min/m²), and partly by a threefold increase in the A-VO₂ difference (from 40 to 120 mL/L), with a decrease in mixed venous oxygen saturation from 75% to 25%.

The myocardium nearly maximally extracts oxygen from blood at rest. The coronary sinus oxygen saturation is low (<40%), and the myocardium cannot use an increase in oxygen extraction as a compensatory mechanism for inadequate coronary flow.

Reflex Control of Cardiac Output

Under normal conditions, the heart has a large functional reserve; it is not the limiting factor in determining cardiac output. The arterial (perfusion) pressure and the cardiac output are adjusted to meet the needs of the body as they vary with posture and activity. The regulatory mechanisms involve sensory and effector components. The sensory components include peripheral receptors that react to changes in blood pressure (e.g., baroreceptors in aortic arch and carotid sinuses), blood volume (e.g., stretch receptors in the atria, Bainbridge reflex), and ventilation (e.g., carotid chemoreceptors). In addition there are loci in the cortex, hypothalamus, and diencephalon of the brain that react to emotions, anxiety, anticipation, exercise, hypoxia, and temperature. Cardiac output is modulated through changes in heart rate, stroke volume, and vasomotor tone that are mediated by

direct parasympathetic and sympathetic neural pathways and by circulating catecholamines. Other humoral factors, such as adrenocortical steroids, thyroid hormones, insulin, and glucagons, have been shown to have an effect on cardiac function, but the importance of these hormones for regulation of cardiac output is unclear.

Direct sympathetic neural stimulation and circulating catecholamines exert a powerful stimulatory effect, increasing heart rate and contractile state, whereas vagal stimulation results in a decrease in heart rate and contractile state. The sympathetic and parasympathetic systems interact with each other in a complex fashion to influence cardiovascular performance. Generally, two types of interactions exist: accentuated antagonism and reciprocal excitation.⁴ Accentuated antagonism refers to the finding that the negative inotropic and chronotropic effects of vagal stimulation are more pronounced when vagal stimulation occurs in the presence of an increased adrenergic tone. Reciprocal excitation refers to the paradoxical effects of stimulation by one division on the autonomic nervous system, which results in effects normally expected from stimulation by the opposite autonomic division. The most common example of this is the production of positive inotropic effects by vagal stimulation or acetylcholine administration under experimental conditions.⁴

The factors that help regulate cardiac output are summarized in Table 6-1. The regulation system of cardiac output can become dysfunctional and result in syncope as a result of enhanced atrial and peripheral baroreceptor sensitivity, autonomic dysfunction, or complete heart block. In a critically ill cardiac patient, the normal regulatory mechanisms are usually saturated by maximal sympathetic and catecholamine stimulation. Under these conditions, the major determinants of cardiac output are no longer the neurohormonal pathways that regulate the normal cardiovascular system, but rather the interaction between the heart and the peripheral vasculature. The mechanical determinants of ventricular pump function are of paramount importance.

Table 6-1. Factors That Influence Cardiac Output

	Effects
Sympathetic tone	↑ contractile state, ↑ heart rate
Vagal tone	↓ contractile state
Right vagus	↓ sinus node activity, sinus bradycardia
Left vagus	↓ atrioventricular conduction
Volume load	↑ heart rate (Bainbridge reflex)
Baroreceptor stimulation (aortic arch, carotid sinus)	↓ contractile state
Calcium administration	↑ contractile state
Hormones (epinephrine, glucagon, thyroxine)	↑ contractile state, ↑ heart rate
Drugs	
Positive inotropes	
Phosphodiesterase inhibitors (milrinone, amrinone, theophylline)	↑ contractile state, ↑ heart rate
Digitalis glycosides	↑ contractile state, ↓ atrio- ventricular conduction
Adrenergic stimulants (dopamine, dobutamine)	↑ contractile state, ↑ heart rate
Negative inotropes	
β-adrenergic antagonists	↓ contractile state, ↓ heart rate
Calcium channel blockers	↓ contractile state, ↓ atrio- ventricular conduction

Left Ventricular Performance

Pressure-Volume Loop

Although the integrity of left ventricular and right ventricular function and pulmonary and peripheral circulations is important, most cardiovascular dysfunction in adults is the result of impaired left ventricular function. The performance of the left ventricle can be understood by examining the relationship between left ventricular pressure and volume during a single beat in the pressure-volume plane (Fig. 6-1). Instantaneous intraventricular pressure is plotted on the *y* axis, and instantaneous ventricular volume is plotted on the *x* axis. At end-diastole (point *a*), ventricular pressure is relatively low, and ventricular volume is relatively high. The segment *ab* represents isovolumic contraction, with an increase in intraventricular pressure, but no ejection. Point *b* represents the start of ejection, coincident with the opening of the aortic valve when ventricular pressure exceeds aortic pressure. At end-systole (point *c*), the aortic valve closes, and a period of isovolumic relaxation commences (segment *cd*). The mitral valve opens at point *d*, when ventricular pressure decreases to less than atrial pressure, and ventricular filling commences.

The difference between the end-diastolic and end-systolic volumes represents the volume ejected in that beat (stroke volume), and the ratio of stroke volume to end-diastolic volume

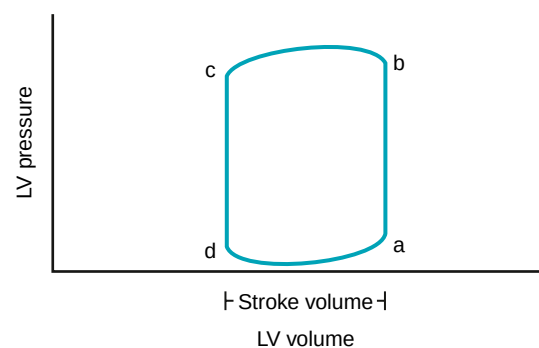


Figure 6-1. For a single cardiac cycle, instantaneous left ventricular (LV) pressure is plotted against LV volume. Point *a* represents end-diastole and the start of isovolumic contraction. Ventricular pressure increases without any change in volume until ejection starts at point *b*, which represents the opening of the aortic valve. During ejection, ventricular volume decreases. Point *c* represents end-systole and the start of isovolumic relaxation. Aortic valve closure occurs near end-systole. Ventricular pressure continues to decrease until ventricular filling starts with the opening of the mitral valve at point *d*. Ventricular pressure increases very slightly during diastolic filling.

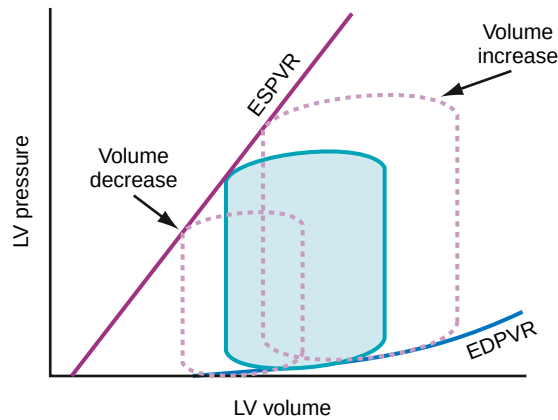


Figure 6-2. Three different pressure-volume (PV) loops are shown representing beats at three different preloads. Control conditions are represented by the shaded PV loop. An increase in preload (e.g., a large volume load) is associated with an increase in diastolic filling and a shift in the end-systolic PV point to the left. The added stretch causes a stronger contraction and an increase in the pressure developed during systole and in stroke volume. The PV loop is larger and shifted to the right (*broken lines*). Conversely, a decrease in preload, such as a loss of blood volume, results in a smaller PV loop which is shifted to the left (*broken lines*). The end-systolic points of the three variably loaded beats fall on a straight line. This line represents the end-systolic pressure-volume relationship (ESPVR). A similar but curvilinear relationship is formed by the end-diastolic PV points—the end-diastolic pressure-volume relationship (EDPVR).

is the ejection fraction. In the absence of aortic stenosis, the ventricular pressure at end-systole is the same as the pressure in the proximal aorta, and approximates systolic blood pressure (actually the pressure at the diastolic notch in the aortic pressure-time course). Cardiac output is the product of stroke volume and heart rate. The pressure-volume loop provides a useful way to analyze the effects of contractile state, preload, and afterload on cardiac output.

Effect of Alterations in Preload on the Pressure-Volume Loop

Preload is defined as the stretch of the myocardium before activation and is readily indexed by end-diastolic volume. Within physiologic ranges, the greater the stretch on the myocardium, the stronger the ensuing contraction; this is known as the Frank-Starling relationship.⁵ From studies in isolated heart preparations in which preload, afterload, and contractile state were controlled, it has been shown that an increase in preload, produced by an increase in end-diastolic volume, results in an increase in the end-systolic pressure and the stroke volume of the ensuing beat.⁶⁻⁸

Three pressure-volume loops under three different preload conditions are shown in Figure 6-2. For the purpose of illustration, it is assumed that heart rate, contractile state, and afterload remain constant. Baseline conditions are represented by the shaded loop. A decrease in preload as a result of loss of blood volume, if not associated with any other change in afterload or contractile state, results in a smaller end-diastolic volume and a smaller pressure-volume loop that is shifted to the left. Conversely, a volume load results in a larger pressure-volume loop that is shifted to the right. An isolated increase in preload without any change in afterload or contractile state results in increases

in stroke volume and end-systolic pressure if heart rate, afterload, and contractile state are unchanged. These conditions do not apply precisely in vivo. Isolated changes in preload, afterload, contractile state, or heart rate occur rarely because these changes are usually a response to, or in themselves result in, compensatory neurohormonal reflexes, which influence all these variables in a complex fashion. It may be useful, however, for an understanding of cardiovascular dynamics to analyze these factors separately.

End-Systolic Pressure-Volume Relationship

In Figure 6-2, the end-systolic points of all three pressure-volume loops fall on a straight line. This line is termed the *end-systolic pressure-volume relationship* (ESPVR) and is constant for a given contractile state.⁹ A similar but nonlinear relationship can be constructed for the end-diastolic points—the end-diastolic pressure-volume relationship (EDPVR). The ESPVR and EDPVR have been shown to be relatively load independent at a given contractile state^{10,11}; however, the ESPVR is not absolutely load independent, probably because of the positive and negative inotropic effects of ejection.¹²⁻¹⁴ For practical purposes, at a given contractile state, the cardiac pressure-volume loop is always bound by the ESPVR and the EDPVR. For a given contractile state, the ESPVR can conveniently be expressed as follows (see Fig. 6-2):

$$P_{es} = E_{es} (V_{es} - V_o) \quad [2]$$

where P_{es} is end-systolic pressure, V_{es} is end-systolic volume, V_o is the volume axis intercept, and E_{es} is the slope of the ESPVR.^{6,9,15} Because of its relative load independence, E_{es} has been proposed as an index of contractile state.⁹ V_o represents the volume at which the ventricle can no longer generate force. This dead volume is a function of heart size. A smaller heart can contract down to a smaller volume than a large heart.

Effect of Changes in Contractile State

The contractile state of the heart refers to the intrinsic ability of the myocardium at a given load to generate force during contraction. Myocardial contractile state is influenced by several endogenous and exogenous factors (see Table 6-1). In the pressure-volume plane, an increase in myocardial contractile state results in an increase in force development at any given ventricular volume. Conversely, the “dead volume” of the ventricle is unchanged because heart size has not changed. These changes manifest in the pressure-volume plane as an increase in the slope of the ESPVR without a change in V_o .⁹ In Figure 6-3, preload, afterload, and heart rate are assumed to be constant. Under these conditions, an increase in contractile state results in an increase in stroke volume and end-systolic pressure. Conversely, in the absence of any compensatory mechanisms, a reduction in myocardial contractility results in a reduction in systolic pressure and stroke volume. Some common compensatory mechanisms are discussed later; first, the effect of changes in afterload must be considered.

Effect of Changes in Afterload

Afterload is the load the ventricle must overcome to eject volume, and, in the absence of valve disease, is determined mainly by the properties of the arterial system. An increase in afterload results in an increase in end-systolic pressure at the expense of ejection.

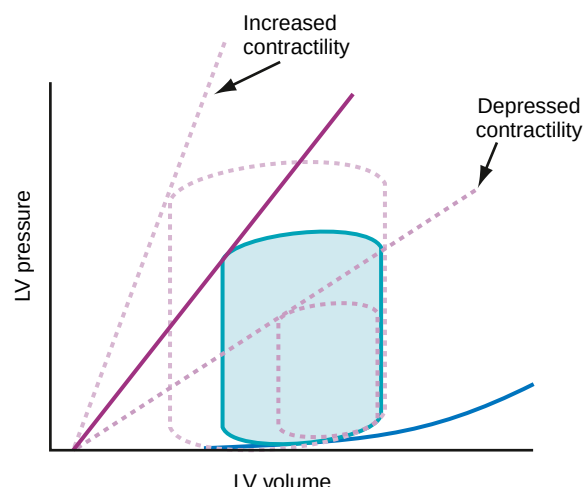


Figure 6-3. The effect of an increase in contractile state on the pressure-volume loop and the end-systolic pressure-volume relationship is shown.

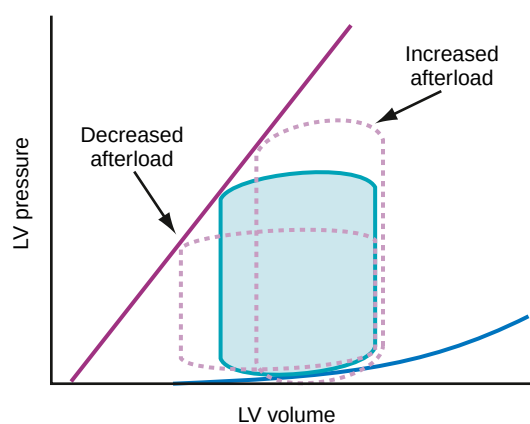


Figure 6-4. The effect of changes in afterload is shown in three beats at different afterloads. An increase in afterload results in an increase in end-systolic pressure, but a decrease in stroke volume. A decrease in afterload has opposite effects. The end-systolic pressure-volume points do not deviate significantly from the end-systolic pressure-volume relationship (ESPVR). The ESPVR is insensitive to changes in afterload.

The effect on the pressure-volume loop is shown schematically in Figure 6-4. Stroke volume, ejection fraction, and, assuming no change in heart rate, cardiac output are decreased despite a constant contractile state. This is a good illustration of the load dependence and limitations of cardiac output and ejection fraction as clinical indices of contractile state. As shown in Figure 6-4, an increase in afterload, without a change in contractile state, results in changes in the shape of the pressure-volume relationship, but the end-systolic points do not deviate significantly from the ESPVR. This is an idealized figure; as stated previously, the end-systolic points are load dependent,^{12,14} but a simplified view suffices for illustration and allows the conceptual expression of the interaction between left ventricular function and the arterial system.

To understand ventriculoarterial coupling, it is useful to view the arterial system also in terms of pressure-volume or pressure-stroke volume relationships, as proposed by Sunagawa

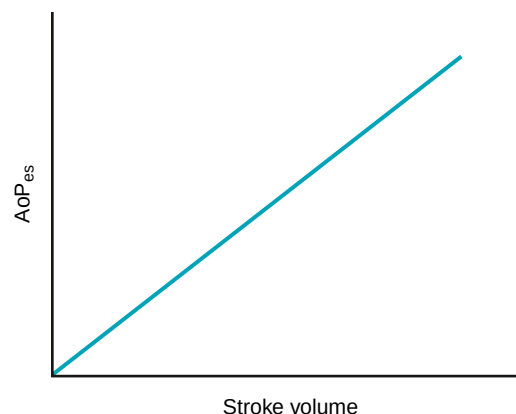


Figure 6-5. The systolic pressure-volume relationship of the arterial system. The volume of this system at any given time is a function of the stroke volume, which determines the volume increase during systole, and of the vascular resistance to blood flow out of the arterial system and into the venous system. The change in pressure for a given change in volume is a function of the effective compliance of the arterial system. For a given cardiac cycle and assuming constant afterload, aortic end-systolic pressure (AoP_{es}) is linearly related to stroke volume. The slope of this relationship is termed the arterial elastance (E_a) and is an index of afterload.

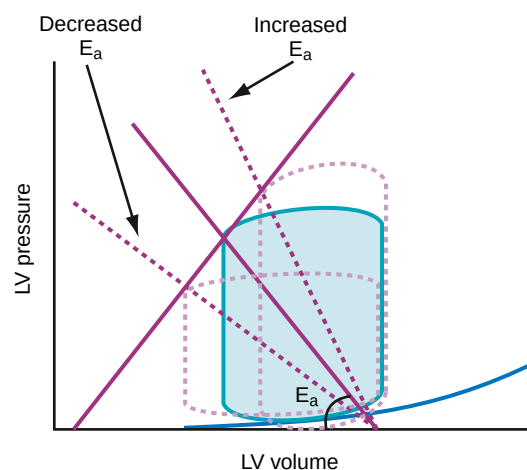


Figure 6-6. The arterial elastance (end-systolic pressure divided by stroke volume) is superimposed on the pressure-volume loops for three variably afterload beats. An increase in afterload is represented by an increase in the slope of the arterial elastance (E_a).

and colleagues.¹⁶ In this study, the relationship between stroke volume and arterial end-systolic pressure is linear, and it is assumed that the relationship passes through the origin (Fig. 6-5). The slope of this relationship is termed the *arterial elastance* (E_a), and is the end-systolic pressure divided by the stroke volume. E_a can be expressed in the ventricular pressure-volume plane (Fig. 6-6). E_a is represented by the slope of a line connecting end-diastolic volume on the volume axis and the upper left corner of the pressure-volume loop. This approach is simplified and not absolutely correct because the arterial pressure-volume relationship probably does not truly pass through the origin.¹⁷ The concept of arterial elastance and the ESPVR can be used, however, to predict analytically the effect of changes in afterload on end-systolic pressure and cardiac output.

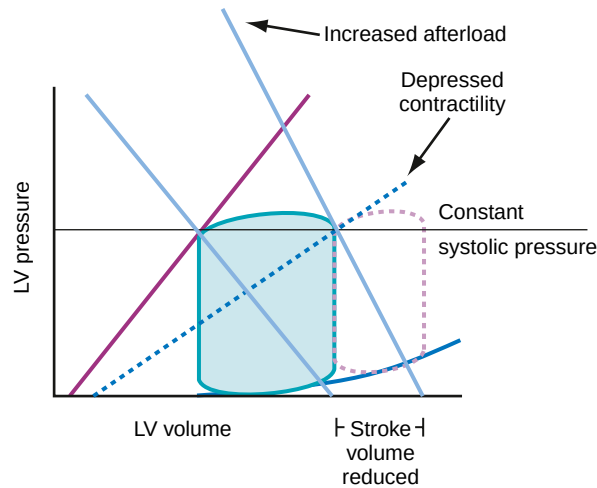


Figure 6-7. Acute myocardial infarction results in a reduction in contractile state owing to a loss of muscle mass. This results in a decrease in the slope of the end-systolic pressure-volume relationship (ESPVR). The volume axis intercept (V_0) increases by the theoretical volume enclosed by the dead muscle, shifting the ESPVR to the right. Compensatory mechanisms result in an increase in end-diastolic volume and afterload. These changes result in a reduction in stroke volume and an increase in filling pressures.

Application of the Pressure-Volume Approach to Pathologic Conditions

Acute Systolic Dysfunction

The framework of the pressure-volume approach as described previously allows the conceptualization of the interaction among cardiac function, preload, and afterload. Figure 6-7 represents a hypothetical situation in a patient with an acute myocardial infarction. Acute myocardial infarction results in the loss of a segment of functioning myocardium, while the rest of the heart is preserved. Assuming for simplicity that ischemia or neurohormonal stimuli do not alter the contractile state of the surviving myocardium, the ventricle can be modeled as two compartments: one with a normal ESPVR and one with an ESPVR that approximates the EDPVR.¹⁸ The combined effect is to reduce the slope of the ESPVR (E_{es}), representing a reduction in overall myocardial contractility, and an increase in the volume intercept (V_0). The increase in V_0 represents the contribution of the volume of the nonfunctioning segment of the ventricle to the “dead volume.”

As a result of these changes, the heart is able to maintain an adequate systemic perfusion pressure, but at the expense of an increase in end-diastolic volume and end-diastolic pressure. The increases in end-diastolic volume and pressure are mediated by neurohormonal reflexes, which result in fluid retention and an increase in vascular resistance. The increase in vascular resistance is reflected in the pressure-volume plane as an increase in arterial elastance (E_a). The clinical syndrome of heart failure as a result of acute systolic dysfunction results from the increase in end-diastolic filling pressure, which causes pulmonary congestion or peripheral edema, and the reduction in stroke volume, which is the result of the decrease in E_{es} and the increase in E_a . To some extent, an increase in heart rate may compensate for the reduction in stroke volume to maintain cardiac output.

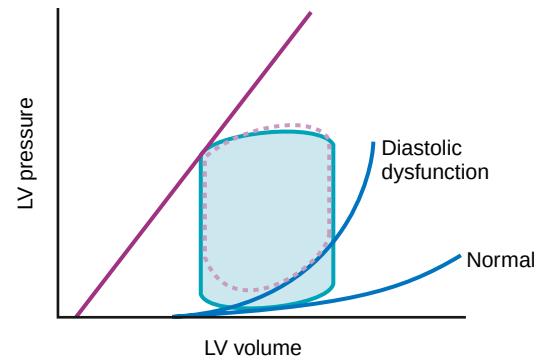


Figure 6-8. Diastolic dysfunction resulting from impaired distensibility manifests in the pressure-volume plane as an increase in the slope or leftward shift of the end-systolic pressure-volume relationship (ESPVR). The ventricle requires a higher filling pressure to distend sufficiently to receive an adequate end-diastolic volume.

Diastolic Dysfunction

Inasmuch as left ventricular systolic function represents the ejection of adequate volume, diastolic function can simply be viewed as the process of filling of the left ventricle. Normal diastolic function is defined as adequate filling of the left ventricle, without exceeding a pulmonary venous pressure of 12 mm Hg.¹⁹ From the pressure-volume approach, it is clear that the end-diastolic pressure is a function of end-diastolic volume and EDPVR. Systolic dysfunction, resulting in an increase in end-diastolic volume and end-diastolic pressure, also meets this definition. In this case, the abnormality is primarily in systole, however, if systole is defined as adequate ejection, given adequate filling.

Isolated diastolic dysfunction commonly can result from impaired ventricular distensibility, external compression of the left ventricle, or obstruction to filling of the left ventricle.²⁰⁻²² Impaired distensibility as a result of chronic hypertension is a common cause of diastolic dysfunction and is represented in the pressure-volume plane as a steep or left-shifted EDPVR (Fig. 6-8). With significant diastolic dysfunction, adequate filling sufficient to maintain stroke volume is achieved only at the expense of an elevated end-diastolic filling pressure. Diastolic dysfunction, without any systolic dysfunction, can produce symptoms of pulmonary congestion and congestive heart failure.^{21,23} The effect of external compression such as pericardial tamponade or constriction similarly results in a leftward shift of the EDPVR by reducing capacitance.

Aortic Stenosis

Aortic stenosis is a special form of systolic dysfunction. The stenosed aortic valve imposes a resistance to ejection that must be overcome by the ventricle to maintain an adequate stroke volume and systemic perfusion pressure. The resistance to ejection results in a pressure gradient across the valve. The effect on the ventricle is an increase in the effective arterial elastance, which in this case incorporates the stenotic valve and does not reflect pure arterial properties. The increase in end-systolic pressure results in an increase in end-systolic ventricular wall stress. Over time, the ventricle compensates by concentric hypertrophy, which reduces the wall stress. The effect of this hypertrophy is to shift the ESPVR to the left. Concentric hypertrophy is also a common cause of diastolic dysfunction that manifests as an elevated EDPVR (Fig. 6-9).^{24,25}

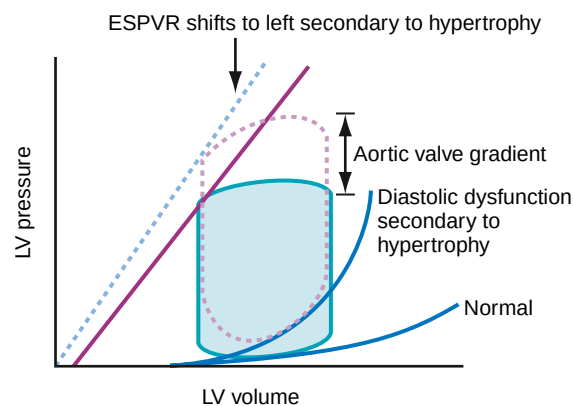


Figure 6-9. Aortic stenosis imposes an added afterload on the left ventricle, which must generate an increased end-systolic pressure to overcome the aortic valve gradient. Concentric left ventricular hypertrophy results in a leftward shift in the end-systolic pressure-volume relationship (ESPVR) with a small increase in the slope of the ESPVR (E_{es}). Hypertrophy also results in diastolic dysfunction, with a steeper end-diastolic pressure-volume relationship (EDPVR). These changes result in a reduction in stroke volume and an increase in filling pressures.

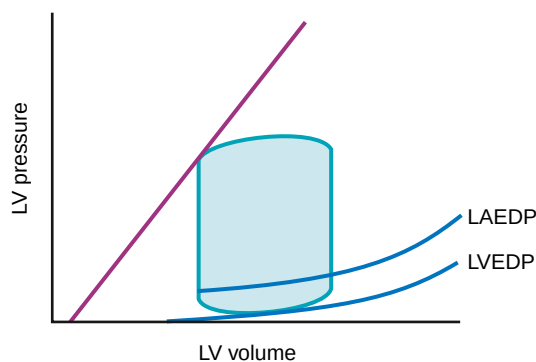


Figure 6-10. Mitral stenosis imposes a resistance to left ventricular filling. This results in a diastolic pressure gradient between the left atrium and left ventricle. Adequate ventricular filling is maintained at the expense of an increase in left atrial end-diastolic pressure (LAEDP). LVEDP, left ventricular end-diastolic pressure.

Mitral Stenosis

Mitral stenosis is a special form of diastolic dysfunction. The stenotic mitral valve imposes a resistance to left ventricular filling, which results in a pressure gradient between the left atrium and the left ventricle. The increased atrial pressure is reflected into the pulmonary venous system, and can result in symptoms of pulmonary congestion and congestive heart failure. This is best visualized in the pressure-volume plane by plotting end-diastolic left atrial pressure superimposed on the ventricular pressure (Fig. 6-10). Atrial pressure exceeds ventricular diastolic pressure throughout diastole by an amount that depends on the effective mitral valve area and the flow across the valve.²⁶

Valvular Regurgitation

Mitral and aortic regurgitation result in increased ventricular filling in diastole, with an increase above normal in end-diastolic volume that results in an increase in total stroke volume. The

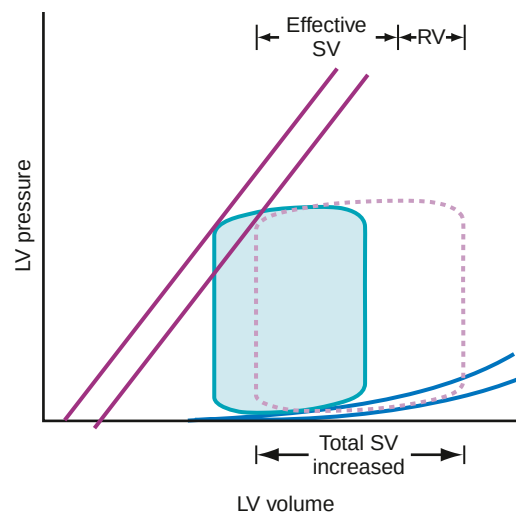


Figure 6-11. Chronic mitral or aortic regurgitation imposes a chronic volume load on the left ventricle owing to the added burden of the regurgitant volume (RV). The increase in preload results in an increase in total stroke volume, although effective stroke volume usually is unchanged. In acute regurgitation, filling pressures are markedly increased, but with chronic regurgitation, the ventricle dilates, and the end-systolic pressure-volume relationship (ESPVR) and end-diastolic pressure-volume relationship (EDPVR) shift to the right, enabling the heart to accommodate the added volume load with smaller increases in filling pressures.

effective stroke volume is the difference between total stroke volume and regurgitant volume. In acute valvular regurgitation, the increase in ventricular filling results in high filling pressures as the ventricle is forced to operate on the steep portion of its EDPVR; this can result in acute pulmonary edema. Over time, the ventricle adapts its systolic and diastolic properties and dilates to accommodate the increase in end-diastolic volume, while limiting the increase in filling pressure. This activity results in a right shift in the ESPVR and EDPVR.²⁴ Figure 6-11 shows these effects for compensated, chronic valvular regurgitation. Ventricular dilation results in an increase in V_0 . In the compensated phase, contractile state is preserved, and the slope of the ESPVR does not change significantly, but shifts to a higher operating volume range. Chronic severe regurgitation, if uncorrected, can lead to systolic dysfunction, resulting in a dilated cardiomyopathy.

Dilated Cardiomyopathy

Chronic, severe systolic dysfunction can result from coronary ischemia, valvular regurgitation or other causes of chronic volume overload, and intrinsic myocardial processes. The common pathophysiology is that the ventricle dilates to compensate for chronic volume overload. The ventricular dilation, imposed by regurgitation, shunts, or other abnormalities of the peripheral circulation or in primary myocardial disease, is the only way that the heart can maintain an adequate perfusion pressure. The changes in the pressure-volume plane are characterized by a reduction in the slope of the ESPVR as a result of a decrease in contractile state, and a right shift in the ESPVR and EDPVR secondary to dilation of the left ventricle (Fig. 6-12).²⁷

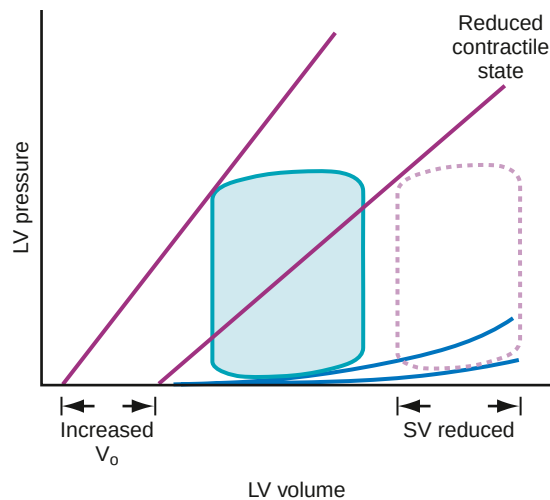


Figure 6-12. Severe chronic systolic dysfunction results in the development of a dilated cardiomyopathy. The slope of the ESPVR (E_{es}) is reduced, and the end-systolic pressure-volume relationship (ESPVR) and end-diastolic pressure-volume relationship (EDPVR) are displaced to the right because of ventricular dilation.

Limitation of the Pressure-Volume Approach

For clinicians, the real value of the pressure-volume approach lies in its use as a conceptual model to understand the physiologic and pathologic determinants of cardiac function and hemodynamics. Invasive and noninvasive determination of the ESPVR and EDPVR in conscious animals and humans has been described,^{6,27-29} but has not been implemented routinely in clinical diagnosis or therapy for several reasons. In a single heart, it is simple to interpret a change in the baseline ESPVR, but comparisons between populations or individuals are difficult because the slope and intercept of the ESPVR depend on cardiac size.

The lack of a universally acceptable correction for cardiac size makes it difficult to define a normal range for the E_{es} . This difficulty is compounded by the fact that V_o cannot be measured directly in vivo, but is determined by extrapolation and is subject to large errors.³⁰ In addition, the timing of end-systole is not always clear-cut. End-systole is defined as the upper left corner of the pressure-volume loop, but this does not always correspond with either aortic valve closure or maximal ventricular elastance, especially in mitral regurgitation.³¹ Apart from difficulties in comparing pressure-volume relationships, the determination of these relationships in vivo requires alterations in loading conditions over a wide range. The changes in loading conditions themselves may directly affect the slope of the ESPVR through reflex alterations in contractile state and heart rate.

Lastly, ESPVR is depicted in this chapter as a linear relationship with a slope and an intercept that are readily determined. Several studies have suggested, however, that the ESPVR becomes nonlinear at high contractile states and with heart failure.³²⁻³⁵ This nonlinearity may make a slope measurement sensitive to the range of data collection and complicate comparison. These limitations do not diminish the effectiveness of the pressure-volume relationship as an analytical tool to understand the physiologic and pathophysiologic determinants of cardiac output.

Conclusion

The function of the cardiovascular system is to provide adequate tissue oxygenation by the circulation of oxygenated blood. Mixed venous oxygen saturation is determined by the balance between oxygen delivery and oxygen consumption. Under normal conditions, the heart has a large functional reserve, and cardiac output is regulated by neurohormonal mechanisms to meet the needs of the body as they change with posture and activity, so that at rest mixed venous oxygen saturation is at least 70%. Left ventricular dysfunction is a common cause of cardiovascular insufficiency. In this setting, regulatory mechanisms are saturated by maximal sympathetic autonomic stimulation, and cardiac output becomes limited by left ventricular performance. Ventricular performance and its coupling to the vasculature can be analyzed within the pressure-volume plane. This approach provides a clinically useful, mechanistic framework for understanding integrated cardiovascular function in critically ill patients.

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Coronary Physiology and Pathophysiology

Andrew Peter Selwyn

CHAPTER

7

Determinants of Myocardial Oxygen Consumption Vessel Wall and Local Control of Coronary Blood Flow

Pathophysiology

A CLEAR UNDERSTANDING of the physiologic control of coronary blood flow is essential to considering and treating the underlying pathophysiology in patients who are acutely ill in a cardiac intensive care unit.

Determinants of Myocardial Oxygen Consumption

The working myocardium requires a coronary blood flow of 70 to 90 mL/100 g of myocardium per minute to provide for an oxygen consumption of 8 to 15 mL/100 g of tissue per minute at rest for contraction and relaxation. This figure rapidly increases fivefold to sixfold with exercise or sympathetic arousal. At rest, the heart consumes most of the oxygen contained in its blood supply. Any increase in demand must be met by an increase in blood flow. An understanding of the control of coronary blood flow in physiologic and pathologic states is essential.

With each beat, developed muscle tension requires oxygen, and total tension developed in unit time is directly proportional to the oxygen needs of the working myocardium. The frequency of developed tension (heart rate) is also quantitatively important with regard to oxygen consumption, whereas stroke volume (muscle shortening) has a smaller impact on the needs for oxygen and blood supply. Excitation and contraction coupling and changes in calcium flux influence contractility, which also has an important impact on the demands for oxygen and blood flow.

Myocardial demand for oxygen and blood is determined by developed systolic wall tension, heart rate, and contractility. Coronary blood supply is determined by metabolic demands, autoregulation, blood oxygen-carrying capacity, diastolic time, neurohumoral factors, and extravascular compressive forces (Fig. 7-1). The following sections discuss the dominating controlling influences of metabolic regulation and autoregulation.

Metabolic Control

The myocardium operates by using aerobic metabolism, and the prevailing tissue oxygen level provides a powerful signal for the control of coronary resistance vessels and blood flow to regulate oxygen supply and maintain tissue oxygen tension. Within each

beat, the tissue oxygen level exerts the most powerful effect on coronary vascular resistance within the myocardium. Coronary occlusion causes instantaneous coronary resistance vessel dilation to facilitate blood flow. Similarly, increases in myocardial work increase oxygen consumption and lead to immediate and precisely regulated dilation of resistance vessels with increases in coronary blood flow to maintain the oxygen supply to tissues. Tissue oxygen tension likely signals the coronary resistance vessels through local mechanisms, such as the release of adenosine, tissue levels of carbon dioxide, pH, nitric oxide, and other substances as discussed later.¹⁻³

Autoregulation

The heart provides pressure and blood flow to many organs (i.e., perfusion), and the vascular resistance in each region of the body varies from minute to minute. As a result, alterations in pressure and flow in the ascending aorta can affect the coronary circulation, which must maintain local perfusion to the myocardium (pressure $\times$ flow per unit of tissue) and meet the local needs of the working heart muscle. Aortic pressure can decrease to approximately 50 mm Hg or increase to approximately 150 mm Hg in health, and the coronary resistance vessels are capable of

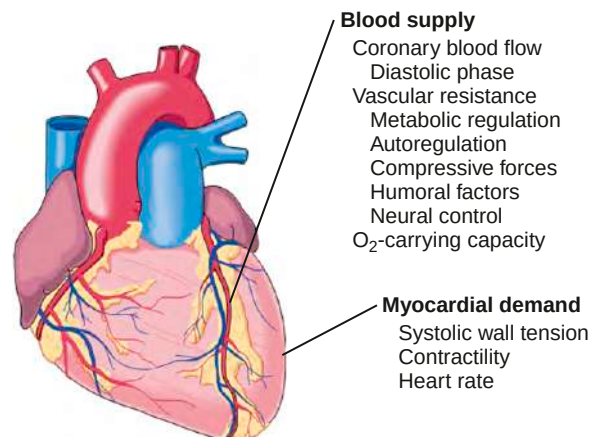


Figure 7-1. Control of myocardial blood flow and oxygen consumption and demand. (Adapted from Ardehali A, Ports TA: Myocardial oxygen supply and demand. *Chest* 1990;98:699.)

adapting to maintain a constant and necessary level of coronary blood flow. This autoregulation is a protective mechanism and is probably mediated by the local release of nitric oxide by the endothelium and local constriction of vascular smooth muscle cells with increasing intraluminal pressure (the myogenic reflex). The preceding mechanisms are likely transduced via pressure-sensitive and flow-sensitive channels on the endothelium and vascular smooth muscle cells.²⁻⁴ The presence of atherosclerotic narrowing in epicardial coronary arteries impairs autoregulation, narrowing the range of aortic pressure within which changing coronary resistance can maintain myocardial perfusion at different aortic pressures. Similarly, hypertension and left ventricular hypertrophy also can impair the regulation of myocardial blood flow.

Vessel Wall and Local Control of Coronary Blood Flow

Blood Flow

The coronary vasculature is subject to neural innervation and the effects of circulating mediators such as serotonin, adenosine diphosphate, epinephrine, and vasopressin. These are in addition to the mechanisms that respond to the oxygen and metabolic needs of the heart (see previous sections on metabolic control and autoregulation). The local vascular endothelium seems to transduce many of these physiologic signals, including local shear force, pulse pressure, sympathetic stimulation, and blood flow itself. It responds by exerting its own local control on vascular smooth muscle cells by governing constriction and relaxation. To be specific, vascular endothelial cells possess membrane-associated channels sensitive to many circulating and local regulators, such as shear forces, flow, serotonin, and thrombin. The endothelium is also sensitive to α -adrenergic sympathetic stimulation and aggregating platelets. These signals can cause the endothelium to release locally vasodilators, such as nitric oxide, endothelium-dependent hyperpolarizing factor, and prostacyclin, or vasoconstrictors, such as endothelin-1 and thromboxane. These local responses provide physiologic control in each segment of the coronary circulation.

The healthy coronary arteries maintain the ability to control local vasomotion, maintain an anticoagulant surface, and present a biologic barrier that prevents infiltration and proliferation (Fig. 7-2). These key defensive mechanisms are important in health, and a clear understanding of them is important in the development of diseases such as atherosclerosis.

Epicardial Coronary Arteries

Healthy epicardial arteries offer little resistance to coronary blood flow. The endothelium can respond locally to shear forces, blood flow, and sympathetic stimulation by producing and releasing nitric oxide from L-arginine, prostacyclin, and endothelium-derived hyperpolarizing factor, all of which mediate local vasodilation when required, controlling shear stress and blood velocity, while preserving flow. The coronary endothelium can also mediate constriction through the release of endothelin-1, myogenic reflex, and local release of thromboxane. Other essential and intrinsic properties of the healthy vascular endothelium include the maintenance of an anticoagulant surface, prevention of inflammatory cell infiltration, and the control of cell growth.²⁻⁵

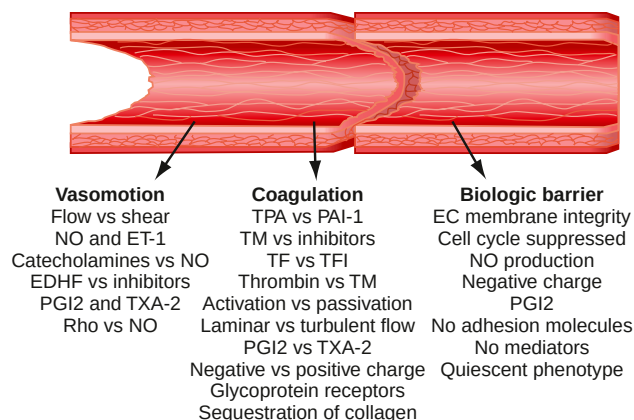


Figure 7-2. Mechanisms present in healthy coronary arteries that control local vasomotion, maintain an anticoagulant surface, and sustain a biologic barrier that prevents infiltration and cell proliferation. EC, endothelial cells; EDHF, endothelium-derived hyperpolarizing factor; ET-1, endothelin-1; NO, nitric oxide; PAI-1, plasminogen activator inhibitor-1; PGI2, prostacyclin; Rho, Rho proteins; TF, tissue factor; TM, thrombomodulin; TXA-2, thromboxane A2.

Resistance Vessels

The resistance vessels are subject to the needs of the myocardium for oxygen and are primarily responsible for exerting the metabolic control and autoregulation previously described in detail for the coronary blood supply. Locally, the endothelial release of nitric oxide also mediates dilation of resistance vessels as part of the response to metabolic demand. There is continuous release of nitric oxide to control the basal dilator tone of these vessels.²⁻⁶

Extravascular Compression of Coronary Blood Supply

The intracavity pressure and the vascular compression achieved by contracting heart muscle act to obstruct coronary blood flow during systole, even causing reversed flow in intramyocardial vessels. In health, diastolic driving pressures overcome diastolic compressive forces because the aortic diastolic pressure is higher than the pressure in the coronary sinus or right atrium. Intracavity pressures and vascular compression are important forces influencing flow during systole and diastole. These myocardial or extravascular forces are more prominent in the inner layer of the left ventricle (i.e., the subendocardium). Flow in the epicardium is generally 25% higher than that in the endocardium. Increases in wall stress in health and disease place greater demands for oxygen and blood flow in the subendocardial layers. This layer also exhibits the greatest susceptibility to limitations of flow in disease states, however. Increased wall tension (ventricular hypertrophy) and decreased perfusion pressure (e.g., coronary stenoses and shock) are more likely to jeopardize subendocardial coronary flow.¹

Neural Control and Reflexes

α_1 -Adrenergic and α_2 -adrenergic innervation can produce coronary constriction. This sympathetic stimulation also produces increases in heart rate and myocardial work, increasing myocardial oxygen demand, which leads to the dominating effect of coronary vasodilation through increased metabolic demand. β_2 -Adrenergic stimulation produces coronary dilation, whereas

parasympathetic stimulation dilates only the small coronary arteries. The chemoreceptors can indirectly alter sympathetic stimulation of the heart, affecting developed tension, heart rate, myocardial oxygen demand, and coronary resistance. The carotid sinus nerve mediates sympathetic stimulation and coronary dilation. The sympathetic receptors seem to cause coronary dilation, and there are receptors that can also lead to coronary dilation through muscarinic pathways. Parasympathetic stimulation via the coronary circulation can lead to bradycardia and hypotension (i.e., the Bezold-Jarisch reflex). Finally, continuous modulation of α -adrenergic sympathetic outflow seems to exert a tonic level of constrictor tone on the coronary circulation, which is opposed by the dilator effect of the continuous production of nitric oxide by a healthy endothelium.¹⁻⁵

Pathophysiology

Common cardiovascular risk factors, in particular, hypercholesterolemia, impair the production of an important endothelium-derived relaxing factor, nitric oxide, by the vascular endothelium in the epicardial arteries and the coronary resistance vessels. This impaired production of nitric oxide results in the failure of endothelium-dependent dilation in response to shear stress, blood flow, and the sympathetic stimulation of exercise. The lack of reflex dilation is replaced by abnormal constriction. These risk factors interfere with a wide range of endothelial functions, including nitric oxide production by uncoupling the enzymes that produce nitric oxide, oxidant stress, disabling necessary cofactors, and inhibiting the mRNA that governs the production of nitric oxide by nitric oxide synthase.

Atherosclerosis

Atherosclerosis leads to local accumulation of matrix, inflammatory cells, debris, cholesterol crystals, and smooth muscle cells, which all lead to focal stenoses in epicardial arteries. When stenosis is sufficiently severe, a pressure gradient develops across the lesion, and eventually blood flow decreases as each stenosis progresses. The effect of plaque and stenosis on coronary blood flow depends on the minimum cross-sectional area of narrowing; blood viscosity; vessel wall function; loss of laminar flow; development of turbulence; and the severity, length, and complexity of the lesion. In the presence of stenoses greater than 70%, small increases in blood flow greatly increase the pressure gradient across the stenosis. In the aforementioned circumstances, exercise increases myocardial oxygen demand producing resistant vessel dilation, a decrease in poststenotic pressure and increase in pressure gradient across the stenosis, and a further decrease in poststenotic perfusion pressure to the subendocardium. The minimal cross-sectional area within the stenosis is the most important measure of the lesion's rheologic effect on blood. At this point, small changes in stenosis severity produce exaggerated increases in the pressure gradient to resistance, which jeopardizes coronary blood supply.

Physiologic increases in coronary blood flow are blunted when the stenosis exceeds approximately 45%, and they are abolished when the stenosis exceeds 80%. Resting coronary blood flow declines when the stenosis exceeds 90% to 95%.^{6,7}

Apart from the structural disease and the physical effects of stenosis on flow as described earlier, atherosclerosis is characterized by a dysfunctional endothelium that loses its ability to regulate local vasodilation and permits abnormal and

paradoxical constriction particularly in response to the sympathetic stimulation that occurs during everyday life. This reflex constriction has important consequences at the site of severe stenoses. During physical exercise, exposure to cold, and mental stimulation, sympathetic arousal leads to abnormal or exaggerated reflex constriction stenoses owing to endothelial dysfunction. Worsening resistance and the adverse effects on coronary blood supply contribute to the development of ischemia under these circumstances. In atherosclerosis, the endothelium also loses other healthy functions—the maintenance of an anticoagulant surface, an anti-inflammatory effect, and the local control of growth and cell proliferation. The loss of these functions permits platelet aggregation and thrombus formation locally, infiltration of inflammatory cells, local growth of smooth muscle cells, and extracellular matrix accumulation, all of which contribute to lesion progression.^{1,8}

Collateral Blood Vessels

Preexisting but nonfunctioning vascular channels and collateral blood vessels connect the coronary arteries within the myocardium. If narrowing of large coronary arteries causes a decrease in perfusion pressure, the collateral channels can open immediately, and over a period of days can undergo passive widening to facilitate coronary blood flow between previously unconnected regions of the ventricles. Over weeks, specific cell growth leads to formation of new collateral vessels. This process is stimulated by ischemia, myocardial work, and oxygen demand with growth factors as mediators. Serotonin from platelets can cause opposite effects, such as collateral vessel constriction, and can worsen tissue perfusion. Endothelium-derived relaxing factors such as nitric oxide can dilate collateral vessels and facilitate regional myocardial blood flow.

Preexisting collateral vessels can partially compensate for coronary stenoses and occlusions. If the stimulus for collateral growth is persistent over months, and collateral blood vessels develop, they can become capable of compensating for occlusion of large proximal epicardial arteries. Nevertheless, collateral vessels have limited ability to provide sufficient myocardial perfusion under stress and circumstances of increased demand.

Myocardial Ischemia

Ischemia occurs because myocardial blood flow fails to provide sufficient blood and oxygen to meet the myocardial demand that is required for contraction, relaxation, and cellular metabolism. This failure is commonly caused by decreased blood supply or increased myocardial demand for blood and oxygen when blood supply is fixed by obstructive coronary artery disease. During ischemia, tissue oxygen tension decreases, and aerobic metabolism becomes anaerobic; left ventricular relaxation and then contraction fails within seconds; and there are characteristic changes in the surface electrocardiogram that may or may not be followed by chest tightness (i.e., angina pectoris).

Episodes of transient myocardial ischemia most commonly occur in the presence of one or more atherosclerotic stenoses in the epicardial coronary arteries of 70% or greater. In addition, these atherosclerotic vessels exhibit endothelial dysfunction, and with exercise, mental arousal, or sympathetic stimulation (e.g., cold), their abnormal constriction increases the resistance at stenoses and further limits coronary blood supply, often at a time when there is an increase in myocardial demand for oxygen and blood flow.

In unstable angina and myocardial infarction, coronary blood supply is decreased further by a local procoagulant surface and clot formation at atherosclerotic plaques. Further narrowing can occur, causing occlusion of a diseased epicardial coronary artery.

While abnormal constriction occurs at atherosclerotic stenoses, myocardial demand for oxygen is increased by any increase in heart rate, developed tension, and contractility, often in the presence of some degree of left ventricular hypertrophy or anemia. The mechanisms that lead to transient ischemia often include abnormalities of supply and demand, which coexist and act in concert. During myocardial ischemia, tissue oxygen tension decreases, energy stores decline, inorganic phosphate accumulates, and intracellular calcium can no longer facilitate myocardial relaxation or contraction by myofilaments. There is temporary loss of the healthy transmembrane ion gradients while intracellular pH decreases. Myocardial relaxation fails first, and then contraction fails, followed by characteristic electrocardiogram changes with ST segment depression when there is patchy endocardial ischemia and ST elevation with severe transmural ischemia. If the balance between blood supply and myocardial demand is sustained and severe beyond 20 minutes (with plaque rupture, thrombosis, or sustained stimulation), the above-described myocardial pathology is accompanied by progressive irreversible changes in myocardial membranes, enzymes, and proteins, leading to a central area of myocardial

necrosis that may be a single episode over approximately 6 hours or stuttering and distributed over days. At this stage, the severity of ischemia and the development of necrosis depend almost entirely on the available coronary blood supply.

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Pathophysiology of Acute Coronary Syndromes: Plaque Rupture and Atherothrombosis

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CHAPTER

8

Atherogenesis
Plaque Disruption
Thrombosis

Integrated Pathogenesis of Acute Coronary
Syndromes
Conclusion

THE ACUTE coronary syndromes (unstable angina, myocardial infarction [MI], sudden cardiac death) are a major cause of morbidity and mortality in developed countries. MI alone is the major cause of death in most Western countries.¹ The rapidly increasing prevalence in developing countries, specifically South Asia and Eastern Europe, coupled with an increasing incidence of tobacco abuse, obesity, and diabetes, is predicted to make cardiovascular disease the major global cause of death by 2020.² Atherosclerotic plaque formation within the coronary arteries with subsequent lesion disruption, platelet aggregation, and thrombus formation is the primary cause of acute coronary syndromes in humans.

During the early 1900s, the first description of the clinical presentation of acute MI was published by Obstrastzow and Straschesko.³ Shortly thereafter, Herrick⁴ associated the clinical presentation of acute MI with thrombotic occlusion of the coronary arteries. Much has been learned since these early observations concerning the pathophysiology of coronary artery disease and the acute coronary syndromes. This chapter reviews the pathogenesis of atherosclerosis and explores the mechanisms responsible for the sudden conversion of stable atherosclerotic plaques into unstable life-threatening atherothrombotic lesions.

Atherogenesis

Development

Atherogenesis, or the development of plaques within the walls of blood vessels, is the result of complex interactions involving blood elements, vessel wall abnormalities, and alterations in blood flow. In addition, several pathologic mechanisms play an important role, including inflammation with activation of endothelial cells and monocyte recruitment,⁵⁻⁹ growth with smooth muscle cell proliferation and matrix synthesis,^{10,11} degeneration with lipid accumulation,^{12,13} necrosis, calcification and ossification,^{14,15} and thrombosis.¹⁶ These diverse processes result in the formation of atheromatous plaques that form the substrate for future acute coronary syndromes.

Fatty Streak

Vascular injury and thrombus formation are key events in the formation and progression of atherosclerotic plaques. Fuster and colleagues¹⁷ proposed a pathophysiologic classification of

vascular injury that divides the damage into three types (Fig. 8-1). Type I injury consists of functional deviations from normal endothelial function without obvious morphologic changes. Type II injury involves a deeper form of vascular damage that includes denudation of endothelial cells and intimal damage with maintenance of an intact elastic lamina. Type III injury is represented by endothelial denudation and damage to the intima and media of the vessel wall.

The earliest finding in spontaneous atherosclerosis is an intimal lesion containing lipid-laden macrophages and a few T lymphocytes.¹⁸ In the “response to injury hypothesis” proposed by Ross¹⁹ and others, these “fatty streaks” are thought to result from chronic injury to the arterial endothelium induced by disturbances in coronary blood flow (type I injury) and an increased vascular permeability to lipids and monocytes (Fig. 8-2). The chronic injury is primarily a disturbance in the pattern of blood flow in certain parts of the arterial tree, such as bending, branch points, or both. Certain factors, such as hypercholesterolemia, tobacco abuse, vasoactive amines, glycosylated products, infection, and immune complexes, may potentiate the effect of type I injury on the endothelium.²⁰ This chronic, low-grade damage leads to the accumulation of lipids and macrophages at the site of injury producing the characteristic fatty streak. These lipid-laden macrophages, also known as foam cells, are derived primarily from tissue macrophages. Foam cells are formed when large amounts of intracellular lipids, mainly from modified low-density lipoprotein (LDL), are taken up via a family of macrophage scavenger receptors and internalized into the macrophage.

There is growing evidence that oxidized LDL is a key active component in the generation of atherosclerosis, rather than a passive substance that accumulates within macrophages. It is hypothesized that oxidized LDL has five potentially atherogenic effects: (1) monocyte chemotactic activity, (2) inhibition of macrophage migration out of the vessel wall, (3) enhanced uptake by macrophages, (4) formation of immune complexes, and (5) cytotoxicity (Fig. 8-3).

In the presence of elevated plasma LDL levels, the concentration of LDL within the intima is increased. By poorly understood mechanisms, which may involve the generation of free radicals by cellular lipoxygenases,^{21,22} the LDL molecule undergoes oxidative modification (peroxidation of polysaturated fatty acids) that alters its metabolism. When the LDL contains fatty acid

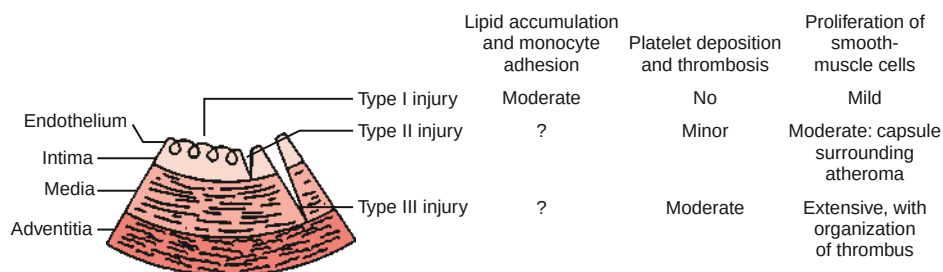


Figure 8-1. Classification of vascular injury and vascular response. See text for details. (From Fuster V, Badimon L, Badimon J, Chesebro J: *The pathogenesis of coronary artery disease and the acute coronary syndromes*. N Engl J Med 1992;326:242-248.)

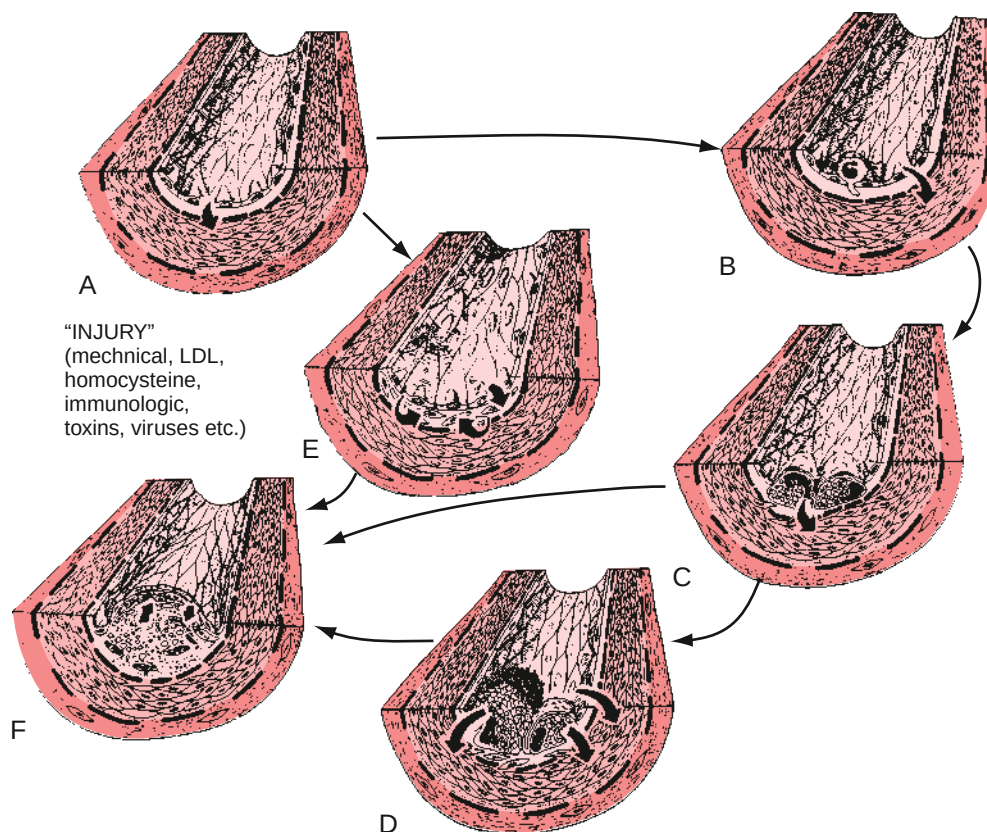


Figure 8-2. Response-to-injury hypothesis. Advanced intimal proliferative lesions of atherosclerosis may occur by at least two pathways. The pathway shown by the *long clockwise arrows* to the right has been observed in experimental hypercholesterolemia. Injury to the endothelium (**A**) may induce growth factor secretion (*short arrows*). Monocytes attach to endothelium (**B**), which may continue to secrete growth factors (*short arrow*). Subendothelial migration of monocytes (**C**) may lead to fatty streak formation and release of growth factors such as platelet-derived growth factor (PDGF) (*short arrow*). Fatty streaks may become directly converted to fibrous plaques (*long arrow* from **C** to **F**) through release of growth factors from macrophages or endothelial cells or both. Macrophages may also stimulate or injure the overlying endothelium. In some cases, plaques may lose their endothelial cover, and platelet attachment may occur (**D**), providing additional sources of growth factors (*short arrows*). Some of the smooth muscle cells in the proliferative lesion itself (**F**) may synthesize and secrete growth factors such as PDGF (*short arrows*). An alternative pathway for the development of advanced atherosclerosis lesions is shown by the *arrows* from **A** to **E** to **F**. In this case, the endothelium may be injured, but remain intact. **A**, Increased endothelial cell turnover may result in growth factor synthesis by endothelial cells. **E**, This may stimulate migration of smooth muscle cells from the media into the intima, accompanied by endogenous production of PDGF by smooth muscle cells and growth factor secretion by the "injured" endothelial cells. **F**, These interactions could lead to fibrous plaque formation and further lesion progression. LDL, low-density lipoprotein. (From Ross R: *The pathogenesis of atherosclerosis: An update*. N Engl J Med 1986;314:458-500.)

lipid peroxides, a rapid propagation amplifies the number of free radicals and leads to extensive fragmentation of the fatty acid chains. These fragments of oxidized fatty acids attach covalently to apoprotein B.^{23,24} By means of specialized receptors, distinct from the LDL receptor, these modified apoprotein B molecules

with the attached fatty acids are recognized by macrophages and taken up by the cell (Fig. 8-4).²⁵ All three major cell types within the artery wall are capable of modifying LDL to a form that is recognizable by a scavenger receptor. In contrast to the LDL receptor, the scavenger LDL receptors are not downregulated in

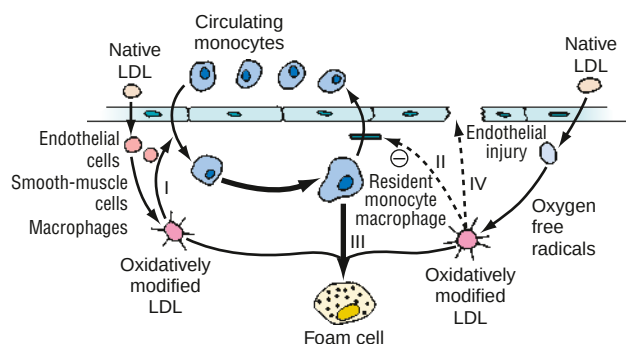


Figure 8-3. Mechanisms by which the oxidation of low-density lipoprotein (LDL) may contribute to atherogenesis, including the recruitment of circulating monocytes by means of the chemotactic factor present in oxidized LDL, but absent in native LDL (I); inhibition by oxidized LDL of the mobility of resident macrophages and their ability to leave the intima (II); cytotoxicity of oxidized LDL, leading to loss of endothelial integrity (III); and uptake of oxidized LDL by macrophages, leading to foam cell formation (IV). Formation of immune complexes is not shown. (From Quinn MT, Parthasarathy S, Steinberg D: Endothelial cell-derived chemotactic activity for mouse peritoneal macrophages and the effects of low density lipoprotein. *Proc Natl Acad Sci U S A* 1985;82:5949-5953.)

the presence of excess ligand. Cells are able to accumulate large amounts of intracellular lipid.

Oxidized LDL within the intima may play a role in the adhesion of circulating monocytes to the arterial wall. More recent studies have shown that oxidized LDL, but not native LDL, is a powerful chemoattractant for circulating monocytes.²⁶ In addition, oxidized LDL is a potent inhibitor of the migration of macrophages out of the intima. By these two mechanisms, oxidized LDL may serve to attract and retain monocytes and macrophages within the vessel wall.

LDL modification by oxidation causes activation, dysfunction, apoptosis, and necrosis in human endothelial cells.²⁷ Activated endothelial cells express leukocyte adhesion molecules, including vascular cell adhesion molecule 1 and intercellular adhesion molecule-1, causing blood cells to adhere at the sites of activation.²⁷ Monocytes and lymphocytes preferentially adhere to these sites. A potent chemotactic agent, monocyte chemoattractant protein 1, is produced by endothelial cells and smooth muscle cells. This same protein has been found in the intima of atherosclerotic lesions and in foam cells. Secretion of monocyte chemoattractant protein 1 by endothelial or smooth muscle cells may be induced by oxidized LDL, suggesting a possible mechanism whereby lipids induce the recruitment of

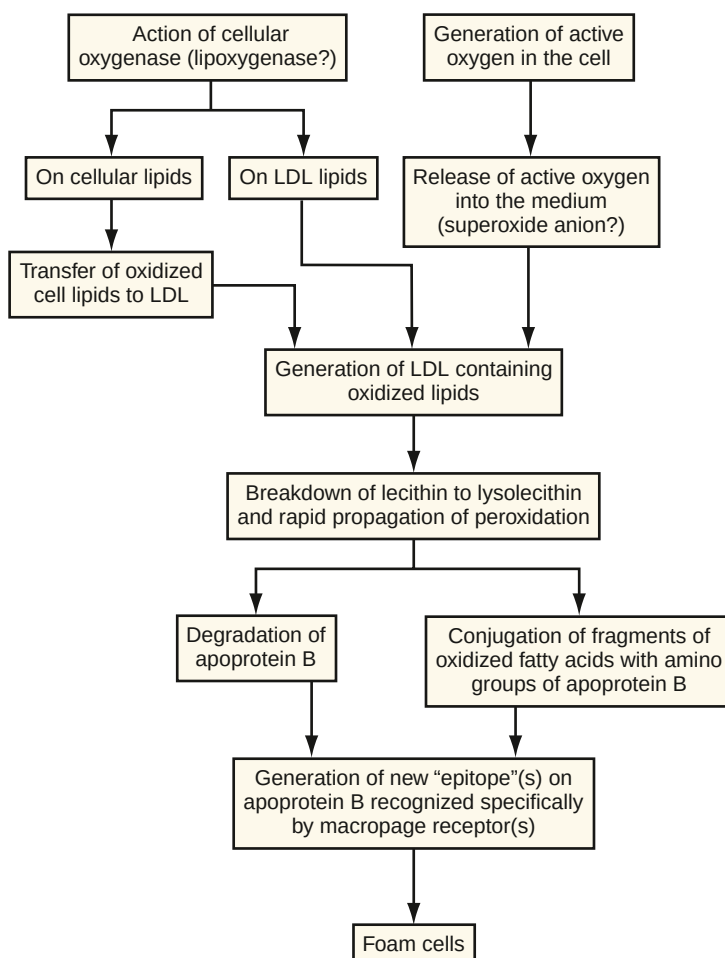


Figure 8-4. Mechanisms of oxidative modification of low-density lipoprotein (LDL) by cells. (From Steinberg D, Parthasarathy S, Carew TE, et al: Beyond cholesterol: modification of low-density lipoprotein that increases its atherogenicity. *N Engl J Med* 1989;320:915-924.)

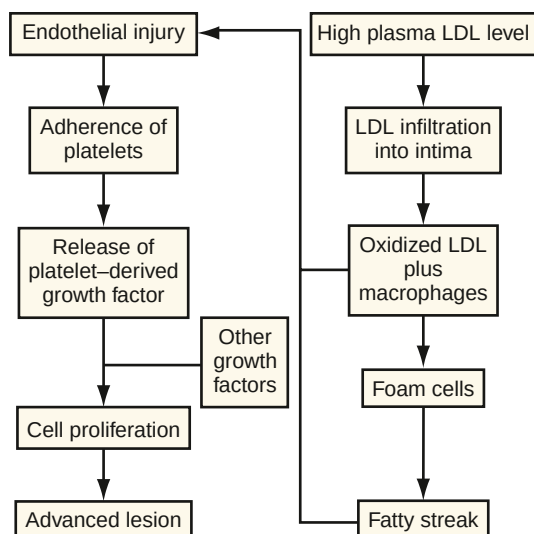


Figure 8-5. Linkage between the lipid infiltration hypothesis and the endothelial injury hypothesis. The lipid infiltration hypothesis (right column) may account for fatty streaks, and the endothelial injury hypothesis (left column) may account for the progression of the fatty streak to more advanced lesions. LDL, low-density lipoprotein. (From Steinberg D, Parthasarathy S, Carew TE, et al: *Beyond cholesterol: modification of low-density lipoprotein that increases its atherogenicity*. *N Engl J Med* 1989;320:915-924.)

macrophages leading to the formation of early atherosclerotic lesions.²⁸

Within the vessel wall, monocytes undergo phenotypic modification by macrophage colony-stimulating factor inducing them to differentiate into tissue macrophages. These macrophages are capable of expressing scavenger receptors leading to internalization of oxidized LDL and the creation of foam cells and fatty streaks.

Plaque Formation

With time, fatty streaks progress into mature atherosclerotic plaques (Fig. 8-5). Macrophages recruited into the area may release toxic products that cause further damage leading to denudation of the endothelium and intimal injury (type II injury). This deeper form of injury leads to platelet adhesion. Adherent platelets, along with recruited macrophages and damaged endothelium release growth factors, such as platelet-derived growth factor (PDGF), epidermal growth factor- β , and somatomedin C. These growth factors may lead to migration and proliferation of vascular smooth muscle cells, and stimulate the production of collagen, elastin, and glycoproteins. These proteins provide the connective tissue matrix of the newly formed plaque and give it structural support. Cholesterol, derived from insudated blood lipid or extruded from dying foam cells, becomes entrapped within this matrix. The lipid and connective tissue matrix are covered by a fibromuscular cap consisting of smooth muscle cells, collagen (types I and III), and a single layer of endothelial cells. This complex constitutes the mature atherosclerotic plaque (Fig. 8-6A). Vascular smooth muscle cells synthesize and assemble the collagen fibrils, and furnish the bulk of the noncollagenous portion of the extracellular matrix of the cap. The fibromuscular cap is a dynamic structure undergoing constant remodeling through

the synthesis and breakdown of essential components (Fig. 8-7; see also Plate I).

The microscopic changes that occur in spontaneous atherosclerosis have been described by Stary¹⁸ and modified by the American Heart Association (AHA).²⁹ Using autopsy results from the coronary arteries and aortas of young people, Stary described five distinct lesions. A Stary I lesion, not apparent macroscopically, consists of isolated macrophages or foam cells within the intima of the involved vessel. These lesions are noted in 45% of infants up to 8 months of age, and eventually regress. A Stary II lesion, which is seen in adolescents, is characterized by numerous foam cells, lipid-containing smooth muscle cells, and a minimal amount of scattered extracellular lipid. Macroscopically, with Sudan IV staining, these lesions appear as a flat or raised fatty streak. In some children, more advanced lesions are noted that are characterized by an increased amount of extracellular lipid and the appearance of a raised fatty streak (Stary III) or a single confluent extracellular core (Stary IV). In adults, usually beginning in the third decade of life, two types of lesions are noted in the coronary arteries. Some plaques are mostly fibromuscular, whereas others are fibrolipid with a cap of smooth muscle cells and collagen. These latter lesions are designated as Stary V lesions.

The first three lesion types in the AHA classification are similar to those in the original Stary description. In the AHA classification, a type IV lesion has a predominance of extracellular, mostly diffuse lipid, whereas a type Va lesion has localized lipid content surrounded by a thin capsule. Additionally, type V lesions are classified further according to the amount of stenosis and fibrosis (types Vb and Vc). Type IV or Va lesions may progress slowly over time into more advanced type V lesions or undergo disruption resulting in a type VI lesion represented by a ruptured plaque with overlying thrombus (Fig. 8-8).

The composition of nonruptured atheromatous plaques is highly variable, and the factors controlling this process are poorly understood. Mature plaques consist of two components: soft, lipid-rich, atheromatous gruel and hard, collagen-rich, sclerotic tissue. The relative amounts of each component may differ with the individual plaque, but generally two populations of lesions predominate (see Fig. 8-6B). One group consists of fibrointimal lesions characterized by large amounts of fibrous tissue and relatively little atheromatous gruel. The second population consists of lipid-laden lesions with a cholesterol-rich central core and a thin outer capsule.

Differences in plaque composition have important clinical implications. Plaques causing severe stenosis tend to have a higher fibrous and lower lipid content than less stenotic lesions.³⁰ Several studies have shown, however, the less stenotic, lipid-laden plaques to be the more clinically dangerous lesions.³¹ As discussed in this chapter, the soft atheromatous center may predispose the plaque to rupture, exposing the highly thrombogenic gruel and subintimal elements to blood flow, and leading to the formation of thrombus and acute myocardial ischemia in many cases.

Progression of Atherosclerosis

Atherosclerosis is a dynamic process that, without intervention, is progressive. Serial angiographic studies have shown that atherosclerotic plaques tend to enlarge over time, and that a significant number of lesions progress to total occlusion. The risk of progression to total occlusion seems to be related to

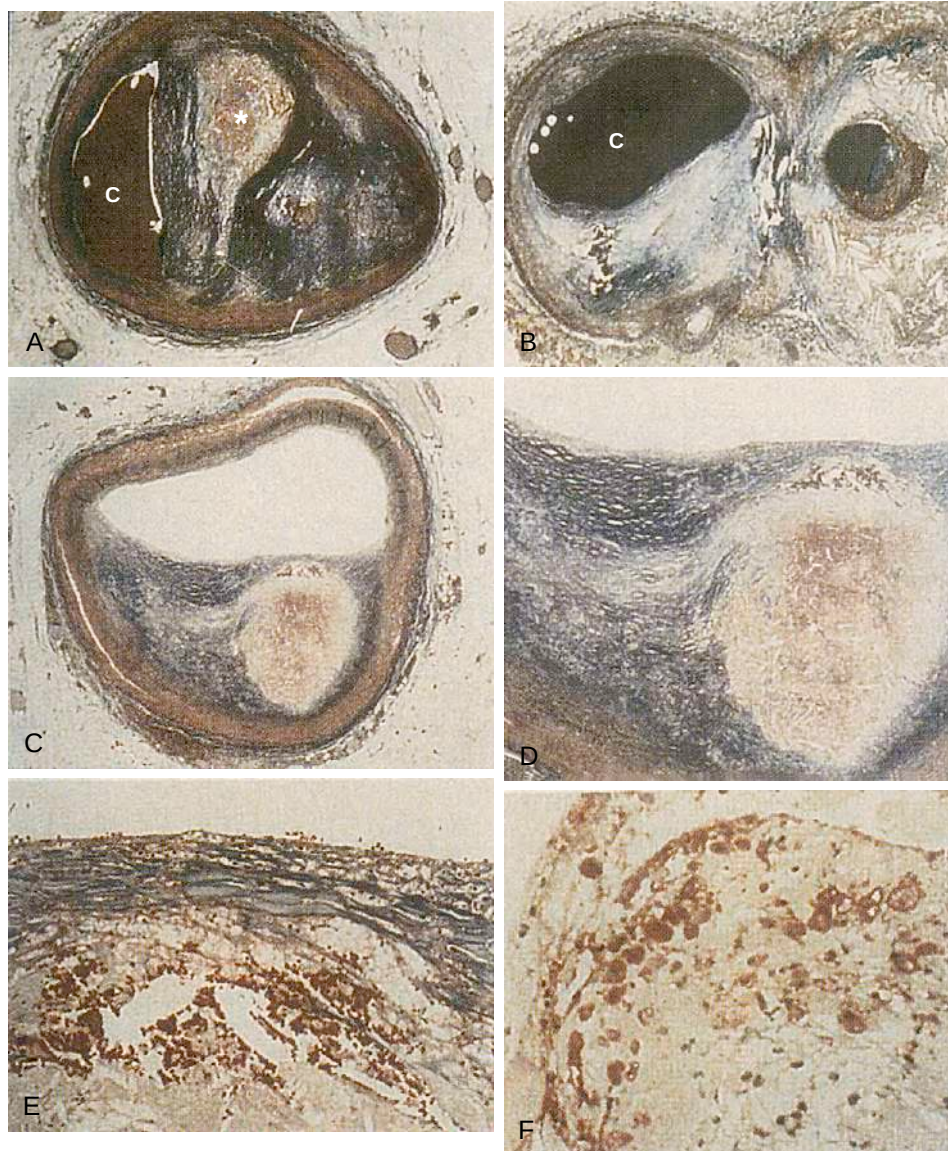


Figure 8-6. Photomicrographs illustrating the relationship between plaque composition and vulnerability. **A**, A mature atherosclerotic plaque consisting of two main components: soft lipid-rich gruel (asterisk) and hard collagen-rich sclerotic tissue (blue). **B**, Two adjacent plaques, one located in the circumflex branch (left) and another in the proximal side branch (right). Although both plaques have been exposed to the same systemic risk factors, the plaque to the left is collagenous and stable, but the plaque to the right is atheromatous and vulnerable, with disrupted surface and superimposed nonocclusive thrombosis (red). **C-E**, Vulnerable plaque containing a core of soft atheromatous gruel (devoid of blue-stained collagen) separated from the vascular lumen by a thin cap of fibrous tissue infiltrated by foam cells that can be seen clearly at high magnification (**E**), indicating ongoing disease activity. Such a thin, macrophage-infiltrated cap is probably very weak and vulnerable, actually disrupted nearby, explaining why erythrocytes (red) can be seen in the gruel just beneath the macrophage-infiltrated cap. **F**, Atherectomy specimen from culprit lesion in non-Q wave myocardial infarction. At high magnification it can be seen clearly that this plaque specimen is heavily infiltrated by red-stained macrophages. **A-E**, Trichrome stain. **F**, Immunostaining for macrophages using monoclonal antibody PG-M1 from Dako. (From Falk E, Shah PK, Fuster V: *Coronary plaque disruption*. *Circulation* 1995;92:657-671.)

the initial severity of the lesion, with more obstructive lesions progressing to total occlusion more frequently than less severe lesions.³² The factors that govern plaque progression are incompletely understood, but two mechanisms have been proposed. One mechanism involves continuation of the myointimal proliferative process produced by the chronic endothelial injury responsible for the early lesions of atherosclerosis.¹⁰ The second mechanism, which may be more important in rapidly growing plaques, involves recurrent minor fissuring of the atheromatous

plaque (type Va lesion undergoing type III injury) with subsequent thrombus formation and fibrotic organization.

Chronic Endothelial Injury

In the “response-to-injury hypothesis,” progression of atherosclerotic lesions occurs via the same mechanisms responsible for the initial myointimal lesion. At least two separate processes seem to be involved. One pathway involves gross endothelial cell damage and monocyte, macrophage, and platelet recruitment

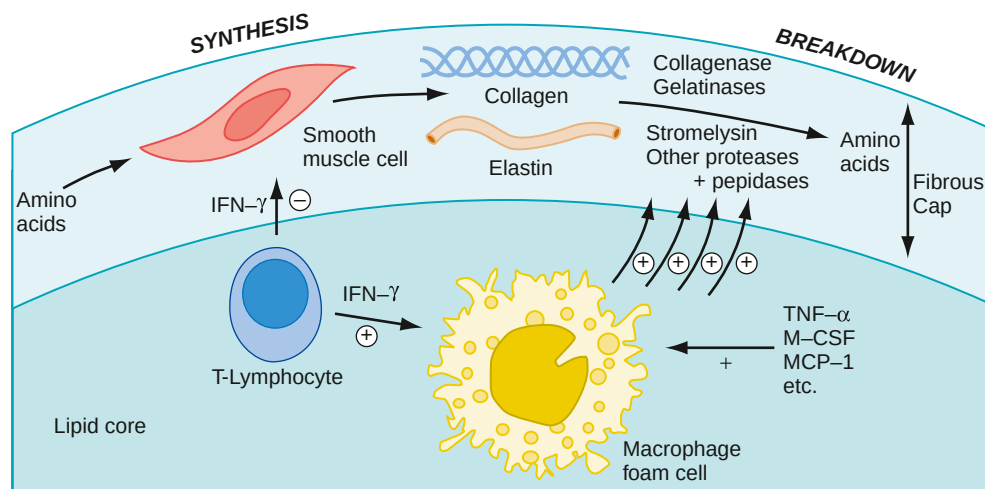


Figure 8-7. Color diagram showing metabolism of collagen and elastin in the plaque's fibrous cap. The vascular smooth muscle cell synthesizes the extracellular matrix proteins, collagen, and elastin. In the unstable plaque, interferon- γ (IFN- γ) secreted by activated T cells may inhibit collagen synthesis, interfering with the maintenance and repair of the collagenous framework of the plaque's fibrous cap. The activated macrophage secretes metalloproteinases that can degrade collagen and elastin. Degradation of the extracellular matrix can weaken the fibrous cap, rendering it particularly susceptible to rupture and precipitating acute coronary syndromes. IFN- γ secreted by T lymphocytes can activate the macrophage. Plaques also contain other activators of macrophages, such as tumor necrosis factor- α (TNF- α), macrophage colony-stimulating factor (M-CSF), and macrophage chemoattractant protein-1 (MCP-1). (From Libby P: *Molecular bases of the acute coronary syndromes*. *Circulation* 1995;91:2844-2850.)

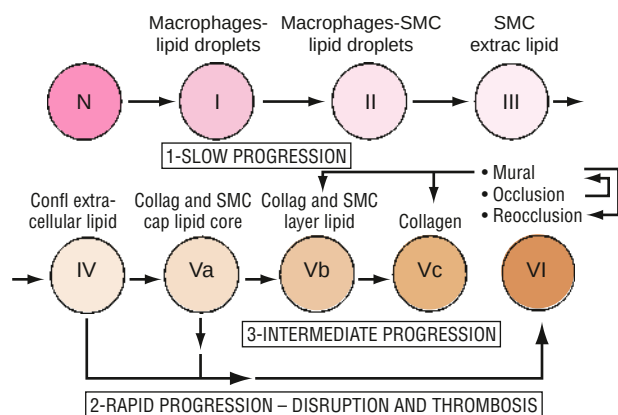


Figure 8-8. Schematic of coronary atherosclerosis progression according to lesion morphology. See text for details. SMC, smooth muscle cells. (From Fuster V: *Mechanisms leading to myocardial infarction: insights from studies of vascular biology*. *Circulation* 1994;90:2126-2146.)

with growth factor secretion leading to the formation and progression of fibrous plaques. A second pathway involves direct stimulation of endothelial cells without obvious injury. This process may increase endothelial cell turnover with increased growth factor production leading to smooth muscle cell migration and increased production of PDGF. Through these interactions, further growth of the initial fibrous plaque may occur (see Fig. 8-2).¹⁰

Recurrent Thrombosis

The second proposed mechanism of atherosclerotic progression involves recurrent minor plaque disruption with subsequent thrombus formation followed by fibrotic organization. Plaque

disruption is a common event, and may be asymptomatic in many patients.³³ As discussed in greater detail later, rupture of lipid-laden plaque exposes the highly thrombogenic atheromatous core and subendothelial components of the arterial wall to the circulation. This exposure results in platelet adhesion and activation with the release of growth factors and the stimulation of the coagulation cascade. This sequence of events results in the formation of thrombus, superimposed on the damaged plaque, which eventually undergoes fibrotic organization with subsequent incremental narrowing of the arterial lumen. In this model, recurrent subclinical events may lead to progressive plaque growth and, ultimately, vessel occlusion.

Several lines of evidence point to an important role of mural thrombus formation in the progression of atherosclerosis. Autopsy studies of coronary artery disease patients who died of cardiac and noncardiac causes reveal the presence of plaques with healed fissures with various stages of thrombus formation and organization and old organized coronary thrombi that are difficult to distinguish from primary atherosclerotic changes seen in the arterial wall.³³⁻³⁵ In situ hybridization techniques and monoclonal antibodies directed at platelets, fibrin, fibrinogen, and their degradation products reveal increased amounts of these substances within the intima, neointima, and deeper medial layer in patients with coronary artery disease.^{36,37} These observations suggest that products of organized thrombus are important in the growth of atherosclerotic plaques.

Platelets and mural thrombi may contribute to the progression of atherosclerosis by mechanisms other than the addition of organized fibrous layers to the plaque. As noted previously, adherent platelets are capable of secreting various mitogenic factors, including PDGF, transforming growth factor- β , and others. These factors may be involved in the proliferation, hypertrophy, and migration of smooth muscle cells, which are important

steps in intimal thickening and plaque growth.¹⁷ Studies from animals with thrombocytopenia or lacking von Willebrand factor (a protein required for platelet adhesion) have shown a reduced amount of atherosclerotic plaque formation and growth. Thrombin produced after vascular injury may become incorporated into the thrombus and extracellular matrix, and may be released slowly over time during periods of spontaneous fibrinolysis or remodeling of the thrombus. Thrombin may bind to platelet receptors and cause platelet activation or to smooth muscle cells resulting in proliferation. Through these mechanisms it is possible that platelets and thrombin play a role in the early and late stages of atherosclerotic progression.

Plaque Disruption

The formation of atherosclerotic plaques within the coronary arteries may gradually impede blood flow by progressive obstruction of the vessel lumen. Initially, these lesions are silent except during periods of increased myocardial oxygen demand. When coronary blood flow cannot be increased to meet the demand of the myocardium, ischemia results and causes characteristic exertional angina. With time, the atherosclerotic plaque may slowly enlarge, producing a greater degree of occlusion that results in symptoms with progressively lesser degrees of exertion.

The pathophysiology of acute coronary syndromes, including unstable angina, MI, and sudden cardiac death, is significantly different. These clinical entities represent a continuum of disease characterized by an *abrupt* reduction in coronary blood flow. Current concepts hold that this abruptly reduced coronary blood flow is caused by atherosclerotic plaque fissuring or rupturing that leads to the formation of thrombus, which, superimposed on a pre-existent lesion, severely limits flow (see Fig. 8-6B).³⁸⁻⁴¹

The risk of plaque fissuring or rupturing is related to the intrinsic properties of individual plaques (vulnerability) and extrinsic factors acting on the plaque itself (rupture triggers). The former predisposes plaques to rupture, whereas the latter may precipitate disruption if vulnerable plaques are present.

Vulnerability

Pathoanatomic examination of intact and disrupted plaques and in vitro mechanical testing of isolated fibrous caps indicate that the vulnerability of a given plaque to rupture depends on several factors: size and consistency of the atheromatous core, thickness and collagen content of the fibrous cap covering the core, the degree of inflammation within the cap, and cap fatigue (see Fig. 8-6C and D).

Core Size and Content

The size and consistency of individual plaques vary greatly from lesion to lesion. As previously described, atherosclerotic plaques are composed of two main components whose ratio may vary within a given plaque. The typical plaque, especially in the most highly stenotic lesions, contains more hard fibrous tissue than soft atheromatous gruel. Plaques containing a larger amount of gruel tend to be identified more often beneath thrombi in acute coronary syndromes, however.³¹ Several investigators have shown that the culprit lesions responsible for acute coronary syndromes tend to have a lipid-laden core occupying greater than 40% of the plaque.⁴²

The composition and size of the atheromatous core are important in determining vulnerability. The core is rich in extracellular lipids, especially cholesterol and its esters.⁴³ Plaques are softened and made more prone to rupture by an increased amount of extracellular lipids in the form of cholesterol esters. Conversely, lipids in the form of cholesterol crystals have the opposite effect on plaque stability.

Cap Thickness and Content

Fibrous caps covering the lipid cores of atherosclerotic lesions vary in thickness, cellularity, matrix composition, and collagen content, all of which are important determinants of plaque stability.⁴⁴ Disrupted caps tend to contain fewer cells that synthesize collagen than intact caps.^{42,45} This lack of collagen may weaken the fibrous cap, leaving the plaque prone to rupturing, which tends to occur in areas where the cap is the thinnest and often most heavily infiltrated by foam cells. In eccentric plaques, rupturing usually occurs in the shoulder region, defined as the junction between plaque and the adjacent, less diseased vessel wall. The cap in these shoulder regions is often thin and heavily infiltrated with macrophages.⁴⁴

Inflammation

The concept that the inflammatory response may play a role in atherosclerosis dates back to Virchow, who postulated that atherosclerosis results from the local reaction of the vessel wall to the insudation of blood products. More recently, a growing body of evidence supports the concept that inflammation is involved in plaque disruption leading to acute coronary syndromes.

Several studies have shown that disrupted fibrous caps are heavily infiltrated by lipid-laden macrophages or foam cells (see Fig. 8-6E and F).³¹ Postmortem examination of thrombosed coronary arteries has shown foam cell infiltration in most plaque rupture sites. Atherectomy specimens from culprit lesions responsible for acute coronary syndromes show significantly increased amounts of macrophages compared with specimens from patients with stable angina. Although the morphology of the plaque itself may vary, the cellular composition at the site of rupture is remarkably consistent with macrophages being the dominant cell.

Experimental evidence from in vitro⁴⁶ and in vivo systems⁴⁴ suggests that the macrophages present in atherosclerotic plaques are involved in active inflammation. Other components of the inflammatory response, including T lymphocytes, mast cells, and neutrophils, have been found in atherosclerotic plaques.⁴⁷ Interferon- γ , a cytokine produced within atheromas by activated T cells,⁴⁸ may play a crucial role in this process. Interferon- γ decreases interstitial collagen synthesis within the fibrous cap, inhibits smooth muscle cell proliferation, activates the apoptosis pathway in smooth muscle cells, and activates macrophages.⁴⁹ Active inflammation in areas of high stress may weaken the fibrous cap further and contribute to plaque rupture.

T-cell cytokines also induce the production of large amounts of molecules downstream in the cytokine cascade resulting in elevated levels of interleukin-6 and C-reactive protein in the peripheral circulation, which amplifies local and systemic inflammation. Elevated levels of C-reactive protein and interleukin-6 in patients with acute coronary syndromes are associated with a worse prognosis.

When activated, macrophages are capable of causing weakening of plaque structure by several mechanisms. These cells may

degrade the extracellular matrix by secreting various proteolytic enzymes. One such group of enzymes is the matrix metalloproteinases (MMPs). The MMPs are a family of zinc-dependent and calcium-dependent enzymes that are important in the resorption of the extracellular matrix in normal and pathologic conditions. These enzymes may be divided into subgroups based broadly on substrate preference.⁵¹ The MMP subgroups include collagenases, gelatinases, stromelysin, and membrane-type MMPs that act on various substrates, including collagen, elastin, proteoglycan, lamin, fibronectin, and basement membrane components. Taken together, these MMPs are capable of completely degrading all extracellular components, and may play a role in atherogenesis and plaque disruption. In addition, MMPs can be proinflammatory by facilitating inflammatory cells.

MMPs are secreted by macrophages, smooth muscle cells, and lymphocytes found within atherosclerotic plaques. Production and secretion of MMPs is a balance between several different factors. Numerous cytokines and growth factors, including interleukin-1, PDGF, and tumor necrosis factor- α , have been shown to induce the synthesis of MMPs. Conversely, several unrelated substances have been shown to inhibit MMP production, including heparin, corticosteroids, and tumor necrosis factor- β . MMPs are secreted as proenzymes or zymogens and require an activation step to become capable of degrading the extracellular matrix. When activated, the effects of the MMPs are controlled by a family of naturally occurring specific inhibitors, the tissue inhibitors of metalloproteinases. Several lines of investigation point to a possible role for MMPs in plaque rupture. Messenger RNA transcripts of one MMP family member, stromelysin, have been identified in macrophages and smooth muscle cells in fibrous and lipid-laden plaques.⁵² Other MMPs have been found in atherosclerotic, but not normal arteries.⁵³ Atherectomy specimens from patients with unstable angina have shown increased intracellular gelatinase B production compared with specimens from patients with stable angina.⁵⁴

Chronic immune stimulation within the atheroma may lead to the elaboration of several factors including cytokines and metalloproteinases that alter the structural integrity of the fibrous cap by inhibiting collagen synthesis and increasing matrix degradation. Taken together, these factors reduce the structural integrity of the plaque, rendering the fibrous cap weak and prone to rupture in a susceptible region of the plaque. More recent studies using in situ zymographic techniques have revealed a net excess of metalloproteinase activity and matrix degradation within fibrous caps, especially at the vulnerable shoulder region of plaques.⁵⁰

Rupture Triggers

Atherosclerotic plaques are constantly exposed to various mechanical and hemodynamic forces that may precipitate disruption of a vulnerable lesion. The importance of several external forces has been shown, including cap tension, cap and plaque compression, intraplaque hemorrhage, circumferential bending, longitudinal flexion, and hemodynamic forces.

Cap Tension

The blood pressure inside the artery exerts radial and circumferential forces across the arterial wall, which must be counteracted by tension within the wall to maintain vessel integrity. The circumferential tension is described by the law of Laplace, which relates intracavity pressure (blood pressure) and lumen radius

(vessel diameter) (Fig. 8-9). The higher the blood pressure or the larger the luminal diameter, the greater the tension is within the wall.⁵⁵ If components within the wall are unable to bear the tension, the stress may be redistributed to the adjacent structures. In coronary artery disease, the soft atheromatous core is unable to bear the imposed load resulting in a shift of these forces to the fibrous cap. Studies using simulated and real plaques have shown that soft eccentric pools of atheromatous gruel lead to the concentration of stress on the adjacent cap, especially near the shoulder region.³⁰ These areas of increased stress correlate with the actual area of plaque rupture in most specimens.⁵⁶

The consistency of the atheromatous gruel and the thickness of the fibrous cap are important determinants of plaque rupture. Atheromatous gruel with increased amounts of extracellular lipid in the form of cholesterol esters tends to be softer. Softer plaques are less able to handle increased wall stress, and redistribute these forces to the fibrous cap predisposing the lesion to rupture. The thickness of the fibrous cap is also an important factor in determining the ability of a given lesion to handle circumferential stress, with the thinner caps developing a greater amount of stress. Mildly to moderately stenotic lesions are associated with greater circumferential wall tension rather than more severe lesions. Active newer plaques are also noted to have positive remodeling of their vessel size as postulated by Glagov⁵⁷ and confirmed by intravascular ultrasound. This increase in vessel diameter can additionally contribute to increased wall stress promoting plaque rupture. These observations, along with several other factors, may help to explain why the less occlusive lesions tend to be the most clinically volatile.

Cap and Plaque Compression

In addition to rupture from the lumen into the plaque, the reverse process of disruption from the interior of the plaque into the vessel lumen may occur. This process is likely to be secondary to an increase in intraplaque pressure caused by vasospasm,

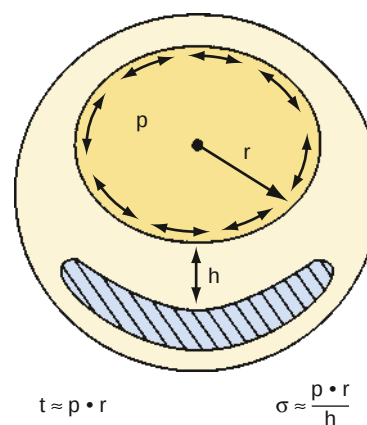


Figure 8-9. Circumferential tension on the fibrous cap of an atherosclerotic plaque containing a lipid pool (hatched area) is determined by the law of Laplace, which relates tension (t) to the intralumen pressure (p) and the lumen radius (r). The mean circumferential stress on the fibrous cap is related to circumferential tension and cap thickness (h). (From MacIsaac A, Thomas JD, Topol EJ: *Toward the quiescent coronary plaque*. *J Am Coll Cardiol* 1993;22:1228-1241.)

intraplaque hemorrhage, plaque edema, and collapse of compliant stenosis.

Vasospasm may rupture plaques by compressing the atheromatous core and blowing the fibrous cap into the lumen.⁵⁸ Intraplaque hemorrhage is an important contributor to the transformation of stable plaques into unstable lesions.⁵⁹ Microvascular incompetence is a likely source of intraplaque hemorrhage, although the exact mechanism is unknown. The rapid accumulation of erythrocyte-derived cholesterol contributes to the expansion of the volume of the necrotic core. In addition, it serves as a potent inflammatory stimulus resulting in greater macrophage density. These factors may increase plaque vulnerability to rerupture. Collapse of a severe but compliant stenosis because of negative transmural pressure may cause buckling of the vessel wall, which may disrupt the plaque.

Circumferential Bending

The propagating pulse wave generated by the systolic contraction of the heart produces changes in the lumen size and shape. The normal cyclic diastolic-systolic change in lumen diameter is 10%, although this number may be altered with advancing age or coronary disease.⁵⁵ The change in lumen configuration may produce deformation and bending of the atherosclerotic plaque, especially in the shoulder region.⁶⁰ Over time, these cyclic changes may weaken the plaque and lead to disruption. Sudden changes in vascular tone may also produce a bending of plaques that may cause rupture.

Longitudinal Flexion

With the beating of the heart, the coronary arteries tethered to the surface of the myocardium are subjected to longitudinal deformation. Similar to circumferential bending, this stretching of the arterial wall may weaken plaques or, with acute changes in the contractility of the heart, lead to plaque rupture.³¹

Hemodynamic Factors

Hemodynamic stress tends to be less than the mechanical forces produced by blood and pulse pressure. Hemodynamic factors such as shear stress can cause endothelial cell injury, however. Increased shear stress through stenotic lesions can theoretically

lead to plaque disruption, although this concept has not been shown in angiographic studies.⁶¹

Thrombosis

Thrombus formation is central to the development of acute coronary syndromes. Intrinsic and extrinsic factors may combine to cause rupture of the fibrous cap with exposure of the plaque's central components to the circulating blood and subsequent thrombosis.

Platelet Biology

Aggregation and activation of platelets play an essential role in normal hemostasis and acute coronary syndromes. After injury to the vessel wall, such as in plaque rupture, platelets are involved in the body's initial response (primary hemostasis). Effective primary hemostasis requires three critical events to occur: (1) platelet adherence, (2) platelet activation with granule release, and (3) platelet aggregation.

Platelet Adherence

Damage to the vessel wall exposes the highly thrombogenic sub-endothelial substrate and atheromatous core (specifically collagen and tissue factor) to circulating blood. Platelet adherence to the subendothelial collagen occurs almost immediately through interaction with platelet glycoprotein VI. Adhesion of platelets depends on many platelet receptors and adhesive membrane glycoproteins (Fig. 8-10).⁶² Glycoprotein Ib in the platelet membrane is important in the initial contact of platelets with von Willebrand factor in the subendothelium. von Willebrand factor forms a link between receptors on platelets and subendothelial collagen fibrils allowing platelets to remain attached to the vessel wall despite high shear forces. The membrane receptor complex, glycoprotein IIb/IIIa, binds many relevant proteins, including von Willebrand factor, fibrinogen, and fibronectin.⁶³ This complex plays a crucial role in initial platelet adhesion and platelet aggregation. Through this series of complex receptor-substrate interactions, the platelets form a firmly adherent monolayer and provide a foundation for further clot formation. This collagen-initiated pathway for platelet activation is independent of thrombin.

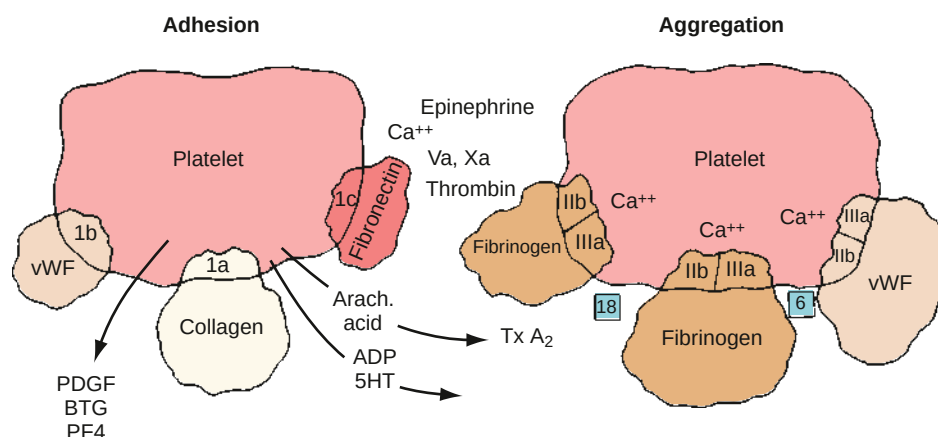


Figure 8-10. Schematic of platelet activation and receptor sites. 1a, 1b, 1c, and IIb/IIIa, glycoprotein receptor sites; 5HT, serotonin; ADP, adenosine diphosphate; Arach acid, arachidonic acid; BTG, β -thromboglobulin; PDGF, platelet-derived growth factor; PF4, platelet factor 4; TxA₂, thromboxane A₂; Va, activated factor V; vWF, von Willebrand factor; Xa, activated factor X. (From Myler RK, Frink RJ, Shaw RE, et al: *The unstable plaque: pathophysiology and therapeutic implications*. *J Invasive Cardiol* 1990;2:117-128.)

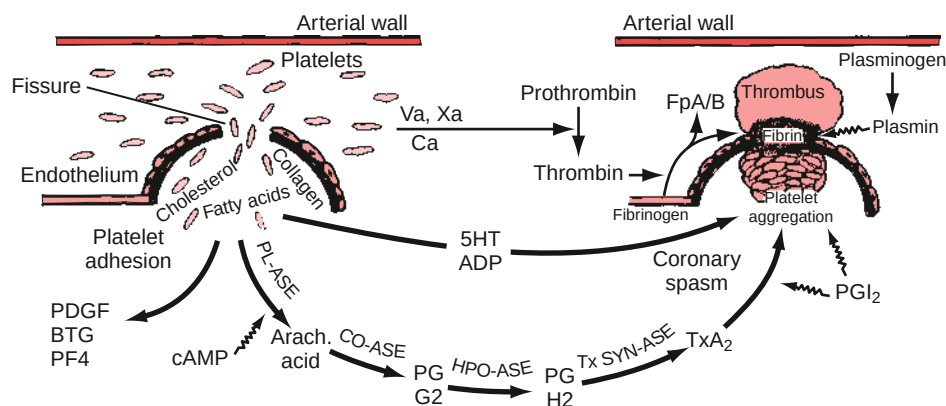


Figure 8-11. Schematic of unstable plaque. cAMP, cyclic adenosine monophosphate; CO-ASE, cyclooxygenase; FpA/B, fibrinopeptide A and B; HPO-ASE, hydroperoxidase; PG, prostaglandin; PI-ASE, phospholipase A2; Tx SYN-ASE, thromboxane synthetase. Other abbreviations correspond with those in Figure 8-10. (From Myler RK, Frink RJ, Shaw RE, et al: *The unstable plaque: pathophysiology and therapeutic implications. J Invasive Cardiol* 1990;2:117-128.)

Platelet Activation and Aggregation

Platelet adhesion leads to the release of certain intracellular products that result in further platelet activity. Platelet activation and secretion are regulated by several factors, including a change in the level of cyclic nucleotides, the influx of calcium, the hydrolysis of membrane phospholipids, and the phosphorylation of crucial intracellular proteins. Binding of agonists such as epinephrine, collagen, and thrombin to platelet receptors activates phospholipase C and phospholipase A_2 , membrane enzymes that catalyze the release of arachidonic acid. Through a series of complex reactions (Fig. 8-11), the released arachidonic acid is eventually converted to thromboxane A_2 and prostacyclin. These two products have opposite effects on platelet activation and vessel wall tone. Thromboxane A_2 is a powerful stimulus for platelet activation and aggregation and produces vasoconstriction, whereas prostacyclin acts to inhibit platelet activation and is a vasodilator. By selective production (or inhibition) of these two substances, changes in the level of platelet activation and vessel wall tone may be achieved.⁶⁴

Other active products secreted by platelets include endoglycosidases and heparin-cleaving enzymes from lysosomes, calcium, serotonin, adenosine diphosphate (ADP) from dense granules, von Willebrand factor, fibronectin, thrombospondin, and PDGF from α granules. These products have many important roles, including modification of coronary vascular tone, cellular proliferation and migration, and interaction with the coagulation system. It has been shown that PDGF is important in the proliferation and migration of smooth muscle cells after vessel damage.¹⁰ Released ADP binds to specific receptors that change the conformation of the glycoprotein IIb/IIIa complex so that it binds von Willebrand factor, fibrinogen, and fibronectin, linking adjacent platelets into a hemostatic plug.

Coagulation Cascade

The coagulation cascade system also plays a key role in normal hemostasis (secondary hemostasis) and acute coronary syndromes. The coagulation system comprises several plasma proteins involved in a series of reactions that culminate in the production of thrombin, which converts fibrinogen to fibrin. The fibrin produced via this system is important in strengthening the primary hemostatic plug formed by platelets.

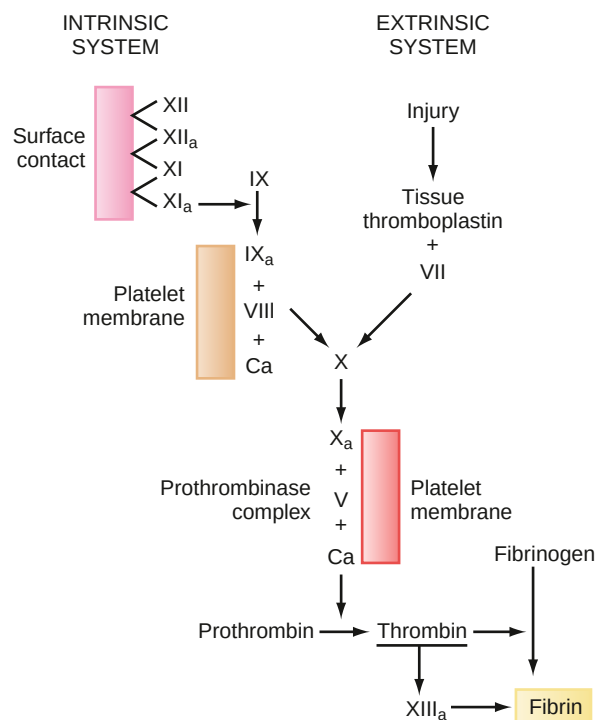


Figure 8-12. Intrinsic and extrinsic systems of the coagulation cascade. Note interaction between clotting factors (XII, XIIa, XI, XIa, IX, IXa, VII, VIII, X, Xa, and XIIa) and the platelet membrane. (Modified from Fuster V, Stein B, Ambrose JA, et al: *Atherosclerotic plaque rupture and thrombosis: evolving concepts*. *Circulation* 1990;82[Suppl 1]:II-47-II-59.)

The coagulation cascade can be divided into the intrinsic and the extrinsic pathways (Fig. 8-12). Both involve a series of reactions that require the formation of surface-bound complexes and the conversion of inactive precursor proteins into active proteases. The intrinsic pathway (factors XII, XIIa, XI, and XIa) is activated by exposure of blood components to the negatively charged, damaged subendothelium and medial surfaces of the vessel. The extrinsic pathway is activated by interaction of tissue factor released from the damaged vessel wall and factor VII.

Ultimately, these two pathways produce complexes that activate factor X. Activated factor X interacts with factor V, calcium, and phospholipid to form a complex that catalyzes the conversion of prothrombin to thrombin. This reaction is accelerated 1000-fold on the surface of activated platelets.

Thrombin has multiple functions in hemostasis, of which the primary function is the conversion of plasma fibrinogen to fibrin. After conversion to fibrin, the modified molecule polymerizes into an insoluble gel. The fibrin polymer is stabilized by cross-linking with other fibrin strands through the action of factor XIIIa, which results in an adherent thrombus. In addition, thrombin activates factors V, VIII, and XIII, and stimulates platelet secretion and aggregation.

Fibrinolysis

Balancing the prothrombotic events after vessel wall injury are several hemostatic mechanisms that favor fibrinolysis, decrease platelet aggregation, and cause vasodilation. Tissue plasminogen activator is the main physiologic activator of the fibrinolytic system with Hageman factor fragments and urokinase playing a minor role. Tissue plasminogen activator converts plasminogen adsorbed to the fibrin clot to plasmin. The plasmin acts to degrade the fibrin polymer into fragments resulting in clot lysis. Circulating thrombin stimulates several mechanisms designed to limit clot formation. The thrombin itself is inactivated by plasma protease inhibitors,⁶⁵ especially antithrombin III, which also inhibits activated factors VII, IX, and X. The thrombin also stimulates endothelial cells to release tissue plasminogen activator and produce prostacyclin and nitrous oxide, which act in concert to inhibit platelet aggregation and cause vasodilation.

Intact endothelial cells have several other important functions after vessel wall injury. These cells produce protein C, protein S, and heparin-like glycosaminoglycans that act to neutralize thrombin and activated factors V and VIII. In addition, stimulation of adenylyl cyclase and accumulation of cyclic adenosine monophosphate within these cells lead to inhibition of phospholipase A₂ and decreased production of thromboxane A₂ that causes increased vasodilation.

The diverse actions of the intrinsic fibrinolytic system act to offset the thrombogenic stimulus of vessel wall injury. In the usual situation, a delicate balance is maintained that results in the formation of enough thrombus to provide hemostasis at the site of vascular injury without producing significant flow disturbance within the vessel. After a significantly strong thrombogenic stimulus (i.e., deep vessel injury), however, massive platelet activation with subsequent fibrin deposition may overwhelm the intrinsic fibrinolytic system and cause thrombus formation, thrombus growth, and vessel vasospasm that leads to a significant reduction in blood flow.

Factors That Influence Thrombus Formation

Several local and systemic factors present at the time of plaque rupture may influence the degree and duration of thrombus deposition after vessel wall injury. Interaction of these factors may account for the different pathologic and clinical manifestations of acute coronary syndromes.

Local Factors

Degree of Vessel Wall Injury

The degree of vessel wall injury plays an important role in the biochemical response to plaque rupture. With mild amounts of vascular injury (superficial type III vascular damage), platelet

adherence reaches a maximum within 5 to 10 minutes, and results in a thrombus that can be dislodged by flowing blood. In contrast, deep vessel injury (deep type III injury) with exposure of fibrillar collagen results in markedly enhanced platelet deposition and thrombus formation that cannot be dislodged even at increased shear rates.⁶⁶ Tissue factor exposed by deeper injury likely contributes to the increased thrombogenicity by activating the extrinsic coagulation system.

Degree of Stenosis

The amount of platelet adherence is also determined by their transport into the injured area.⁶³ Transport of platelets is determined by the shear rate, which is the difference in blood velocity between the center of the vessel and along the vessel wall. Shear rates increase with decreasing vessel diameter (i.e., increased stenosis) and with increasing flow. In vitro studies mimicking mild vascular injury with exposure of de-endothelialized vessels to low shear rates show the adherence of only a single layer of platelets. With the same amount of injury, but at higher shear rates, the initial platelet deposition rate and maximal extent of deposition are significantly increased.⁶⁷

The degree of stenosis may influence the severity of thrombus formation by other mechanisms. That platelet deposition is greater with increasing amounts of stenosis suggests that platelet activation may be induced by shear forces generated by the sudden change in vessel geometry.⁶⁸ In addition, the flow characteristics of blood through the atherosclerotic lesion are partly determined by the extent of diameter stenosis. Flow is accelerated as blood passes through a stenosis and decelerates distal to the lesion. The sudden deceleration induces flow separation and recirculation vortices. The high shear rate area (the stenosis) favors platelet deposition, whereas the low shear rate area (the poststenotic recirculation zone) favors the deposition of fibrin. The combination of higher shear rates with large changes in flow dynamics seen in the more severely stenotic vessels results in a thrombus that is richer in platelets at the apex and contains larger amounts of fibrin distally.⁶³ These platelet-rich regions may be less amenable to fibrinolysis.⁶⁹

Residual Thrombosis

The presence of residual thrombus predisposes to recurrent thrombotic vessel occlusion by two mechanisms. The residual thrombus may encroach into the vessel lumen and cause a more stenotic lesion with increased shear rates, which may lead to further platelet activation and deposition.⁶⁶ Residual thrombus is a powerful thrombogenic stimulus. The degree of platelet deposition is increased twofold to fourfold on the surface of residual thrombi compared with on the surface of deeply injured arterial walls,⁷⁰ and the thrombi continue to grow despite heparin treatment.⁷¹ Residual thrombi may offset the effects of the natural fibrinolytic system and add to the extent of thrombosis after plaque rupture.

Systemic Factors

Experimental and clinical studies suggest that primary hypercoagulability can enhance thrombus formation. In this model, after plaque disruption, individuals with one or two "thrombogenic risk factors" may form a small amount of thrombus that is clinically silent. In other individuals with more prothrombotic risk factors, a larger thrombus may be formed after the same degree of vessel injury resulting in a more occlusive lesion that may produce unstable angina or acute MI.⁷²

The level of circulating catecholamines at the time of plaque disruption may have important consequences. Platelet aggregation and thrombin generation can be promoted by catecholamines.⁶⁸ Such diverse factors as cigarette smoking, emotional state, and time of day have a direct effect on catecholamine levels and may provide a link between these clinically recognized risk factors and acute coronary syndromes.

Metabolic abnormalities such as the metabolic syndrome or any of its components, including diabetes, hypertension, and obesity, may increase thrombogenicity mediated through the inflammation they induce. Patients with hypercholesterolemia show increased platelet reactivity at sites of vascular damage⁷³ and hypercoagulability.⁷⁴ There is evidence that platelet reactivity and coagulation are increased in diabetics, suggesting a direct mechanism for a prothrombotic state that may be responsible for the increased incidence of MI in these patients.⁶⁸

Finally, defective naturally occurring fibrinolysis may contribute to enhanced thrombus formation. High levels of naturally occurring inhibitors, such as plasminogen-activator inhibitor,⁷⁵ may predispose to an increased risk of acute coronary syndromes. High levels of lipoprotein(a) may also be important in ischemic heart disease. Apolipoprotein(a) is a glycoprotein present in lipoprotein(a) that has close structural homology with plasminogen.⁷⁶ This close homology may enable apolipoprotein(a) to act as a competitive inhibitor of plasminogen and cause a prothrombotic state. In addition, increased levels of other hemostatic proteins, such as fibrinogen and factor VII, have been identified in patients with ischemic heart disease.⁶⁸ Fibrinogen and factor VII activity are increased with advancing age, obesity, hyperlipidemia, diabetes, smoking, and emotional stress, all factors associated with an increased risk of MI.

Integrated Pathogenesis of Acute Coronary Syndromes

The acute coronary syndromes, unstable angina, non-ST elevation MI, ST elevation MI, and sudden cardiac death, all result from acute reductions in coronary blood flow. In these disease processes, atherosclerotic plaque rupture occurs and initiates a cascade of events that culminates in the formation of a thrombus overlying the damaged area. After plaque rupture and thrombus formation, there are different clinical outcomes influenced by location of the plaque rupture, existence of collaterals, the extent of the vessel injury, the degree of stenosis, and the thrombotic-thrombolytic equilibrium at the time of rupture (Fig. 8-13).

Conclusion

Coronary atherosclerosis is the most common cause of ischemic heart disease. Atherosclerosis without thrombosis is generally a benign disease, however. Disrupted atheromatous plaques are commonly associated with the formation of mural or occlusive thrombi, usually adherent to the area of damage. Certain types of plaques—those rich in lipids and surrounded by a thin fibrous cap—are the most prone to rupture. Numerous factors, intrinsic and extrinsic to the plaque itself, interact to cause the formation of a vulnerable lesion and, ultimately, plaque disruption. Fissuring or rupturing of plaques plays a fundamental role in the onset of acute coronary syndromes. In addition, repetitive damage to

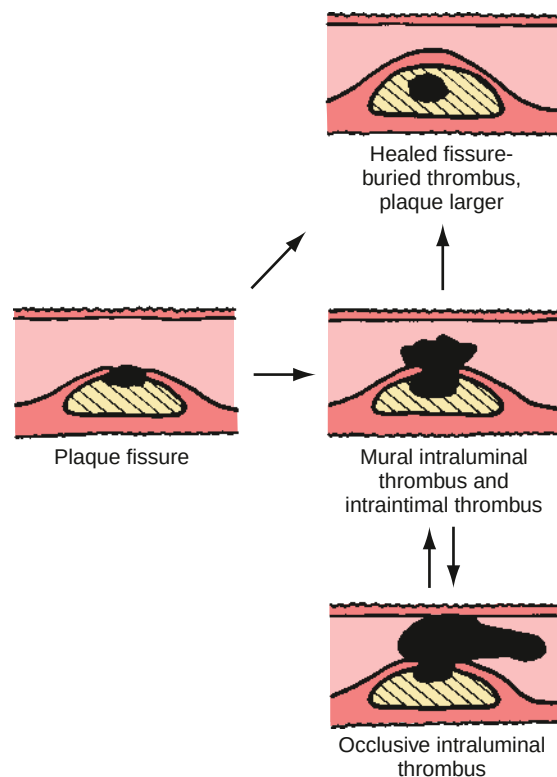


Figure 8-13. Schematic representation of the proposed outcome of atherosclerotic plaque fissuring. *Left panel*, Initial plaque fissure. *Upper right panel*, Fissure is sealed, and the incorporated thrombus undergoes fibrotic organization, contributing to the progression of coronary artery disease. *Middle right panel*, Fissure leads to intrainimal and intraluminal thrombosis resulting in partial or transient reduction of coronary flow as seen in unstable angina. *Lower right panel*, Fissure results in occlusive thrombosis, which, if persistent, can lead to myocardial infarction or sudden ischemic death, particularly in the absence of collateral flow. (From Davies M, Thomas A: *Plaque fissuring—the cause of acute myocardial infarction, sudden death, and crescendo angina*. *Br Heart J* 1985;53:363-373.)

the plaque with thrombosis and fibrotic organization is important in the insidious progression of coronary artery disease.

Over the past several years, much has been learned concerning the specific mechanisms involved in the pathophysiology of acute coronary syndromes. As discussed in subsequent chapters, this improved understanding has led to the development of treatments directed at specific steps in the pathogenesis of unstable angina, MI, and sudden cardiac death. Through these and future advances, physicians and scientists may hope to make a significant impact on the number one cause of death in industrialized society.

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Regulation of Hemostasis and Thrombosis

Maureane Hoffman

CHAPTER

9

Overview and Definitions

Hemostasis

Regulatory Mechanisms to Control Coagulation

Clinical Laboratory Testing

What Can Go Wrong with Hemostasis

Overview and Definitions

COAGULATION is the clotting of blood or plasma. Hemostasis is the process by which bleeding is stopped, and is the first component of the host response to injury. Its product is a hemostatic plug or hemostatic clot. Thrombosis is inappropriate clot formation within an intact vascular structure. Its product is a thrombus. Blood coagulation can occur at a site of injury (hemostasis), within an intact vessel (thrombosis), or in a test tube, but hemostasis is a physiologic process that can occur only in a living, bleeding organism.

Hemostasis consists of primary hemostasis, in which platelets adhere and are activated at a site of injury, and secondary hemostasis, in which the initial platelet plug is consolidated in a meshwork of fibrin. The hemostatic process represents a delicate, tightly regulated balance between effective activation of local hemostatic mechanisms in response to injury and control by regulatory mechanisms that prevent inappropriate activation or extension of coagulation reactions. The interactions of the protein components of coagulation can be studied in cell-free plasma and have been described as a “cascade” of proteolytic reactions. By contrast, the process of hemostasis occurs on cell surfaces in a tissue environment and is subject to regulation by various biochemical and cellular mechanisms.

The adequacy of procoagulant levels can be assessed in the routine plasma clotting assays: the prothrombin time (PT) and activated partial thromboplastin time (aPTT). Platelet number and function can be assessed in the clinical laboratory. Levels of individual plasma coagulation inhibitors and other regulatory proteins can also be assayed. There is no laboratory test, however, that can provide a global assessment of the adequacy of hemostasis or the risk of thrombosis. Each laboratory test gives only a part of the picture, and the assessment of hemostatic function always requires that laboratory results be interpreted in the context of the clinical picture.

Hemostasis

Because hemostasis involves more than simply getting blood to clot—it must clot at the right time and place and only to the extent needed to stop bleeding—our understanding of hemostasis must include a consideration not only of the proteins, but

also the cellular and tissue components that are needed to regulate the coagulation process adequately in vivo.

Necessary Components

Vascular Bed

It is very important that blood not clot within the vascular system. In the baseline state, vascular endothelial cells provide a nonthrombogenic interface with the circulating blood. Endothelial cells do not normally express molecules that support platelet adhesion or promote activation and activity of the coagulation proteins. In addition, the antithrombotic features of the endothelial surface go beyond simply being “inert” with respect to coagulation. The endothelium also expresses molecules that actively downregulate the coagulation reactions on its surface: principally thrombomodulin to localize activated protein C to the endothelial surface, and heparan sulfates to localize antithrombin (AT) to the endothelial surface. A further discussion of these mechanisms is presented in the section on thrombosis. These properties are crucial in preventing coagulation from being initiated at inappropriate sites within the vasculature and preventing appropriately initiated hemostatic reactions from spreading within the vascular tree.

Extravascular Tissues

When an injury disrupts a blood vessel, it allows blood to contact extravascular cells and matrix. Extracellular matrix proteins, such as collagen, fibronectin, thrombospondin, and laminin, interact with adhesive receptors on blood platelets and support formation of the initial platelet plug at the site of injury. Perivascular tissues also express significant levels of tissue factor (TF).^{1,2} Exposure of TF to blood initiates the process of thrombin generation on the surfaces of adherent platelets and ultimately leads to stabilization of the initial platelet plug in a fibrin clot (i.e., secondary hemostasis). Different tissues express different complements of matrix components and procoagulants. The tissue environment plays a role in determining the intensity of the procoagulant response to an injury.

Platelets

Membrane receptors for collagen and other subendothelial and extravascular matrix proteins are present on the platelet membrane and mediate binding of unactivated platelets at sites of

injury.³⁻⁵ Platelet binding is also mediated by von Willebrand factor (vWF) bridging between collagen and the platelet receptor glycoprotein (GP) Ib. These receptor binding events also transmit an activation signal to the platelets. Full platelet activation also requires stimulation by thrombin, however, which is produced as the coagulation reactions are initiated. The platelet surface receptor for fibrinogen, GPIIb/IIIa, rapidly changes conformation from an inactive to an active form on platelet activation.⁶ This change in conformation allows platelet aggregates to be stabilized by binding to fibrinogen even before conversion to fibrin begins. Platelet activation also initiates the synthesis of prostaglandins and thromboxanes—compounds that modulate platelet activation and promote vasoconstriction.⁷

Platelet adhesion and activation at a site of injury, in concert with local vasoconstriction, provides initial hemostasis for small caliber vessels. When hemostasis is achieved by these mechanisms, the subsequent stabilization of the platelet plug in a fibrin meshwork can proceed more effectively than if bleeding continues. Initial hemostasis may be established even if a deficiency of plasma coagulation proteins is present. The platelet plug is insufficient, however, to provide long-term hemostasis, and delayed rebleeding occurs if it is not reinforced by a stable fibrin clot during secondary hemostasis.

Coagulation Proteins

Adequate levels and function of each of a series of procoagulant proteins are required for hemostasis. The coagulation proteins can be organized into several groups based on their structural features.

The vitamin K–dependent factors include factors II (prothrombin), VII, IX, and X. These factors each have a structural domain in which several glutamic acid residues are post-translationally modified to γ -carboxyglutamic acid (Gla) residues by a vitamin K–dependent carboxylase.⁸ The vitamin K cofactor is oxidized from a quinone to an epoxide in the process. A vitamin K epoxide reductase cycles the vitamin K back to the quinone form to allow carboxylation of additional glutamic acid residues. The negatively charged Gla residues bind calcium ions. These binding interactions hold the Gla-containing proteins in their active conformation. The calcium-bound form of the Gla-domain is responsible for mediating binding of the coagulation factors to phospholipid membranes. Lipids with negatively charged head groups, particularly phosphatidylserine, are required for binding and activity of the Gla-containing factors.

The carboxylation process is inhibited by the anticoagulant warfarin, which competes with vitamin K for binding to the reductase.⁹ Inhibition by warfarin results in the production of undercarboxylated forms of the vitamin K–dependent proteins, which are nonfunctional.

The vitamin K–dependent procoagulants are zymogens (inactive precursors) of serine proteases. Each is activated by cleavage of at least one peptide bond. The activated form is indicated by the letter “a.” Factors VIIa, IXa, and Xa each require calcium ions, a suitable cell (phospholipid) membrane surface, and a protein cofactor for their activity in hemostasis.

Factor IIa (thrombin) is a little different from the activated forms of the other vitamin K–dependent factors. Its Gla domain is released from the protease domain during activation. It no longer binds directly to phospholipid membranes. It also does not require a cofactor to cleave fibrinogen and initiate fibrin assembly, or to activate platelet receptors. Factor IIa that escapes

the vicinity of a hemostatic plug can bind, however, to a cofactor on endothelial cell surfaces, thrombomodulin.¹⁰ After binding to thrombomodulin, factor IIa can no longer activate platelets or cleave fibrinogen. Instead, it triggers an antithrombotic pathway by activating protein C on the endothelial surface.

Proteins C and S are also vitamin K–dependent factors. They do not act as procoagulants, but rather as antithrombotics on endothelial surfaces.¹¹ Protein C is the zymogen of a protease, whereas protein S has no enzymatic activity, but serves as a cofactor for activated protein C. The activated protein C/protein S complex cleaves and inactivates factor Va and factor VIIIa, preventing propagation of thrombin generation on normal healthy endothelium.

Factors V and VIII are large structurally related glycoproteins that act as cofactors. They have no enzymatic activity of their own, but when activated by proteolytic cleavage, they dramatically enhance the proteolytic activity of factors Xa and IXa.

Factor VIII circulates in a noncovalent complex with vWF, which prolongs its half-life in the circulation. The vWF/factor VIII complex binds to the platelet surface via GPIb as vWF mediates adhesion of platelets to collagen under high shear conditions. Cleavage and activation of factor VIII releases it from vWF so that it can assemble into a complex with factor IXa on the platelet surface, where it activates factor X.

Factor V circulates in the plasma, and it is packaged in the alpha granules of platelets. It is released on platelet activation in a partially activated form. Plasma and platelet-derived factor V can be fully activated by cleavage by factor Xa or IIa. Factor Va then assembles into a complex with factor Xa on the platelet surface, where it activates prothrombin to factor IIa.

TF is also a cofactor, but is structurally unrelated to any of the other coagulation factors. Instead, it is related to one class of cytokine receptors.¹² This lineage emphasizes the close evolutionary and physiologic links between the coagulation system and the other components of the host response to injury. Rather than circulating in the plasma as do the other coagulation factors, TF is a transmembrane protein.¹³ TF serves as the cellular receptor and cofactor for factor VIIa. It is primarily expressed on cells outside the vascular space under normal conditions, although monocytes and endothelial cells can express TF in response to inflammatory cytokines. The factor VIIa/TF complex can activate factor IX and factor X, and is the major initiator of hemostatic coagulation.¹³

Another group of related proteins are the *contact factors*—factors XI and XII, prekallikrein, and high-molecular-weight kininogen. These proteins share the feature of binding to charged surfaces. The only one of this group that is needed for normal hemostasis is factor XI.¹⁴ The other contact factors may play a role, however, in thrombosis in some settings. Factor XI is a zymogen that can be activated to a protease by factor XIIa, but is likely activated primarily by thrombin during the hemostatic process. Factor XIa activates factor IX.

Fibrinogen provides the key structural component of the hemostatic clot. Two small peptides, fibrinopeptides A and B, are cleaved from fibrinogen by thrombin, and the resulting fibrin monomer polymerizes into a network of fibers. The fibrin polymer is stabilized further when it is cross-linked by activated factor XIII. Factor XIIIa is a transglutaminase that is activated by thrombin coincident with fibrin formation.¹⁵

Thrombin plays a key role in activating procoagulant and anticoagulant factors and triggering formation of fibrin. In addition,

thrombin has cytokine-like activities that bridge the transition between hemostasis, inflammatory/immune responses, and wound healing. Thrombin is truly a multifunctional molecule that affects the host response to injury at many levels.

Even before the structure and function of the various factors had been defined, their interactions had been studied during plasma clotting. In the 1960s, two groups proposed a “waterfall” or “cascade” model of the interactions of the coagulation factors leading to thrombin generation. These schemes were composed of a sequential series of steps in which activation of one clotting factor led to the activation of another, finally leading to a burst of thrombin generation.^{16,17} At that time, each clotting factor was thought to exist as a proenzyme that was activated by proteolysis. The existence of cofactors without enzymatic activity was not recognized until later. The original models were subsequently modified as information about the coagulation factors accumulated and eventually evolved into the Y-shaped scheme shown in Figure 9-1. The “cascade” model shows distinct intrinsic and extrinsic pathways that are initiated by factor XIIa and the factor VIIa/TF complex. The pathways converge on a “common” pathway at the level of the factor Xa/factor Va (prothrombinase) complex.

This scheme was not proposed as a literal model of the hemostatic process *in vivo*; rather, it was derived from studies of plasma clotting in a test tube and was intended to represent the biochemical interactions of the procoagulant factors. The coagulation “cascade” does reflect well the process of plasma clotting,

as in the PT and aPTT tests. The lack of any other clear and predictive concept of hemostasis has meant, however, that until more recently most physicians have also viewed the “cascade” as a model of physiology, and the PT and aPTT as reflecting the risk of clinical bleeding.

The limitations of the coagulation cascade as a model of the hemostatic process *in vivo* are highlighted by certain clinical observations. Patients deficient in the initial components of the intrinsic pathway—factor XII, high-molecular-weight kininogen, or prekallikrein—have a greatly prolonged aPTT, but no bleeding tendency. Patients deficient in factor XI also have a prolonged aPTT, but usually have a mild to moderate bleeding tendency. Other components of the intrinsic pathway have a crucial role in hemostasis because patients deficient in factor VIII or factor IX have a serious bleeding tendency even though the extrinsic pathway is intact. Similarly, patients deficient in factor VII also have a serious bleeding tendency even though the intrinsic pathway is intact. Although the cascade model accurately reflects the protein interactions that lead to plasma clotting, and is an essential guide to interpretation of PT and aPTT results, it is not an adequate model of hemostasis *in vivo*.

The numbering of the coagulation factors does not follow their order in the cascade. The coagulation factors were numbered roughly in the order in which they were discovered. Because many workers had described the same molecules under different names, designating them with roman numerals seemed the fairest way to reconcile the nomenclature confusion.¹⁸

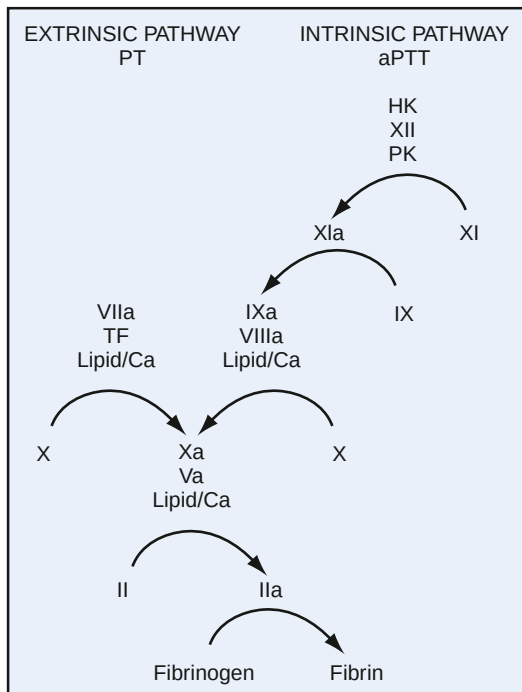


Figure 9-1. The extrinsic and intrinsic pathways in the modern cascade model of coagulation. These two pathways are conceived as each leading to formation of the factor Xa/Va complex, which generates thrombin (IIa). *Lipid/Ca* indicates that the reaction requires a phospholipid surface and calcium ions. These pathways are assayed clinically using the prothrombin time (PT) and activated partial thromboplastin time (aPTT). HK, high-molecular-weight kininogen; PK, prekallikrein.

Process of Hemostasis

Having all the right ingredients is not enough to ensure an effective hemostatic process. Cellular interactions are crucial to directing and controlling hemostasis. Normal hemostasis is impossible in the absence of platelets. In addition, TF is an integral membrane protein, and its activity is normally associated with cells, but platelets have little TF activity. Interactions between at least these two types of cells are necessary. Because different cells express different levels of procoagulants and anticoagulants and have different complements of receptors, it is logical that simply representing the cells involved in coagulation as phospholipid vesicles overlooks the active role of cells in directing hemostasis. Hemostasis *in vivo* can be conceptualized as occurring in a stepwise process, regulated by cellular components,¹⁹ as described subsequently.

Step 1: Initiation of Coagulation on Tissue Factor–Bearing Cells

The process of thrombin generation is initiated when TF-bearing cells are exposed to blood at a site of injury. TF is a transmembrane protein that acts as a receptor and cofactor for factor VII. When bound to TF, zymogen factor VII is rapidly converted to factor VIIa through mechanisms not yet completely understood, but that may involve factor Xa or noncoagulation proteases. The resulting factor VIIa/TF complex catalyzes activation of factor X and activation of factor IX. The factors Xa and IXa formed on TF-bearing cells have very distinct and separate functions in initiating blood coagulation.²⁰ The factor Xa formed on TF-bearing cells interacts with its cofactor, factor Va, to form prothrombinase complexes and generate small amounts of thrombin on the TF cells (Fig. 9-2). The small amounts of factor Va required for prothrombinase assembly on TF-bearing cells are activated by

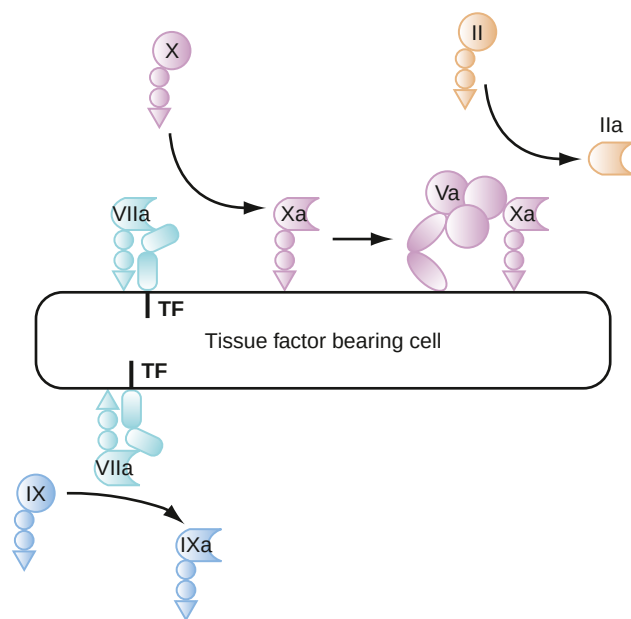


Figure 9-2. The initiation step in a cell-based model of hemostasis. Initiation occurs on the tissue factor (TF)-bearing cell as activated factor X combines with its cofactor, factor Va, to activate small amounts of thrombin.

factor Xa,²¹ activated by noncoagulation proteases produced by the cells,²² or released from platelets that adhere nearby. The activity of the factor Xa formed by the factor VIIa/TF complex is largely restricted to the TF-bearing cell because factor Xa that dissociates from the cell surface is rapidly inhibited by tissue factor pathway inhibitor (TFPI) or AT in the fluid phase.

In contrast to factor Xa, the factor IXa activated by factor VIIa/TF does not act on the TF-bearing cell and does not play a significant role in the initiation phase of coagulation. Factor IXa can diffuse to adjacent platelet surfaces because it is not inhibited by TFPI and is inhibited much more slowly by AT than factor Xa. Factor IXa can bind to a specific platelet surface receptor²³; interact with its cofactor, factor VIIIa; and begin to activate factor X directly on the platelet surface.

The small amount of thrombin produced on the TF-bearing cells is insufficient to clot fibrinogen, but it is sufficient to initiate events that amplify the initial procoagulant signal and “prime” the clotting system for a subsequent burst of platelet surface thrombin generation. This thrombin is responsible for^{24,25} (1) activating platelets, (2) activating factor V, (3) activating factor VIII and dissociating factor VIII from vWF, and (4) activating factor XI.

It is likely that most (extravascular) TF is bound to factor VIIa even in the absence of an injury, and that low levels of factor IXa, factor Xa, and thrombin are produced on TF-bearing cells at all times. This process is kept separated from key components of hemostasis, however, by an intact vessel wall. The very large components of the coagulation process are platelets and factor VIII bound to multimeric vWF. These components normally come into contact with the extravascular compartment only when an injury disrupts the vessel wall. Platelets and factor VIII/vWF leave the vascular space and adhere to collagen and other matrix components at the site of injury.

Step 2: Amplification of the Procoagulant Signal by Thrombin Generated on the Tissue Factor–Bearing Cell

Binding of platelets to collagen or via vWF during primary hemostasis leads to partial platelet activation. The coagulation process is most effectively initiated, however, when enough thrombin is generated on or near the TF-bearing cells to trigger full activation of platelets. Thrombin diffuses through the fluid phase and binds to its receptor GPIb²⁶ and cleaves its proteolytically activated receptors.²⁷ These two receptor types synergize in mediating platelet activation. The small amounts of thrombin generated during the initiation step are also responsible for activation of coagulation factors XI and VIII on the platelet surface in the amplification step, as illustrated in [Figure 9-3](#).

Platelets not only plug the vascular defect at a site of injury, but also provide the specialized membrane surface on which activation of many of the coagulation proteins occurs. Unactivated platelets express a very low level of phosphatidylserine, the primary procoagulant phospholipid, on their surfaces. On activation, phosphatidylserine is rapidly translocated from the inner to the outer leaflet of the platelet plasma membrane. It is then available to support binding and activity of the coagulation complexes.²⁸

Platelet secretion of granule contents occurs more slowly after activation than membrane surface changes. Dense and alpha granules within the platelet cytoplasm contain numerous components that play a role in the coagulation process, such as partially activated factor V, factor VIII/vWF, factor XIII, fibrinogen, protease inhibitors, and platelet agonists (adenosine diphosphate [ADP], epinephrine, and serotonin). Secretion of these platelet agonists enhances platelet activation further. When platelets are activated, the cofactors Va and VIIIa are rapidly localized on the platelet surface.²⁹ Factor IXa formed by the factor VIIa/TF complex can diffuse through the fluid phase, bind to the surface of activated platelets, and assemble into a complex with factor VIIIa. Factor XI activated by thrombin on the platelet surface^{25,30} can activate more factor IX from the plasma to factor IXa. At the end of the amplification phase, the platelets accumulated at the injury site are activated and have bound activated coagulation factors on their surfaces.

Step 3: Propagation of Thrombin Generation on the Platelet Surface

The multiple positive feedback mechanisms of the amplification phase rapidly lead to a burst of thrombin generation in the propagation phase, as illustrated in [Figure 9-4](#). The “tenase” (factor IXa/factor VIIIa) complexes progressively activate factor X from the plasma to factor Xa on the platelet surface. Factor Xa then associates with factor Va to support a burst of thrombin generation of sufficient magnitude to produce a stable fibrin clot.

The large amount of thrombin generated on the platelet surface is responsible for stabilizing the hemostatic clot in more ways than just promoting fibrin polymerization. Most of the thrombin generated during the hemostatic process is produced after the initial fibrin clot is formed. The platelet-produced thrombin also stabilizes the clot by (1) activating factor XIII,³¹ (2) activating the thrombin-activated fibrinolysis inhibitor,³² (3) cleaving the platelet PAR-4 receptor,³³ and (4) being incorporated into the structure of the clot. Activated factor XIII covalently cross-links the fibrin strands and increases resistance to plasmin degradation. Thrombin-activated fibrinolysis inhibitor also increases resistance to fibrinolysis by cleaving off lysines

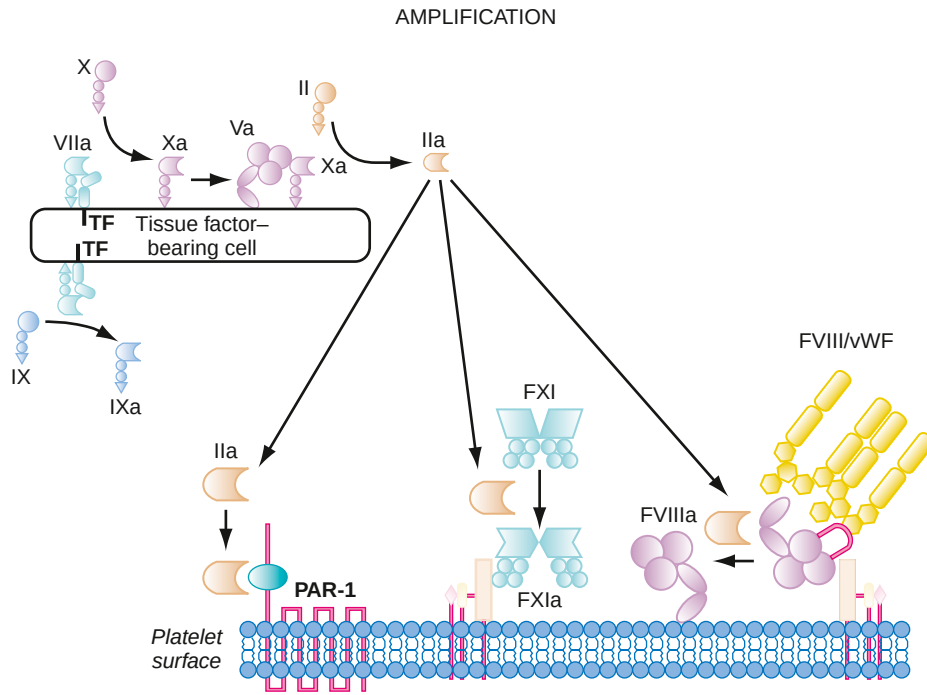


Figure 9-3. Amplification step in a cell-based model of hemostasis. The small amount of thrombin generated on tissue factor (TF)-bearing cells amplifies the procoagulant response by diffusing to the platelet surface, where it activates platelets via the protease activated receptor-1 (PAR-1), activates factor XI, and activates factor VIII and releases it from its carrier molecule von Willebrand factor (vWF).

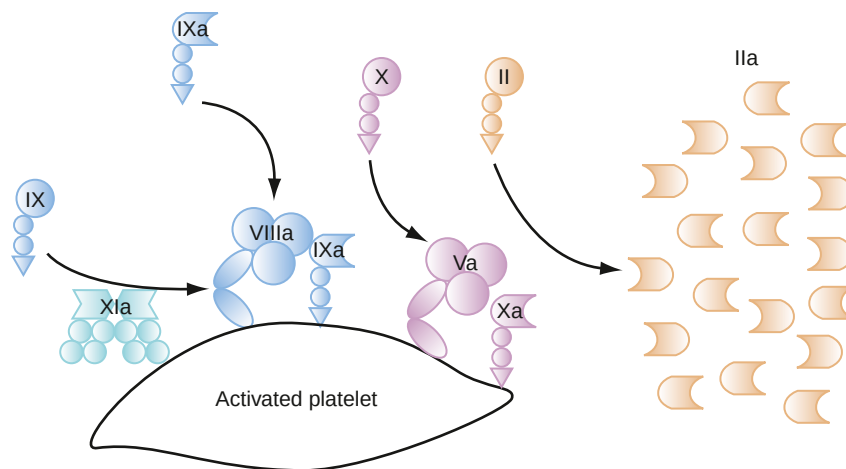


Figure 9-4. Propagation step in a cell-based model of hemostasis. The activated coagulation factors bound to the platelet surface during the amplification phase progressively activate factor X and factor II from the plasma, resulting in a large burst of thrombin production.

from the fibrin strands that serve as sites for fibrinolytic enzyme binding. Activation of platelet PAR-4 receptors promotes clot contraction, which pulls together the edges of a wound and makes the hemostatic plug more dense and impermeable. "Excess" thrombin produced during the hemostatic process can remain bound within the fibrin polymer and retains its proteolytic activity. It can rapidly activate more platelets and clot more fibrinogen if the hemostatic plug is disrupted and bleeding resumes.

The role of factor XI in hemostasis has been controversial because even severe factor XI deficiency does not result in a hemorrhagic tendency as severe as that in severe factor VIII or factor IX deficiency. This situation can be explained if factor XI is viewed as a "booster" of thrombin generation. Factor XI is not essential for platelet-surface thrombin generation, as are factor IX and factor VIII. Rather, factor XIa activates additional factor IXa on the platelet surface to supplement factor

IXa/factor VIIIa complex formation and enhance platelet surface factor Xa and thrombin generation. Its deficiency does not compromise hemostasis to as great an extent as factor IX or factor VIII deficiency.

Our knowledge of the platelet contribution to thrombin generation continues to evolve. There is evidence that there are multiple types of activated platelets. Platelets with the highest procoagulant activity are produced when they are stimulated with thrombin and collagen; these have been referred to as COAT (*collagen and thrombin stimulated*) platelets.³⁴ These platelets have enhanced thrombin-generating ability because of enhanced binding of tenase and prothrombinase components.^{35,36} The in vivo relevance of the COAT platelet phenomenon is unclear, but it may be that the greatest procoagulant activity is generated on platelets that have bound to collagen matrix and been exposed to thrombin. When the exposed collagen is covered by a platelet/fibrin layer, additional platelets that

accumulate are not activated to the COAT state—tending to damp down the procoagulant signal when the area of the wound has been walled off by a hemostatic clot.

Even though each phase of the cell-based model of hemostasis has been depicted as a discrete step, the phases should be viewed as an overlapping continuum of events. Thrombin produced on the platelet surface early in the propagation phase may initially cleave substrates on the platelet surface and continue to amplify the procoagulant response, in addition to leaving the platelet and promoting fibrin assembly.

The cell-based model of hemostasis shows us that the extrinsic and intrinsic pathways are not redundant. We can consider the extrinsic pathway to consist of the factor VIIa/TF complex working with the factor Xa/Va complex, and the intrinsic pathway to consist of factor XIa working with the complexes of factors VIIIa/IXa and factors Xa/Va. The extrinsic pathway operates on the TF-bearing cell to produce small amounts of thrombin that initiate the coagulation process and amplify the initial procoagulant signal. By contrast, the intrinsic pathway operates on activated platelet surfaces to produce the large burst of thrombin that leads to formation and stabilization of the fibrin clot.

Regulatory Mechanisms to Control Coagulation

Although the inability to provide effective hemostasis is a serious problem, the inability to limit coagulation to sites of hemostasis is at least as great a problem. Multiple biochemical and cellular regulatory mechanisms have evolved to limit and localize the coagulation reactions. The coagulation reactions do not “cascade” unimpeded into a torrent of thrombin production, but must instead overcome a series of regulatory barriers.

Plasma Protease Inhibitors

Several circulating protease inhibitors can inactivate one or more of the coagulation proteases. The coagulation proteases are relatively protected from inhibition while bound to a membrane surface. Proteases that escape into the fluid phase are subject to inhibition, however. The presence of inhibitors does not prevent activation and activity of coagulation, but tends to confine the coagulation proteases to act on the cell surfaces on which they were activated.

AT (formerly called antithrombin III) plays a particularly important role in regulating hemostasis. AT is a serine protease inhibitor (serpin) that can inhibit most of the procoagulant factors, including factors IIa, VIIa, IXa, Xa, and XIa. The effectiveness of AT is increased by binding to heparinoids on the endothelial surfaces and by exogenous heparins. Hereditary and acquired deficiencies of AT lead to a significant thrombotic tendency.³⁷

TFPI is also an important control mechanism. This molecule is a multifunctional Kunitz-type inhibitor.³⁸ One of its Kunitz domains inhibits factor Xa. When it has bound factor Xa, another Kunitz domain can bind factor VIIa in the factor VIIa/TF complex. TFPI can assist in localizing factor Xa to the cell surface on which it was activated and limiting the activity of the TF pathway.

Not only are the plasma protease inhibitors key players in confining a clot to the proper location, but they also impose a threshold effect on activation of coagulation.³⁹ In the presence

of inhibitors, coagulation does not proceed unless procoagulant factors are generated in sufficient amounts to overcome the effects of inhibitors. If the triggering event is not sufficiently strong, the system returns to baseline rather than continuing through the coagulation process. Under pathologic conditions, the trigger for clotting may be so strong as to overwhelm the control mechanisms and lead to disseminated intravascular coagulation or thrombosis.

Endothelial Antithrombotic Mechanisms

When a fibrin/platelet clot is formed over an area of injury, the clotting process must be terminated to avoid thrombotic occlusion in adjacent normal areas of the vasculature. If the coagulation mechanism were not controlled, clotting could extend throughout the vascular tree after even a modest procoagulant stimulus.

Endothelial cells play a major role in confining the coagulation reactions to a site of injury. Conversely, endothelial damage or dysfunction can play a major role in promoting thrombosis. Endothelial cells have several types of anticoagulant/antithrombotic activities (Fig. 9-5). The protein C/protein S/thrombomodulin system is activated in response to thrombin generation.⁴⁰ Some of the thrombin formed during hemostasis can diffuse away or be swept downstream from a site of injury. When thrombin reaches an intact endothelial cell, it binds to thrombomodulin on its surface. The thrombin/thrombomodulin complex activates protein C, which is localized to the endothelial surface by binding to the endothelial protein C receptor (EPCR). The activated protein C can move into a complex with its cofactor, protein S, and inactivate any factor Va or factor VIIIa that has found its way to the endothelial cell membrane; this prevents the generation of additional thrombin in the intact vasculature.

Endothelial cells also localize anticoagulant protease inhibitors to their surfaces. AT binds to the glycosaminoglycan heparan sulfate on the endothelial surface, which enhances inactivation of proteases near the endothelium.⁴¹ TFPI can also be bound to heparan sulfate or linked to the endothelial surface via a glycosyl phosphatidylinositol (GPI) anchor. Endothelial

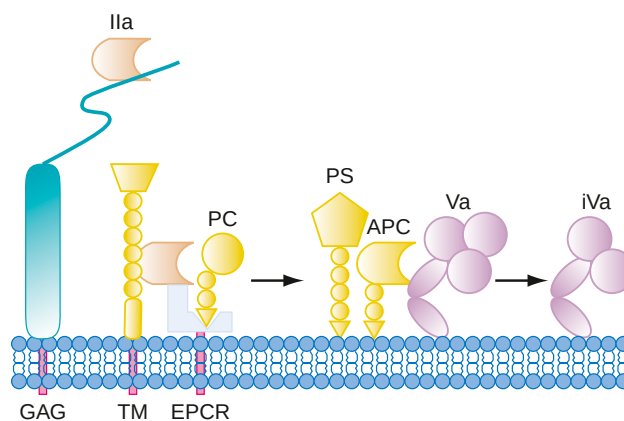


Figure 9-5. Antithrombotic mechanisms of the endothelial cell surface. Endothelial cells express glycosaminoglycan (GAG) molecules containing heparan sulfate to which thrombin and antithrombin can bind. They also express thrombomodulin (TM) and the endothelial protein C receptor (EPCR), which localize components of the protein C/protein S system to the endothelial surface.

cells also inhibit platelet activation by releasing the inhibitors prostacyclin and nitric oxide, and degrading ADP by their membrane ecto-ADPase, CD39.⁴²

Fibrinolysis

Even as the fibrin clot is being formed in the body, the fibrinolytic system is being initiated to disrupt it. The final effector of the fibrinolytic system is plasmin, which cleaves fibrin into soluble degradation products. Plasmin is produced from the inactive precursor plasminogen by the action of two plasminogen activators: urokinase-type plasminogen activator (uPA) and tissue-type plasminogen activator (tPA). The plasminogen activators are regulated by plasminogen activator inhibitors. Plasminogen is found at a much higher plasma concentration than the plasminogen activators. The availability of the two plasminogen activators in the plasma generally determines the extent of plasmin formation. tPA release from endothelial cells is provoked by thrombin and venous occlusion.⁴³ tPA and plasminogen bind to the evolving fibrin polymer. When plasminogen is activated to plasmin, it cleaves fibrin at specific lysine and arginine residues, resulting in dissolution of the fibrin clot. The fibrinolytic system is crucial to removing an appropriate hemostatic clot as wound healing occurs. It is also essential to removing intravascular thrombi before significant tissue injury can occur. The pulmonary vasculature can release large amounts of fibrinolytic enzymes to remove small thromboemboli that become lodged there.

Intravascular deposition of fibrin is also associated with the development of atherosclerosis. An effective fibrinolytic system tends to protect against the chronic process of atherosclerotic vascular disease and the acute process of thrombosis. Conversely, defects of fibrinolysis increase the risk of atherothrombotic disease. Elevated levels of plasminogen activator inhibitor-1, an inhibitor of fibrinolysis, are associated with an increased risk of atherosclerosis and thrombosis,⁴⁴ as are decreased levels of plasminogen.⁴⁵ The effectiveness of hemostasis *in vivo* depends not only on the procoagulant reactions, but also on the fibrinolytic process.

Clinical Laboratory Testing

The commonly used clinical coagulation tests do not reflect the complexity of hemostasis *in vivo*; this does not mean that the PT and aPTT are useless. Clinicians need to understand what these tests can and cannot tell us. These “screening” coagulation tests are abnormal when there is a deficiency of one or more of the soluble coagulation factors. They do not predict what the risk of clinical bleeding will be. Two patients with identical aPTT values can have drastically different risks of hemorrhage. All of the common coagulation tests, including the PT, aPTT, thrombin clotting time, fibrinogen levels, and coagulation factor levels, tell us something about the plasma level of soluble factors required for hemostasis. Their clinical implications must be evaluated by the ordering physician. Just because the PT and aPTT are within the normal range, it does not follow that the patient is at no risk for bleeding. Conversely, a mild elevation in these clotting times does not mean that the patient is at risk for bleeding after an invasive procedure.

Many whole-blood coagulation tests are being presented as a means of evaluating overall hemostatic status in selected clinical settings. Although whole-blood tests have the advantage

that they may reflect the contributions of platelets to the hemostatic process, they still do not reflect the contributions of the TF-bearing cells and local tissue conditions. Any laboratory test requires skilled interpretation and clinical correlation in evaluating the true risk of bleeding.

What Can Go Wrong with Hemostasis

Hemorrhage

Many patients who develop hemorrhage do not have a pre-existing bleeding tendency. Bleeding after surgical or accidental trauma or during a medical illness is often associated with the development of an acquired coagulopathy. The hallmark of coagulopathy is microvascular bleeding, which is oozing from cut surfaces and minor sites of trauma, such as needle-sticks. Microvascular bleeding can lead to massive blood loss. Causes of coagulopathic bleeding include consumption of coagulation factors and platelets, excessive fibrinolysis, hypothermia, and acidosis.

Consumption of Coagulation Components

Disseminated intravascular coagulation (DIC) normally comes to mind in relation to consumption. Clotting factors and platelets can also be consumed, however, during appropriate physiologic attempts at hemostasis. In this case, it is appropriate to replace the depleted factors with transfusion therapy.

DIC can be much more complicated to manage.⁴⁶ The mainstay of treatment is to treat the underlying disorder, such as sepsis. In early or mild/compensated DIC, administration of low-dose heparin may be considered to control the procoagulant response to inflammation, infection, or malignancy. In more severe or advanced DIC, replacement therapy may be necessary to attempt to manage the bleeding tendency associated with depletion of coagulation factors and platelets.

Excessive Fibrinolysis

The process of fibrinolysis is initiated as the fibrin clot assembles. Fibrin serves as the framework to which plasminogen binds and is activated to plasmin by tPA and uPA. Even when formation of a fibrin clot does not succeed at establishing hemostasis, a significant amount of fibrinolytic activity may still be generated and thwart subsequent efforts at hemostasis. Fibrinolytic inhibitors have proven to be useful in some circumstances.

Hypothermia

Many patients become hypothermic during medical illness or after surgical or accidental trauma.⁴⁷ Hypothermia can directly interfere with the hemostatic process by slowing the activity of the coagulation enzymes. Less well recognized is the finding that platelet adhesion and aggregation is impaired even in mild hypothermia.⁴⁸ In hypothermic coagulopathic patients, increasing the core temperature can have a beneficial effect on bleeding by improving platelet function and coagulation enzyme activity.

Acidosis

Acidosis can have an even more profound effect on the coagulation process than hypothermia, and the two metabolic abnormalities often coexist. A decrease in the pH from 7.4 to 7.2 reduces the activity of each of the coagulation proteases by more than half.⁴⁹ Acidosis should be considered as a possible contributor to coagulopathic bleeding in medical and surgical patients.

Thrombosis

Disruption of the normal regulatory functions of any of the components of hemostasis can result in thrombosis. Generally, thrombosis is a multifactorial problem—congenital and acquired abnormalities in the antithrombotic activities of the vascular endothelium can synergize with enhanced platelet reactivity and alterations in procoagulant or anticoagulant levels ultimately to produce thrombosis. The risk of thrombosis in any given individual at and any given time is a product of the individual's accumulated genetic, environmental, and lifestyle risk factors.

Inflammation can trigger numerous responses that predispose further to thrombosis.⁵⁰ The coagulation and inflammatory responses interface at the levels of the tissue factor pathway, the protein C/protein S system, and the fibrinolytic system. Proinflammatory cytokines can affect all of these coagulation mechanisms, and coagulation proteases, anticoagulants, and fibrinolytic enzymes can modulate inflammation by specific cell receptors. Inflammatory cytokines can promote an increase in tissue factor and a decrease in thrombomodulin by the endothelium.⁵¹ Activation of coagulation is closely linked with the progression of atherosclerotic vascular lesions. Progressively impaired vascular function further predisposes to thrombosis. Ultimately, rupture of an unstable atherosclerotic plaque can expose procoagulant activity and provoke an acute thrombotic event.⁵² Management of cardiovascular disease often involves preventing and managing thrombosis and its consequences. Venous and arterial thrombosis tend to have different mechanisms and risk factors, and are best managed by different strategies.

Venous Thrombosis

The major mechanism of venous thrombosis is related to inappropriate activation of the coagulation reactions—often on inflamed endothelium. Stasis can play an exacerbating role when activated factors are not rapidly diluted in flowing blood. Abnormalities of coagulation factors and increased levels of coagulation factors that potentially increase thrombin generation are linked to venous thrombosis.^{53,54} The inherited hemostatic abnormalities most often associated with venous thromboembolism are factor V Leiden and factor II G20210A mutations, and deficiencies in AT, protein C, and protein S. Acquired abnormalities also play a major role. Major clinical risk factors for venous thromboembolism include malignancy, myeloproliferative disorders, trauma, surgery (especially orthopedic surgery), immobilization or paralysis, and prior venous thromboembolism. Minor risk factors include advanced age, obesity, bed rest, use of hormone replacement therapy or oral contraceptives, pregnancy and postpartum period, and inflammatory bowel disease.

Venous thrombosis is extremely common in hospitalized patients. Although it is often asymptomatic, it is a significant cause of morbidity and of mortality from pulmonary embolism. Incidence of venous thrombosis can be reduced dramatically by the appropriate use of thromboprophylaxis with anticoagulants such as heparin and low-molecular-weight heparins.⁵⁵⁻⁵⁷

Arterial Thrombosis

Arterial thrombosis is primarily related to formation of platelet aggregates at sites of high shear and turbulent flow. As atherosclerotic plaques develop, they not only alter the

nonthrombogenic nature of the endothelium, but also disrupt normal laminar blood flow and produce increased turbulence. Although increased platelet reactivity can contribute to arterial thrombosis, the vascular alterations play a key role in promoting platelet adhesion and activation.⁵⁸ There is also considerable evidence that TF-mediated activation of the coagulation system and thrombin generation can be important contributors to arterial thrombosis.⁵⁹ Thrombin generation at a site of plaque rupture can be the trigger for platelet activation and adhesion.⁶⁰

The risk factors most closely linked to arterial thrombosis are smoking, hypertension, dyslipidemia, and diabetes. Inherited thrombophilia plays much less of a role in arterial than venous thrombosis.⁶¹ Lifestyle changes can have a significant impact on the risk of arterial thrombosis. The most effective management is by therapies targeting platelet activation and adhesion. The results of more recent studies indicate that in addition to the efficacy of aspirin in reducing cardiac events in patients with acute coronary syndromes, more potent antiplatelet and anticoagulant therapies are valuable in high-risk patients.

What Happens after the Bleeding Stops

When hemostasis is completed, the process of wound healing can begin. Many of the activities involved in wound healing are influenced by thrombin. Thrombin plays a major role in platelet activation and degranulation. Several key cytokines modulating wound healing are released from activated platelets, including transforming growth factor- β and platelet-derived growth factor. The amount and rate of thrombin generated during hemostasis influences the initial structure of the fibrin clot—the framework on which cell migration occurs. In addition, thrombin has chemotactic and mitogenic activities for macrophages, fibroblasts, smooth muscle cells, and endothelial cells. Generation of the “right” amount of thrombin during the coagulation process not only may be essential for effective hemostasis, but also may set the stage for effective wound healing. Conversely, thrombin generation at sites of vascular injury plays a role in the development of local inflammatory changes and progression of atherosclerotic lesions.

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Coronary Artery Disease

Acute Myocardial Infarction

SECTION



Diagnosis of Acute Myocardial Infarction

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CHAPTER

10

History
Definition of Myocardial Infarction
Biochemical Markers of Acute Myocardial Infarction
Clinical Evaluation

Electrocardiogram
Imaging Techniques
Reinfarction
Conclusion

MYOCARDIAL INFARCTION (MI) describes the process of myocardial cell death caused by ischemia, or the perfusion imbalance between supply and demand within the coronary arteries resulting from an acute thrombotic process. In the United States in 2006, approximately 16.8 million (7.6%) people had coronary heart disease, and an estimated 935,000 people experienced an acute MI that year, of which more than 150,000 resulted in death.¹ In 2009, it was estimated that approximately every 25 seconds an American would have a coronary event, and about every minute an individual would die from one.¹ The early recognition and diagnosis of acute MI is vital for the institution of therapy to limit myocardial damage and preserve cardiac function.

Acute coronary syndrome (ACS) refers to the constellation of clinical symptoms caused by active myocardial ischemia. Patients with ACS can be grouped into two major categories of acute MI: (1) patients with new ST segment elevation on the electrocardiogram (ECG) that is diagnostic of acute ST segment elevation myocardial infarction (STEMI), and (2) patients with non-ST segment elevation myocardial infarction (NSTEMI) who have positive cardiac biomarkers in an appropriate clinical setting, with or without ECG ST segment depression or T wave inversion.²

International registry data found that of patients who presented with an ACS, 25% experienced NSTEMI, whereas 30% had STEMI.³ Clinical trials have established the benefit of early reperfusion therapy in patients with STEMI and an early invasive strategy in patients with NSTEMI, and so a rapid and accurate assessment of patients with suspected acute MI is essential for optimal management.^{2,4} This chapter describes the diagnostic modalities for the evaluation of patients with suspected acute MI.

History

There have been considerable advances in the detection of myocardial injury and necrosis in the last several decades. As a result, the definition of MI has evolved over time. Beginning in the 1950s, the World Health Organization used epidemiologic data to define acute MI as the presence of at least two of the following three criteria: (1) clinical symptoms suggestive of myocardial ischemia, (2) ECG abnormalities, or (3) elevation in serum markers indicative of myocardial necrosis.⁵ The development of more sensitive and specific biomarkers of myocardial necrosis and precise imaging techniques for ischemic myocardial

Table 10-1. Classification of Myocardial Infarction (MI)

Type	
1	Spontaneous MI resulting from a primary coronary event, such as coronary artery plaque erosion, or rupture, fissure, or dissection
2	MI associated with ischemia secondary to either increased oxygen demand or decreased supply, such as in coronary artery spasm, coronary embolism, anemia, arrhythmia, hypertension, or hypotension
3	Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by new ST segment elevation, new left bundle branch block, or evidence of fresh thrombus in a coronary artery by angiography or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood
4a	MI associated with percutaneous coronary intervention
4b	MI associated with stent thrombosis as documented by angiography or autopsy
5	MI associated with coronary artery bypass graft surgery

Modified and adapted from Thygesen K, Alpert JS, White HD: Universal definition of myocardial infarction. *J Am Coll Cardiol* 2007;50:2173-2195.

dysfunction has led to further refinement of the diagnosis of MI. In 2007, a Global Task Force assembled from the European Society of Cardiology, the American College of Cardiology, the American Heart Association, and the World Heart Federation published a consensus statement that sought to standardize cardiac biomarker detection, incorporate cardiac imaging into the evaluation of a patient with MI, and classify the different types of MIs, furthering the evolution of the definition of acute MI.⁶

Definition of Myocardial Infarction

MI is defined by the presence of myocardial necrosis combined with the clinical presentation of myocardial ischemia. The diagnosis of acute MI requires the increase or decrease (or both) of cardiac biomarkers (preferably troponin) with at least one value greater than the 99th percentile of the upper reference limit and at least one of the following: symptoms of ischemia, ECG changes indicative of active ischemia (new ST segment–T wave changes or new left bundle branch block [LBBB]), or imaging evidence of new regional wall motion abnormality or loss of viable myocardium.⁶ The type of MI can be classified further depending on the etiology of the infarct (Table 10-1).

Biochemical Markers of Acute Myocardial Infarction

The ideal biochemical marker should be present in high concentration in the myocardium, absent in noncardiac tissue, released rapidly in a linear fashion after myocardial necrosis, and present in the serum long enough to be easily detectable by an

inexpensive and widely available assay. Table 10-2 summarizes serum cardiac markers. Cardiac biomarkers are an essential component of the criteria used to establish the diagnosis of acute MI. Troponins have become the preferred biomarkers for the detection of myocardial necrosis and are a class I indication in the diagnosis of MI.⁶⁻⁸ The improved sensitivity and tissue specificity of cardiac troponins compared with creatine kinase MB (CK-MB) and other conventional cardiac biochemical markers of acute MI have been well established.^{8,9} Troponins are not only useful for diagnostic implications, but also impart prognostic information and can assist in the risk stratification of patients presenting with suspected ACS.

In addition to the established biomarkers of myocardial necrosis, B-type natriuretic peptide (BNP) and C-reactive protein (CRP) are pathologically diverse biomarkers that could potentially enhance risk stratification in ACS further. Finally, several novel markers of myocardial ischemia and their usefulness during acute MI are currently being evaluated in clinical studies. To date, measurement of more than one specific biomarker of myocardial necrosis is unnecessary for establishing the diagnosis of MI and is not currently recommended.¹⁰ Certain biomarkers should no longer be used in the evaluation of acute MI because of their poor specificity secondary to their wide tissue distribution, including aspartate aminotransferase, total lactate dehydrogenase, and lactate dehydrogenase isoenzymes.¹¹

Detectable increases in cardiac biomarkers are indicative of myocardial injury. Biomarker elevations are not synonymous with acute MI, however. Many disease states, such as sepsis, hypovolemia, atrial fibrillation, congestive heart failure, pulmonary embolism, myocarditis, intracranial hemorrhage, stroke, and renal failure, can be associated with an increase in cardiac biomarkers. These elevations arise from mechanisms other than thrombotic coronary artery occlusion and require treatment of the underlying cause, rather than the administration of anti-thrombotic and antiplatelet agents.^{12,13}

Serum markers of myocardial necrosis have a vital role in the diagnosis and prognosis of acute MI, but the diagnosis of acute MI is not predicated exclusively on the presence of increased biomarkers. Acute MI should be diagnosed when biomarkers are detected, and the clinical setting is consistent with myocardial ischemia.

Troponin

Cardiac troponins are regulatory proteins that control the calcium-mediated interaction of actin and myosin, which results in contraction and relaxation in striated muscle. The troponin complex comprises three subunits: troponin C, which binds calcium; troponin I, which inhibits actin-myosin interactions; and troponin T, which attaches the troponin complex by binding to tropomyosin and facilitates contraction. Troponin C is expressed by cells in cardiac and skeletal muscle; in contrast, the amino acid sequences of troponins I and T are unique to cardiac muscle. This difference has allowed for the development of rapid, quantitative assays to detect elevations of cardiac troponins in the serum. Troponin is the preferred biomarker for use in the diagnosis of acute MI because of superior tissue specificity and sensitivity for MI and its usefulness as a prognostic indicator.

Diagnosis

Troponin is released early in the course of acute MI. An increased concentration of cardiac troponin is defined as exceeding the 99th percentile of a reference control group. Troponin

Table 10-2. Biochemical Markers of Myocardial Necrosis

Marker	Initial Appearance (hr)	Mean Time to Peak	Return to Basal	Sampling Schedule
Myoglobin	1-4	6-7 hr	24 hr	Frequent; every 1-2 hr after CP
Cardiac troponin I	3-12	24 hr	5-10 days	Initially and 6-9 hr after CP
Cardiac troponin T	3-12	12 hr–2 days	5-14 days	Initially and 6-9 hr after CP
Creatine kinase (CK)	3-12	24 hr	Unknown	Every 8 hr
CK-MB (tissue isoform)	2-6	18 hr	48-72 hr	Initially and 3-4 hr after CP
Lactate dehydrogenase (LDH)	10	24-48 hr	10-14 days	Once at least 24 hr after CP

CK-MB, MB isoenzyme of creatine kinase (CK); CP, chest pain.

Modified and adapted from Adams J, Abendschein DR, Jaffe AS: Biochemical markers of myocardial injury: is MB creatine kinase the choice for the 1990's? *Circulation* 1993;88:750-763.

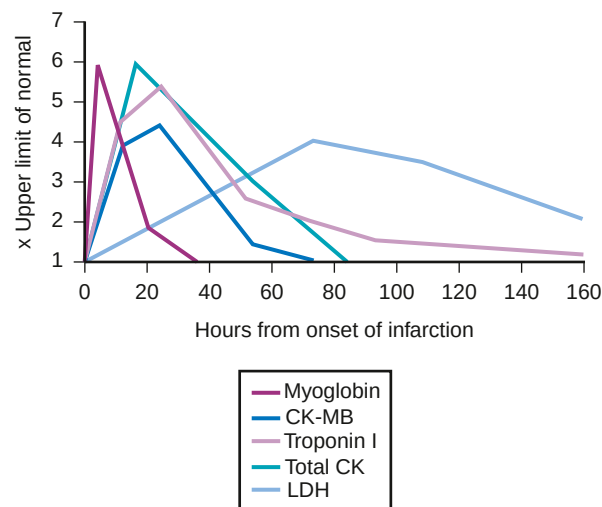


Figure 10-1. Time course of elevation of biochemical markers of acute myocardial infarction. The relative timing and extent of the increase above normal values of the commonly used serum markers after acute myocardial infarction are shown. CK, creatine kinase; CK-MB, creatine kinase MB isoenzyme; LDH, lactate dehydrogenase.

exceeding this limit on at least one occasion in the setting of clinical ischemia is indicative of myocardial necrosis.⁶ Elevated troponin can be detected within 2 to 4 hours after the onset of myocardial injury.¹³ Serum levels can remain increased for 4 to 7 days for troponin I and 10 to 14 days for troponin T (Fig. 10-1).¹⁴

The initial release of troponin is from the cellular cytosol, whereas the persistent elevation is a result of the slower dispersion of troponin from degrading cardiac myofilaments.¹⁵ As a result of these kinetics, the sensitivity of troponin increases with time. At 60 minutes after the onset of acute MI, the sensitivity is approximately 90%, but maximal sensitivity of troponin (approximately 99%) is not achieved until 6 or more hours after the initiation of myocardial necrosis.¹³ Blood samples for the measurement of troponin levels are recommended to be drawn at presentation and 6 to 9 hours later to optimize the clinical sensitivity for ruling in acute MI and the specificity for ruling out acute MI.⁸

The specificity of troponin I is approximately 85% to 95% with serial testing.¹⁶ As a result of this high tissue specificity, cardiac troponin is associated with fewer false-positive results in the setting of concomitant skeletal muscle injury than CK-MB.

This inherent characteristic of troponin has been used in the diagnosis and assessment of myocardial injury in patients with chronic muscle diseases, in marathon runners, in patients after electrical cardioversion, in patients with cardiac contusions, and in patients with perioperative MIs.¹⁶⁻¹⁹ The tissue specificity of cardiac troponin is distinct from the specificity for the mechanism of myocardial injury; if elevated troponins are found in the absence of myocardial ischemia, an evaluation for alternative etiologies of myocardial injury should be pursued.

Despite the ongoing development of increasingly sensitive troponin assays, troponin kinetics do not reliably permit the very early (initial 1 to 3 hours) detection of myocardial necrosis.⁸ In patients presenting within 6 hours of symptom onset, the clinical scenario, ECG findings, and adjunctive imaging techniques are necessary for the rapid and accurate diagnosis of acute MI. In the case of STEMI, reperfusion therapy should not be delayed waiting for confirmatory biomarkers of myocardial injury.

Elevated troponins not only are vital to the diagnosis of NSTEMI, but also serve to direct treatment by identifying patients who would benefit from an early invasive management strategy.²⁰ In the TACTICS-TIMI 18 study, patients with any increase in troponin who underwent early angiography (within 4 to 48 hours) and revascularization (if appropriate) achieved an approximately 55% reduction in the odds of death or MI compared with patients undergoing conservative management.²¹

Prognosis

In addition to the diagnostic value of troponin, cardiac troponins yield prognostic information. Prognosis is related partly to the extent of the increase in troponin in patients with an ischemic mechanism for myocardial injury.²²⁻²⁴ Increased concentrations of troponin are associated with angiographic findings of greater lesion complexity, impaired blood flow in the culprit artery, and decreased coronary microvascular perfusion.²¹

Cardiac troponin has also been proven to be a potent independent indicator of recurrent ischemic events and the risk of death among patients presenting with ACS.²⁵ The TIMI-IIIB trial showed that in patients presenting with ACS, mortality was consistently higher among patients with elevated troponin I (>0.4 ng/mL) at the time of admission. There were statistically significant increases in mortality with increasing levels of troponin I. Even after adjustment for baseline variables, age older than 65, and ST segment depression on ECG, an elevated troponin I had the strongest impact on mortality.²⁶ Additionally, the GUSTO IIa trial

found that elevated troponin T (>0.1 ng/mL) was significantly predictive of 30-day mortality in patients with acute myocardial ischemia even after analysis was adjusted for ECG category and CK-MB level.²⁷ In patients with STEMI, increased troponin is also associated with a significantly higher mortality at 30 days, which persisted even after adjustment for age, heart rate, systolic blood pressure, location of infarction, and Killip class.²⁸

Risk Stratification

Cardiac troponin is a class I indication for risk stratification in patients with ACS.⁸ Patients presenting with clinical evidence of ischemia and positive troponins, even at low levels, have worse outcomes than patients without evidence of elevated troponin.²⁹ The MISSION! trial showed that peak troponin T levels are a good estimate of infarct size and an independent predictor for left ventricular function at 3 months and major adverse cardiac events at 1 year.²³

Creatine Kinase MB

CK is a cytosolic carrier protein for high-energy phosphates.¹³ CK-MB is an isoenzyme of CK that is most abundant in the heart; however, CK-MB also constitutes 1% to 3% of the CK in skeletal muscle, and is present in a small fraction in other organs, such as the small bowel, uterus, prostate, and diaphragm.³⁰ The specificity of CK-MB may be impaired in the setting of major injury to these organs, especially skeletal muscle.

Although cardiac troponin is the preferred marker of myocardial necrosis, CK-MB by mass assay is an acceptable alternative when cardiac troponin is unavailable.⁸ The diagnostic limit for CK-MB is defined as the 99th percentile in a sex-specific reference control group.⁶ All assays for CK-MB show a significant twofold to threefold higher 99th percentile limit for men compared with women. In addition, CK-MB can have twofold to threefold higher concentrations in African Americans than whites. These discrepancies have been attributed to physiologic differences in muscle mass.¹¹ It is recommended that two consecutive measurements of CK-MB above the diagnostic limit be required for sufficient evidence of myocardial necrosis because of the inherent lower tissue specificity of CK-MB compared with troponin.⁸

The temporal increase of CK-MB is similar to that of troponin in that it occurs within 3 to 4 hours after the onset of myocardial injury, but in contrast to troponin, CK-MB decreases to the normal range by 48 to 72 hours (see Fig. 10-1). The rapid decline of CK-MB to the reference interval by 48 to 72 hours allows for the discrimination of early reinfarction when symptoms recur between 72 hours and 2 weeks after the index acute MI, when troponin may still be elevated.⁸ More recent data suggest, however, that serial troponin I values provide similar information.³¹ Similar to troponin, the amount of CK-MB released is useful for estimation of infarct size, which correlates with ejection fraction, incidence of ventricular arrhythmias, and prognosis.¹⁴

Myoglobin

Myoglobin is a ubiquitous, heme-related, low-molecular-weight protein present in cardiac and skeletal muscle. In the setting of myocardial necrosis, myoglobin levels increase rapidly and are detectable within the first 2 to 4 hours. Elevations persist for 12 to 24 hours before being excreted by the kidneys. Myoglobin has a high sensitivity and a high negative predictive value for myocardial death, making it an attractive tool for the early exclusion of acute MI.⁸ Myoglobin is not specific for myocardial necrosis,

however, especially in the presence of skeletal muscle injury and renal insufficiency.¹⁴

A prospective study assessing the use of myoglobin in the early evaluation of acute chest pain revealed that myoglobin level was 100% sensitive for diagnosis of acute MI at 2 hours; the negative predictive value was also 100% with serial testing, but the specificity was low, limiting the clinical usefulness of myoglobin in the evaluation of acute MI.³² When myoglobin was directly compared with troponin in the early detection of coronary ischemia, using the 99th percentile of troponin I as a cutoff (0.07 μ g/L), the cumulative sensitivity of troponin was higher.³³ A multimarker strategy including troponin and myoglobin has not been shown to yield a superior overall diagnostic performance compared with troponin alone.³³

Adjunctive Biomarkers

Two emerging biomarkers that may be useful adjuncts in the diagnosis and prognosis of acute MI are the natriuretic peptides and inflammatory markers. BNP, a counter-regulatory peptide, and its propeptide, NT-proBNP, are released from cardiac myocytes in response to cardiac stretch. After transmural infarction, the plasma concentrations of BNP increase rapidly and peak at approximately 24 hours.⁸ The peak value of BNP has been found to be proportional to the size of the infarction.³⁴ In patients presenting with acute MI, elevated BNP and NT-proBNP levels have been shown to predict a higher risk of death and heart failure, independent of other prognostic variables.¹³

Increased concentrations of inflammatory biomarkers are detectable in a substantial proportion of patients presenting with acute MI; however, the precise basis for this relationship has not been conclusively established. Studies have implicated inflammation as a contributor to plaque compromise in ACS.³⁵ CRP, an acute-phase reactant protein made in the liver, has been the focus of much clinical investigation. In a cohort study of patients with STEMI, the patients with increased CRP were more likely to have complications of acute MI.³⁶ Similarly, several studies have revealed high-sensitivity CRP to be an independent predictor of short-term and long-term outcomes in patients with ACS.⁸ At this time, there are no therapeutic strategies specific to CRP or BNP and NT-proBNP; however, these biomarkers, in conjunction with troponin, may be useful for risk assessment in patients with acute MI.

Novel Cardiac Markers

Several novel markers of myocardial ischemia, such as ischemia-modified albumin, soluble CD-40 ligand, fatty acid binding protein, myeloperoxidase, choline, and cystatin C, are currently being investigated in the setting of acute MI.¹³ Ischemia-modified albumin is among the most thoroughly investigated of these markers.³⁷ It has been observed that the affinity of the N-terminus of human albumin for cobalt is reduced in the setting of acute myocardial ischemia with detectable changes in binding occurring within minutes.³⁸ The sensitivity (83%) of ischemia-modified albumin in the very early period (1 to 3 hours) of myocardial ischemia and its high negative predictive value (96%) make it a promising marker for the immediate detection of ischemia before myocardial necrosis.³⁹ The pursuit of new markers is rapidly progressing; which markers will become clinically useful depends on several factors, including clinical efficacy, assay availability, and cost-effectiveness.

Clinical Evaluation

The evaluation of a patient presenting with acute MI should start with a targeted history that ascertains the following: (1) characterization and duration of chest discomfort and any associated symptoms; (2) prior episodes of myocardial ischemia or MI, percutaneous coronary intervention, or coronary bypass surgery; (3) history of hypertension, diabetes mellitus, tobacco use, and cerebrovascular disease; and (4) assessment of bleeding risk.⁴⁰

The classic description of acute MI consists of crushing, substernal chest pain or viselike tightness with or without radiation to the left arm, neck, jaw, interscapular area, or epigastrium. This presentation is associated with an estimated 24% probability of acute MI; the probability decreases to about 1% if the pain is positional or pleuritic in a patient without a prior history of coronary artery disease (Table 10-3).⁴¹ Alternatively, the chest pain may be described as sharp, burning, or stabbing, which is associated with a 23% probability of acute MI.⁴¹ Patients commonly may deny pain, but describe a sensation of chest discomfort.⁴⁰ The duration of the discomfort is usually prolonged, lasting more than 30 minutes, but may wax and wane, or even remit. There may be associated vagal symptoms of nausea, vomiting, lightheadedness, and diaphoresis.

Elderly patients and women more commonly have atypical presentations that mimic abdominal pathology or a neurologic event (Table 10-4).⁴² One third of all MIs are unrecognized, especially in patients without prior history of MI, and about half of these unrecognized MIs are associated with atypical presentations.^{43,44} Silent myocardial ischemia is defined as objective

documentation of myocardial ischemia in the absence of angina or anginal equivalents.⁴⁵ Diabetes and hypertension are known to be associated with silent ischemia and infarction. The prognosis of acute MI patients, whether symptomatic or asymptomatic, is similar.⁴³

Response of chest pain to antacids, nitroglycerin, or analgesics can be misleading and should not be relied on. Nitroglycerin can relieve esophageal spasm, and, conversely, pain from acute MI may not always respond well to nitroglycerin because the pain is due to infarction rather than ischemia. Studies suggest that esophageal stimulation can cause angina and reduce coronary blood flow in patients with coronary artery disease; however, this response is absent in patients with heart transplant, supporting the notion of a cardioesophageal reflex, which can complicate further the use of response to treatment as a diagnostic tool.⁴⁶

Physical Examination

An uncomplicated acute MI has no pathognomonic physical signs, but the physical examination is crucial in the early assessment of the complications of acute MI and in establishing a differential diagnosis for the chest pain. The general assessment can reveal a restless and anguished patient with or without confusion owing to poor cerebral perfusion. A clenched fist across the chest, known as Levine sign, may be observed. The patient can appear ashen, pale, or diaphoretic and be cool and clammy to the touch. Tachycardia and hypertension indicate high sympathetic tone and are usually consistent with anterior MI. Bradycardia and hypotension signify high vagal tone and may be seen with inferior-posterior MI with or without right ventricular involvement. Hypotension could also be secondary to the development of cardiogenic shock or a result of medication, especially nitroglycerin, morphine sulfate, or β blockade. Visualization of elevated jugular venous pressure is seen as a consequence of significant left or right ventricular dysfunction.

Auscultation for additional heart sounds, cardiac murmurs, and friction rubs is mandatory. A soft S_1 is heard with decreased left ventricular contractility, and an S_4 gallop indicates decreased left ventricular compliance.⁴⁰ Killip and Kimball proposed a

Table 10-3. Value of Clinical Characteristics in Predicting Acute Myocardial Infarction (AMI) in Patients with Chest Pain

Characteristics of Pain	Probability of AMI (%)
Description of pain	
Pressure, tightness, crushing	24
Burning, indigestion	23
Aching	13
Sharp, stabbing	5
Fully positional	4
Definitely pleuritic	0
Radiation of pain	
Radiation to jaw, neck, left arm, or left shoulder	19
Reproducibility	
Pain partially reproducible by chest wall palpation	6
Combination of variables	
Sharp or stabbing pain; no prior angina or MI; pleuritic, positional, or reproducible by palpation	1

Modified and adapted from Lee TH, Cook EF, Weisberg M: Acute chest pain in the emergency room: identification and examination of low-risk patients. *Arch Intern Med* 1985;145:65-69.

Table 10-4. Atypical Symptoms of Myocardial Infarction in Elderly Patients

Symptom	Percentage of Patients with Symptoms		
	65-74 years old	75-84 years old	≥85 years old
Chest pain	77	60	37
Shortness of breath	40	43	43
Sweating	34	23	14
Syncope	3	18	18
Acute confusion	3	8	19
Stroke	2	7	7

Adapted and modified from Bayer AJ, Chadha JS, Farag RR, et al: Changing presentation of myocardial infarction with increasing old age. *J Am Geriatr Soc* 1986; 34:263-266.

Table 10-5. Relationship between Electrocardiogram (ECG) Changes and Diagnosis of Myocardial Infarction (MI)

ECG Finding	Patients Who Had MI (Positive Predictive Value) (%)	MI Patients (Sensitivity) (%)
≥1 mm ST elevation or Q waves in ≥2 leads (not old)	76	45
New ischemia or strain with ≥1 mm ST depression in ≥2 leads (not old)	38	20
Other ST or T wave changes of ischemia or strain (not known to be old)	21	14
Old infarction, ischemia, or strain	8	5
Other new or old abnormality	5	5
Nonspecific ST-T changes	5	7
Normal	2	3

Modified and adapted from Rouan GW, Lee TH, Cook EF, et al: Clinical characteristics and outcome of acute myocardial infarction in patients with initially normal or non-specific electrocardiograms (a report from the multicenter chest pain study). *Am J Cardiol* 1989;64:1087-1092.

prognostic classification in 1967 that is still useful today for the evaluation of patients with acute MI.⁴⁷ The classification scheme is based on the presence of a third heart sound (S_3) and rales on physical examination. Class I patients are without S_3 or rales, class II patients have rales over less than 50% of the lung fields with or without S_3 , class III patients have pulmonary edema with rales covering greater than 50% of the lung fields, and class IV patients are in cardiogenic shock. Evidence of heart failure on physical examination correlates with greater than 25% of myocardial involvement.⁴⁰ A systolic murmur should prompt an evaluation for complications of MI, such as mitral regurgitation from papillary muscle rupture or the formation of a ventricular septal defect, which may also be accompanied by a palpable precordial thrill. All peripheral pulses should be evaluated and documented. The finding of asymmetric or absent pulses, especially in the presence of tearing chest pain with radiation to the back, may indicate the presence of aortic dissection as an alternative diagnosis.

Other causes of cardiac and noncardiac chest pain that may be differentiated by physical examination include pericarditis, pulmonary embolism, costochondritis, pneumothorax, peptic ulcer disease, and acute cholecystitis. The initial clinical evaluation and physical examination should be directed toward expeditiously identifying the most likely etiology of each patient's presentation. The rapid triage of patients with ACS is crucial for the institution of the most appropriate early reperfusion therapy.

Electrocardiogram

The ECG is crucial in the initial assessment of patients with ACS. On arrival to the emergency department, the recommended “door-to-evaluation” time, which includes performing and interpreting the ECG, is 10 minutes.⁴⁰ The 12-lead ECG in the emergency department is the center of the decision pathway. The ECG aids in the diagnosis of acute MI and suggests the distribution of the infarct-related artery and estimates the amount of myocardium at risk.⁶ The presence of ST segment elevation in two contiguous leads or a new LBBB identifies patients who benefit from early reperfusion therapy, either fibrinolytic therapy or primary percutaneous coronary intervention.

Early fibrinolytic therapy should be instituted within 30 minutes of arrival, whereas patients arriving at a facility with primary percutaneous coronary intervention should have a “door-to-balloon” time of 90 minutes or less.⁴⁸ New LBBB or anterior infarction are important predictors of mortality.⁴⁰ In patients with ischemic chest pain, ST segment elevation has a specificity of 91% and a sensitivity of 46% for diagnosing acute MI. Conversely, the probability of acute MI in patients with chest pain and an initially normal ECG is low—approximately 3% (Table 10-5).^{49,50} Comparison with a previous ECG (if available) is indispensable and may help to avoid unnecessary treatment in patients with an abnormal baseline ECG.⁵¹ If the initial ECG is not diagnostic of STEMI, but the patient remains symptomatic, serial ECGs at 5- to 10-minute intervals should be performed to detect acute or evolving changes.⁴⁰

The classic evolution of acute MI on ECG begins with an abnormal T wave that is often prolonged, peaked, or depressed. Most commonly, increased, hyperacute, symmetric T waves are seen in at least two contiguous leads during the early stages of ischemia.⁶ This is followed by ST segment elevation in the leads facing the area of injury with ST segment depression in the reciprocal leads. Increased R wave amplitude and width in conjunction with S wave diminution are often seen in leads exhibiting ST segment elevation.⁶ This evolution may conclude with the formation of Q waves. The time course of development of these changes varies, but usually occurs in minutes to several hours. A more recent study revealed that among patients presenting within 6 hours of symptom onset of STEMI, the patients who exhibited Q waves on their baseline ECG had more advanced disease with worse clinical outcomes.⁵² This study underscores the need for early recognition of acute MI, not only by medical personnel, but also in the community.

In patients with inferior STEMI, right-sided ECG leads should be obtained to screen for ST segment elevation suggestive of right ventricle infarction (class I indication).⁴⁰ Infarction of the right ventricle associated with inferior acute MI has important therapeutic and prognostic implications.⁵³ Right ventricle infarction is likely when the ST segment is elevated 1 mm or more in the right precordial leads from RV_4 to RV_6 . This finding has a sensitivity of about 90% and a specificity of 100% for proximal right coronary artery occlusion.⁵⁴ Other changes

Table 10-6. Sensitivity and Specificity of Electrocardiogram (ECG) Changes in Left Bundle Branch Block for Diagnosis of Acute Myocardial Infarction

ECG Changes	Sensitivity (%)	Specificity (%)
ST segment elevation ≥ 1 mm concordant with QRS polarity	73	92
ST segment depression ≥ 1 mm in leads V_1, V_2, V_3	25	96
ST segment elevation ≥ 5 mm discordant with QRS polarity	31	92
Positive T waves in leads V_5 and V_6	26	92

Modified and adapted from Sgarbossa EB: Recent advances in the electrocardiographic diagnosis of myocardial infarction: left bundle branch block and pacing. *Pacing Clin Electrophysiol* 1996;19:1370-1379.

reported to be associated with right ventricle infarction are (1) ST segment elevation isolated to lead V_1 , (2) elevated ST segments in leads V_1 - V_4 , and (3) T wave inversion isolated to lead V_2 .⁵⁴ The ECG changes of right ventricle infarction are usually transient, persist for hours, and then resolve within a day.

A normal ECG can be seen in 10% of cases of acute MI.⁵⁵ One explanation for this apparent discrepancy is that the infarction is occurring in an electrocardiographically silent area, such as the posterior or lateral wall in the distribution of the left circumflex artery.⁵⁶ Acute posterior injury is suggested by marked ST segment depression in leads V_1 and V_2 in combination with prominent R waves (at least 0.04 second) or an R/S ratio greater than 1 in the anterior precordial leads. These ECG findings are neither sensitive nor specific for posterior infarction, however, and frequently are not evident on the initial ECG.⁵⁷ In the case of patients who present with clinical evidence of acute MI, but have a nondiagnostic ECG, the latest American College of Cardiology/American Heart Association guidelines state that it is reasonable to obtain supplemental posterior ECG leads, V_7 and V_9 , to assess for left circumflex infarction (class IIa indication).² Several studies have shown that ST segment elevation in leads V_7 and V_9 assists in the early identification and treatment of patients with acute posterior wall infarction, who are having ischemic chest pain, but do not display ST segment elevation on the standard 12-lead ECG.^{53,56,57}

Several conditions can potentially confound the ECG diagnosis of acute MI or cause a pseudoinfarct pattern with Q/QS complexes in the absence of MI. These include pre-excitation, obstructive or dilated cardiomyopathy, bundle branch block, left and right ventricular hypertrophy, myocarditis, cor pulmonale, and hyperkalemia.⁶

Bundle Branch Block Patterns and Acute Myocardial Infarction

The presence of LBBB or ventricular pacing can mask the ECG changes of acute MI. In the GUSTO-1 trial, LBBB was seen in about 0.5% and ventricular pacing in about 0.1% of patients with acute MIs.⁵⁸ Based on this finding, Sgarbossa⁵⁹ developed criteria to evaluate for MI in the presence of left ventricular conduction abnormalities (Table 10-6). These changes in the ST segment or T waves, although very specific, are not seen in a significant proportion of patients, and other modalities such as biomarkers and adjunctive imaging may be required for diagnosis.

The same criteria used to assess for acute MI in the presence of LBBB are also applicable to patients with endocardial ventricular pacemakers except for the T wave criteria. The most indicative finding of acute MI in the presence of ventricular pacing was ST segment elevation 5 mm or greater in the leads with predominantly negative QRS complexes.⁵⁹ In right bundle branch

block, the initial pattern of ventricular activation is normal, and the classic pattern of acute MI on ECG is usually not altered.

Imaging Techniques

Noninvasive imaging can assist in the diagnosis and characterization of acute MI. Commonly used imaging techniques in acute and chronic MI are echocardiography, radionuclide ventriculography, myocardial perfusion scintigraphy, and magnetic resonance imaging (MRI).⁶ Imaging techniques are useful in the diagnosis of MI by virtue of their ability to detect myocardial viability, either directly with radionuclide techniques or indirectly with echocardiography or MRI. In the appropriate clinical setting and in the absence of nonischemic causes, demonstration of a new loss of myocardial viability meets the criteria for MI.⁶

Reinfarction

Reinfarction is suspected when there are recurrent clinical signs of myocardial ischemia lasting 20 minutes or longer after an initial MI. The incidence of reinfarction is reported to be less than 20%.³¹ In patients who show evidence of recurrent MI, an immediate measurement of a cardiac biomarker is recommended, followed by a second sample 3 to 6 hours later. Reinfarction is diagnosed if there is an increase of greater than 20% in the second sample.⁶ Traditionally, CK-MB has been used to assess for reinfarction; however, there is increasing evidence that troponin values yield similar information.³¹ The ECG diagnosis of reinfarction should be considered when ST segment elevation of 0.1 mV or more occurs in a patient previously having a lesser degree of ST segment elevation, or if there is the development of new pathognomonic Q waves, in at least two contiguous leads.⁶ The re-elevation of the ST segments can also be seen in life-threatening myocardial rupture, and should prompt an expeditious evaluation for the complications of acute MI.

Conclusion

The rapid recognition and diagnosis of acute MI is crucial for the institution of therapy to restore perfusion, minimize myocardial damage, and preserve cardiac function. The cardiac biomarkers, particularly troponin, have become the hallmark of acute MI, but must always be interpreted in the context of the clinical scenario, ECG, and applicable imaging technique. Advances in the efficiency and sensitivity of diagnostic modalities will improve cardiovascular care in the future, and maintain the decline in the morbidity and mortality associated with acute MI that has marked the last 30 years.⁴⁸

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Use of the Electrocardiogram in Acute Myocardial Infarction

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CHAPTER

11

Inferior Myocardial Infarction
Right Ventricle Myocardial Infarction
Anterior Myocardial Infarction

Left Main Occlusion
Diagnosis in Bundle Branch Block

Inferior Myocardial Infarction

In 80% of cases, the culprit vessel in inferior myocardial infarction (MI) is the right coronary artery. The circumflex artery is the culprit vessel in all other cases, with the rare exception of a distally extending inferoapical “wraparound” left anterior descending artery, which is suggested when there is concomitant ST segment elevation in the precordial leads.¹ ST segment elevation in lead III that exceeds the magnitude of elevation in lead II with reciprocating ST segment depressions in I and aVL of greater than 1 mm strongly suggests the right coronary artery as the culprit over the circumflex artery. The ST segment vector is directed toward the right when the right coronary artery is involved, which accounts for the elevation in lead III greater than lead II (Fig. 11-1). The added findings of electrocardiogram

(ECG) evidence of right ventricle MI increases the specificity for the right coronary artery, and localizes the occlusion to a proximal location.²

Conversely, the circumflex artery is suggested when ST segment elevation in lead III is not greater than lead II, and by the absence of ST segment depression in leads I and aVL.³⁻⁵ An isoelectric or depressed ST segment with a negative T wave in lead V_{4R} is very specific, but insensitive for proximal circumflex artery occlusion.^{6,7} ST segment depression in leads V₁ and V₂ has been reported to be specific for the circumflex artery, although a dominant right coronary artery can produce similar findings. The presence of ST depression in leads V₁ and V₂ with a prominent R wave in lead V₂ can be nonspecific and can suggest involvement of the left ventricular posterior wall or

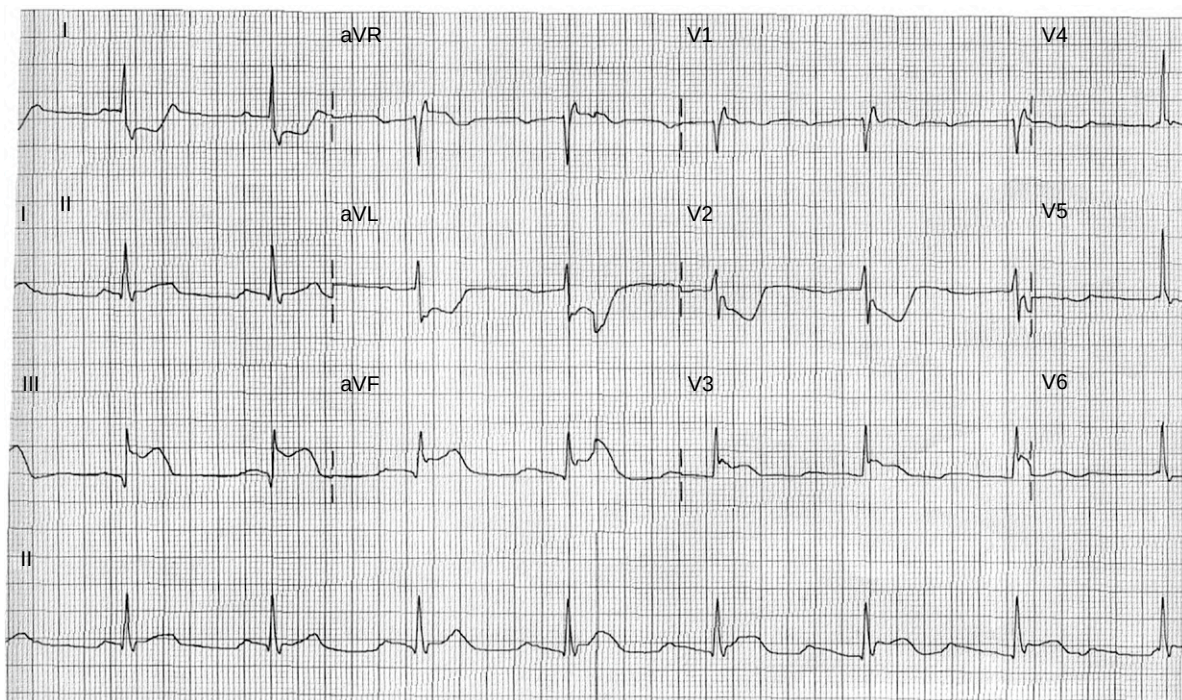


Figure 11-1. Inferior ST elevation myocardial infarction. Elevation in lead III is greater than II and ST depressions in leads I and aVL indicate the right coronary artery as the culprit vessel. Note the posterior injury current and the presence of complete heart block. Elevation in aVR suggests concomitant right ventricular infarction due to occlusion proximal to the RV marginal branches.

concomitant disease in the left anterior descending artery. Performing an ECG with posterior leads (V₇-V₉) can show a primary posterior wall injury pattern with ST segment elevation. A localization schema for inferior MI is summarized in Table 11-1.

Right Ventricle Myocardial Infarction

In the setting of inferior MI, right-sided precordial lead recordings are strongly indicated. The presence of right ventricular involvement portends a worse prognosis and enables the clinician to identify a subgroup of inferior MI with a propensity toward hemodynamic instability and shock leading to increased in-hospital mortality.⁸ Right ventricle MI is always associated with a proximal occlusion of the right coronary artery, before the takeoff of the right ventricular marginal branches. The most sensitive sign is 1 mm of ST segment elevation in lead V_{4R}.⁹ This sign is not fully specific for right ventricle MI, however, because this can be seen in acute pulmonary embolus, anteroseptal MI, and pericarditis. ST segment elevation in lead V₁ in association with elevation in leads II, III, and aV_F is highly correlated with the presence of right ventricular infarction.^{2,10} Isolated right ventricle infarction, although rare, can be easily confused with anterior wall infarction, owing to the anterior location of the right ventricle, with ST segment elevation manifest only in the early precordial leads (V₁-V₃).¹¹

Table 11-1. Inferior Myocardial Infarction: ST Segment Elevation II, III, aV_F

Right Coronary Artery	Circumflex Artery
ST segment elevation III > II	ST segment elevation II ≥ III
ST segment depression >1 mm I, aV _L	ST segment elevation I, aV _L , V ₅ -V ₆
ST segment elevation V _{4R} Or V ₁	ST segment depression V _{4R}

Anterior Myocardial Infarction

In acute anterior MI, ST segment elevation is present in the precordial leads. The challenge in anterior wall MIs lies in identifying the site of occlusion within the vessel in relation to the septal and diagonal branches. In very proximal left anterior descending artery occlusion, before the first septal and diagonal branches, the ST segment is elevated in leads V₁-V₃ and aV_L, with ST segment depression in aV_F.^{12,13} The ST segment deviation vector points toward the base of the heart, and ST segment elevation can be seen in aV_R and aV_L. ST segment elevation exceeding 2.5 mm in V₁ is also highly correlated with occlusion proximal to the first septal branch.¹⁴ Acquired right bundle branch block with a Q wave is an insensitive, but extremely specific marker of proximal occlusion of the left anterior descending artery because the septal perforators supply blood to the right bundle (Fig. 11-2). ST segment elevation in leads V₁-V₃ with elevation in the inferior leads suggests occlusion distal to the origin of the first diagonal branch.¹³ In addition, if aV_L is elevated, it suggests an occlusion distal to the septal branch, but proximal to the diagonal branch. If aV_L is depressed, it suggests an occlusion distal to the diagonal branch, but proximal to the septal branch.¹⁵ In distal left anterior descending artery occlusions, ST segment elevation is seen in leads V₃-V₆ and in the inferior leads. A localization schema for anterior MI is summarized in Table 11-2.

Left Main Occlusion

When the left main coronary artery is occluded, ischemia occurs in the left anterior descending artery and circumflex artery. This ischemia results in an ST segment deviation vector that points toward aV_R. ST segment elevation in aV_R and lead V₁ is frequently present, and there is higher specificity for left main occlusion when aV_R elevation is greater than V₁.¹⁶ With the exception of aV_R and V₁, there is marked precordial and

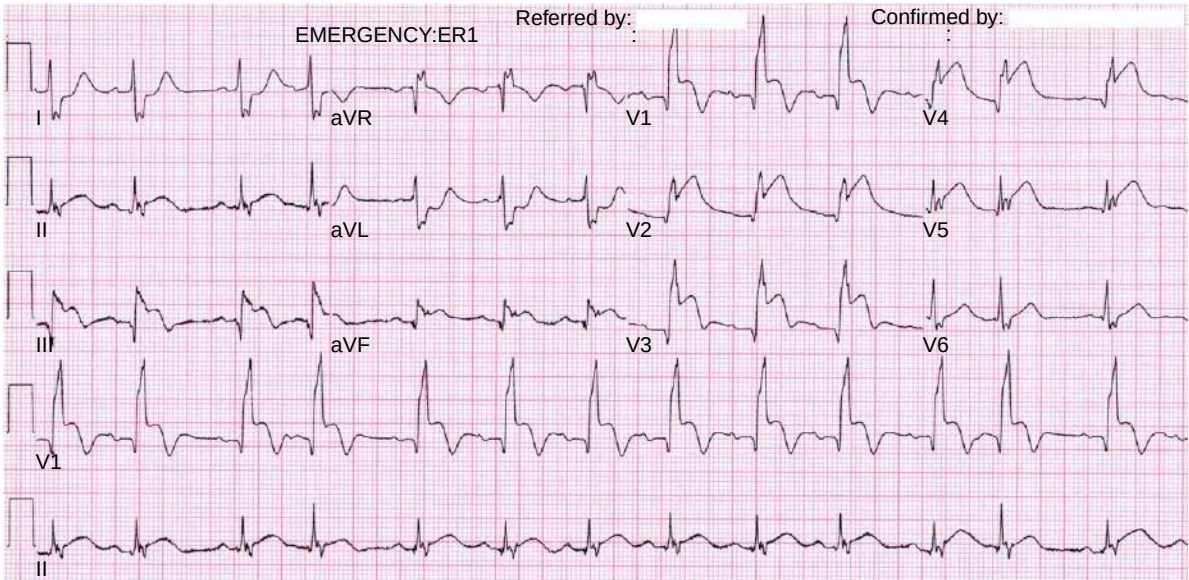


Figure 11-2. Anterior ST elevation myocardial infarction. Occlusion of the proximal left anterior descending artery is indicated by the presence of diffuse precordial ST elevations and right bundle branch block pattern. There is elevation in the II, III, and aV_F because the distal portion of the vessel wraps around the apex to supply the inferior wall.

Table 11-2. Anterior Myocardial Infarction: ST Segment Elevation V ₁ -V ₃		
Left Main Artery	Proximal Left Anterior Descending Artery	Distal Left Anterior Descending Artery
ST segment elevation aVR > V ₁	ST segment elevation V ₁ (>2.5 mm)	ST segment elevation II, III, aVF
Global ST segment depressions	New right bundle branch block	ST segment depression II, III, aVF

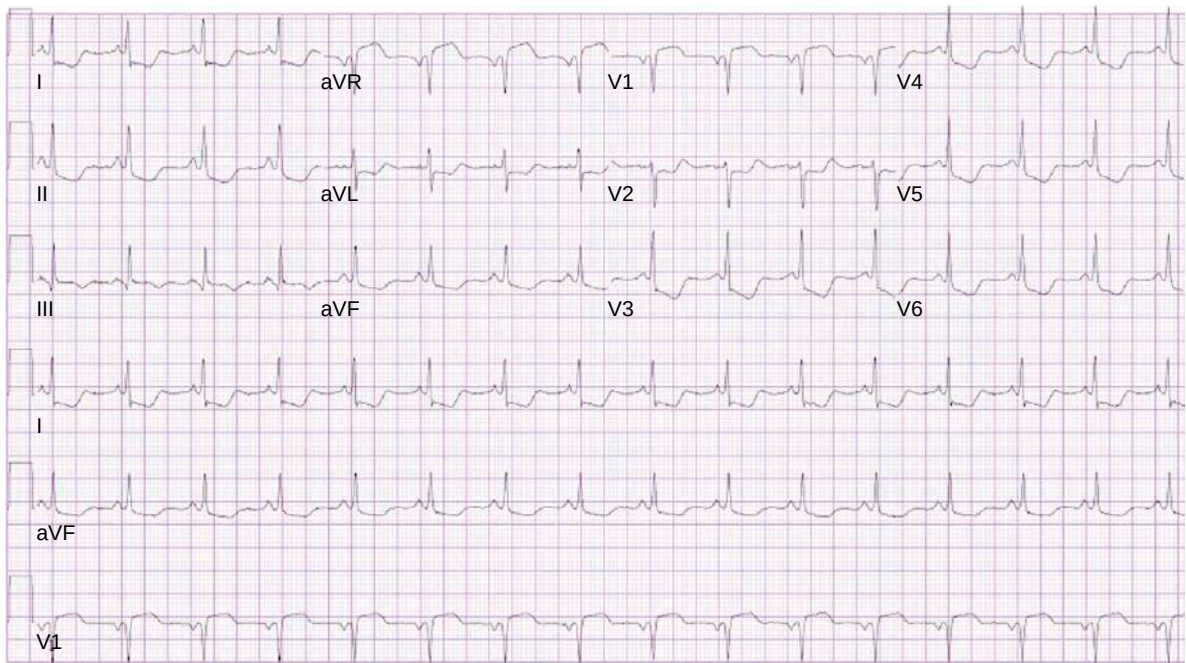


Figure 11-3. Left main coronary artery occlusion. Elevation in aVR and V1 with global ST depressions.

inferior ST segment depression, reflecting posterior and basal wall ischemia (Fig. 11-3).

Diagnosis in Bundle Branch Block

Bundle branch block is present on the initial ECG in approximately 7% of patients presenting with acute MI.¹⁷ Ischemia can be difficult to interpret in right and left bundle branch block because of the delayed depolarization and abnormal repolarization of the corresponding ventricle, and its attendant secondary ST segment changes. In the setting of STEMI, primary ST segment elevations in the precordium and new Q waves are fairly specific in the presence of right bundle branch block.

More challenging is the interpretation of acute MI in the setting of left bundle branch block, which also causes secondary ST segment repolarization changes. Because there is delay in the left ventricular activation in native left bundle branch block or iatrogenic right ventricular pacing, Q waves cannot be used to diagnose infarction. Prominent notching greater than 50 ms in the QRS can indicate prior infarction, however. Two signs are extremely insensitive but have specificity approaching 85% for prior MI in the setting of left bundle branch block. Cabrera sign refers to prominent notching in the ascending limb of the S wave in leads V₃-V₅. A similar finding with prominent notching of the ascending limb of the R wave in lead I, aVL, or V₆ is called Chapman sign.^{18,19}

Based on the GUSTO-1 trial, the Sgarbossa criteria²⁰ were proposed to improve specificity for diagnosis of acute MI in the setting of left bundle branch block. Primary ST segment elevation, 1 mm concordant with the major QRS vector, was given a score of 5, and discordant 5-mm ST segment elevations were assigned a score of 2. ST segment depressions greater than 1 mm in leads V₁-V₃ were given a score of 3. A score of at least 3 was 90% specific for the diagnosis of MI. Discordant 5-mm ST segment elevations were the most specific in pace-induced left bundle branch block.²¹

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Reperfusion Therapies for Acute ST Segment Elevation Myocardial Infarction

CHAPTER

12

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Historical Perspective

**Coronary Occlusion and Reperfusion of Myocardium:
Fibrinolysis and the Development of Fundamental
Concepts Underlying Treatment**

**Coronary Thrombosis and the Pathogenesis of Acute
Myocardial Infarction**

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Special Considerations

Conclusion

Historical Perspective

Thrombosis was implicated as the cause of acute myocardial infarction (MI) almost a century ago.¹ The pathophysiology remained obscure, however, and as recently as 35 years ago most investigators believed that thrombosis was a secondary event.² Clarity followed demonstrations by Chazov and colleagues³ and later Rentrop and coworkers,⁴ who showed angiographically that recanalization was achievable pharmacologically with favorable electrocardiographic (ECG) and clinical consequences. It then became progressively clear that ischemic injury could be attenuated by restoration of myocardial perfusion.⁵

Underlying this rapid paradigm shift was a hypothesis formulated by Braunwald that MI evolves dynamically, that the magnitude of irreversible injury sustained is related to the duration of ischemia, and that the clinical consequences of infarction are largely a reflection of the extent of irreversible injury sustained.⁶ It was postulated that reduction of myocardial oxygen requirements, enhancement of myocardial perfusion, or both when implemented within the first few hours after the onset of myocardial ischemia would mitigate the magnitude of irreversible injury sustained by the myocardium and would improve prognosis. Against this backdrop, the value of induction of reperfusion with pharmacologic agents, percutaneous coronary intervention (PCI), or both ultimately became established and resulted in marked improvements in prognosis. Before this paradigm shift had occurred, early (30-day) mortality from acute ST segment elevation myocardial infarction (STEMI) was greater than 30%. Presently, 30-day mortality is 7%, largely as a

result of reliance on early reperfusion as the linchpin of therapy. This chapter addresses the developments responsible for this profound improvement in survival.

Coronary Occlusion and Reperfusion of Myocardium: Fibrinolysis and the Development of Fundamental Concepts Underlying Treatment

MI remains the leading cause of death in much of the Western world.⁷ Benefit attributable to reduction in myocardial oxygen requirements is modest. Early administration of intravenous β blockers elicited variable and limited reduction in mortality,⁸⁻¹¹ perhaps, although inconsistently, attributable to reduction in infarct size.¹²⁻¹⁴ These observations are consistent with subsequent observations made in the COMMIT Trial,¹⁵ which showed reductions in the incidences of reinfarction and ventricular arrhythmia, but an increased incidence of cardiogenic shock. Beneficial effects of intravenous nitrates were seen with meta-analyses,¹⁶ but often not in individual trials. Before reperfusion became a mainstay of treatment, hospital mortality after acute MI was almost fourfold greater than it is today.^{17,18}

The duration of coronary occlusion was shown to be a determinant of the extent of myocardial damage in laboratory animals in 1941.¹⁹ In the 1970s, it became clear that infarct size was a major determinant of prognosis.^{20,21} This discovery and the subsequent proof that coronary artery thrombosis was often the

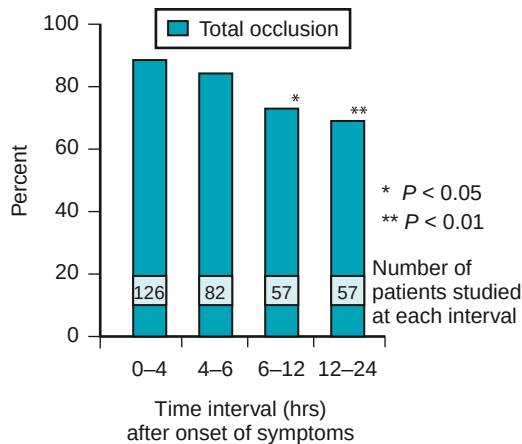


Figure 12-1. Frequency of total coronary occlusion in patients with acute transmural myocardial infarction undergoing angiography at discrete time intervals after the onset of symptoms. There is a significant decrease in the incidence of total coronary occlusion over time: 0 to 4 hours compared with 6 to 12 hours ($P < .05$) and with 12 to 24 hours ($P < .01$). (From DeWood MA, Spores J, Notske R, et al: Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction. *N Engl J Med* 1980;303:899.)

precipitating cause of infarction led to a focus on restoration of blood flow through the infarct-related artery with plasminogen activators.

Coronary Thrombosis and the Pathogenesis of Acute Myocardial Infarction

Although plaque rupture followed by coronary thrombosis is known to precipitate acute MI,^{22,23} its role has been debated extensively. Early autopsy studies of patients who died suddenly failed to show a high incidence of coronary thrombotic occlusion, perhaps because of antemortem or postmortem fibrinolysis. Although Herrick¹ attributed fatal acute MI to a thrombotically occluded coronary artery in 1912, and plaque fissuring was implicated as causal in 1966,²⁴ autopsy studies in the late 1970s did not show preponderant coronary thrombosis in patients who had died of acute MI.^{2,25} These studies led to the speculation that coronary thrombosis was a consequence, rather than the underlying cause, of acute MI.²⁵

In 1980, DeWood and colleagues²⁶ reported the results of coronary angiography performed early after the onset of acute transmural MI. This pivotal study showed a high prevalence of total and subtotal coronary occlusion, particularly within the first 4 hours after the onset of symptoms. The study also showed a high incidence of spontaneous recanalization over time. Within 4 hours of symptom onset, 87% of infarct-obstructed arteries were completely occluded. The prevalence of coronary occlusion was only 65%, however, 12 to 24 hours after onset (Fig. 12-1). When patients with subtotal occlusion of the obstructed artery were included, the prevalence of angiographically demonstrable coronary thrombosis in the first 4 hours was 98%. Angiographic data from a smaller number of patients confirmed that thrombi are almost universally prevalent at the time of occurrence of acute STEMI.²⁷

Efforts to reduce mortality soon focused on rapid restoration of blood flow in thrombotically occluded coronary arteries. It became clear that dissolution of clots postmortem²⁸ explained the failure of earlier autopsy studies to detect the high prevalence of thrombi in victims of sudden cardiac death after acute MI. It is now known that the use of plasminogen activators can reduce early hospital mortality of patients with acute MI to 2% to 6% when early administration and optimal dosing of clot-selective agents are employed.²⁹⁻³¹

Coronary Thrombolytic Agents: Proving the Value of Reperfusion

The maintenance of fluidity of blood depends on a complex balance between thrombosis, thrombolysis, and counter-regulation by inhibition of both processes. In vessels supplying regions of the heart undergoing acute MI, the rupture or fissuring of an underlying atherosclerotic plaque leads to thrombosis with exposure of the blood to the procoagulant effects of exposed type I collagen, von Willebrand factor, and tissue factor in the vessel wall. Activation of platelets accompanying the vascular injury accelerates ongoing thrombosis.^{32,33} Thrombin and fibrin generated by the coagulation cascade may undergo concomitant or subsequent lysis resulting from activation of the fibrinolytic system and conversion of the zymogen plasminogen to the active serine protease, plasmin, by the circulating plasminogen activators, tissue plasminogen activator (t-PA) or urokinase plasminogen activator (UK). These key components of the fibrinolytic system had been identified by 1950,^{28,34} well before acceptance of coronary thrombosis as the crucial step leading to transmural MI.

Circulating plasminogen is activated endogenously by t-PA and UK, resulting in the generation of plasmin that leads to degradation of fibrin to form soluble fibrin degradation products. Such products, activation peptides, and enzyme inhibitor complexes can be measured quantitatively as markers of fibrinolysis. Examples include fibrinopeptide A, prothrombin 1.2 and other prothrombin fragments, a fragment of the fibrinogen β chain (β 1-42), and complexes of thrombin-antithrombin.³⁵⁻³⁸ A specific degradation product of cross-linked fibrin, a fragment known as D-D dimer, reflects degradation of fibrin associated with fibrinogenolysis accompanying a systemic lytic state seen whenever plasminemia is present.^{39,40} Fibrinolysis is inhibited by circulating α_2 -antiplasmin, an inhibitor of plasmin, and by inhibitors of plasminogen activators in blood, primarily plasminogen activator inhibitor 1 (PAI-1).⁴¹ The fibrinolytic system is shown schematically in Figure 12-2.

Simultaneous thrombosis and thrombolysis influences the dynamic impact of thrombotic coronary occlusion. Any strategy designed to reduce myocardial damage must enhance the rapidity and extent of recanalization and promote sustained patency. Exogenously administered plasminogen activators require “conjunctive” measures to ensure that clot lysis is prompt and not retarded or reversed by thrombosis.

Plasminogen activators can paradoxically promote thrombosis. First-generation plasminogen activators, agents that are not fibrin-selective or clot-selective, such as streptokinase (SK), UK, and anisoylated plasminogen activator complex (APSAC), convert circulating and clot-bound plasminogen indiscriminantly

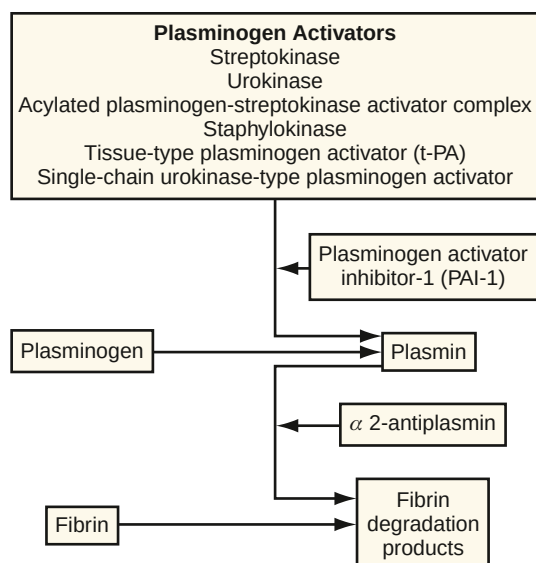


Figure 12-2. Regulation of the plasma fibrinolytic system.
(From Collen D: *Towards improved thrombolytic therapy*. *Lancet* 1993;342:34.)

to plasmin. Rapid depletion of plasma α_2 -antiplasmin occurs with plasminemia, which may generate thrombin from precursors and activation of the coagulation cascade.^{42,43} Procoagulant effects of plasminemia reflect activation of the so-called extrinsic and intrinsic coagulation pathways.⁴⁴⁻⁴⁶ The thrombin activity induced may activate platelets and lead to reocclusion after initially successful clot lysis.⁴⁷ Plasminemia also can lead to a phenomenon we have called plasminogen steal, in which conversion of circulating plasminogen to plasmin induces a leaching of fibrin-associated plasminogen into blood through mass action.⁴⁸ The consequent reduction in clot-associated plasminogen diminishes the intensity of fibrinolysis and reduces the efficacy of plasminogen activators.

Thrombolytic Agents

The available thrombolytic agents are plasminogen activators. These agents function as proteases that directly or indirectly hydrolyze a single peptide bond (Arg⁵⁶¹Val⁵⁶²) on the inactive substrate molecule, plasminogen, to form the active serine protease enzyme, plasmin. Plasmin is responsible for the degradation of fibrin and diverse other proteins, with consequent dissolution of intravascular thrombi. So-called first-generation agents (non-fibrin-selective) include SK, UK, and APSAC. Second-generation and later generation (fibrin-selective) agents include t-PA, single-chain urokinase-type plasminogen activator (scu-PA), staphylokinase, and others, including molecular variants of t-PA such as TNK t-PA (tenecteplase). Agents that are relatively fibrin-specific, such as t-PA, produce less depletion of fibrinogen, less plasminemia, and less depletion of α_2 -antiplasmin than that seen with non-fibrin-specific agents such as SK. Fibrin-bound plasmin generated by clot-selective agents is not susceptible to rapid inhibition by α_2 -antiplasmin in the blood, in contrast to the circulating free plasmin that is neutralized promptly until α_2 -antiplasmin is depleted.²⁸ Table 12-1 summarizes the nomenclature, classification, and mechanism of action of several agents.

Non-Fibrin-Selective Agents

Streptokinase

SK is a protein present in numerous strains of hemolytic streptococci. It is a single-chain polypeptide that lacks the serine residue required for enzymatic activity, but it can activate plasminogen indirectly through an intricate, three-step process.^{49,50} Initially, SK forms an equimolar complex with plasminogen, resulting in exposure of the active site on the plasminogen molecule, which leads to the enzymatic conversion of plasminogen to plasmin by the exposed active site. The plasminogen-SK complex is converted to various, differentially cleaved plasmin-SK complexes,⁵¹ some of which are less active or more rapidly cleared than the SK-plasminogen complex, but can still convert plasminogen to plasmin.⁵²

Because SK is not fibrin-selective, extensive conversion of circulating plasminogen to plasmin occurs with subsequent depletion of fibrinogen, plasminogen, and factors V and VIII from the bloodstream. The accumulation of by-products of fibrinogen breakdown products, depletion of circulating α_2 -antiplasmin, and hyperplasminemia that occur constitute a systemic lytic state. A systemic lytic state occurs with all therapeutically effective doses of non-fibrin-selective plasminogen activators given intravenously. It is less intense with low-dose intracoronary administration.⁵³

The circulating half-life of SK is approximately 18 to 25 minutes. Depletion of fibrinogen to less than 50% of baseline values persists for approximately 24 hours, however. Because of the foreign nature of the protein and the near-universal human exposure to the bacterial sources of the agent (beta-hemolytic streptococci), administration of SK is complicated by inhibition of the administered drug by circulating IgG antibodies and problems of immunogenicity and attendant allergic reactions. In most humans, approximately 350,000 U of SK is necessary to neutralize circulating antibodies, but the range varies widely.⁵⁰⁻⁵⁴ With the conventional clinical dose of 1.5 million U, pretreatment circulating antibody levels do not correlate with subsequent patency rates or clinical outcome.⁵⁵

After administration of SK, anti-SK titers rise quickly and are virtually universally elevated within 5 days, remaining above baseline for 30 months.^{56,57} Consequently, repeated administration of SK is impractical and is not recommended.

The unfavorable profile of adverse reactions associated with SK (presumably attributable to plasmin-mediated activation of kininogen) limits clinical use of this agent to some extent. The overall incidence of hypotension ranges from 10% to 40%.^{50,58} It is highest with rapid infusion.⁵⁹ Severe hypotension requiring pressor agents or fluids occurs in 5% to 10% of patients. Other allergic reactions reported include fever, chills, urticaria, rash, flushing, and muscle pain. In the large-scale ISIS-2 and GUSTO-I trials, the incidence of minor allergic reactions was 4% to 6%.^{30,60} The incidence of anaphylactic shock is low, occurring in 0.7% of patients in GUSTO-I.³⁰

The conventional dose of SK is 1.5 million U administered over 1 hour by intravenous infusion. This regimen was described in 1983,⁶¹ and was used successfully in the GISSI-1 trial in 1986.⁶² More rapid administration can lead to a high incidence of hypotension and should be avoided.

Anisoylated Plasminogen Streptokinase Activator Complex

APSAC is a first-generation plasminogen activator that is a complex of human Lys-plasminogen and SK, with acylation of the plasminogen designed to block the active site until deacylation

Table 12-1. Classification and Characteristics of Plasminogen Activators

Agent	Other Names	Approximate Half-life	Intravenous Dose	Advantages and Disadvantages
First Generation				
Streptokinase	SK	18-25 min	1.5 million U over 1 hr	Not clot selective; immunogenic; reduced patency rates; inexpensive
Urokinase	UK, two-chain urokinase-type plasminogen activator (tCU-PA)	15 min	1.5 million U bolus, then 1.5 million U over 90 min	Not clot selective; nonimmunogenic; patency similar to SK; expensive
Anisoylated plasminogen streptokinase activator complex	APSAC, Anistreplase, Eminase	100 min	30 U bolus	Easy bolus administration; weak clot selectivity; expensive
Second Generation				
Tissue-type plasminogen activator		5 min	15 mg bolus, then 50 mg in first 30 min, then 35 mg in next 60 min	Clot selective; nonimmunogenic; superior patency rates; expensive
One chain	rt-PA, Alteplase, Activase, Actilyse			
Two chain	t-PA, Duteplase			
Single-chain urokinase-type plasminogen activator	SCU-PA, Prourokinase, Saruplase	5 min	20 mg bolus, then 60 mg over 1 hr	Relative clot selectivity
Staphylokinase	STA (bacterial origin)	1-2 min	10 mg over 30 min	Clot selective; may be immunogenic
	STAR (recombinant)			No large clinical trials
Third Generation*				
Vampire bat–plasminogen activator (Bat-PA)				
Mutants: domain deletion or substitution (rt-PA-TNK, r-PA)				
Chimeric plasminogen activators				
Antibody-targeted plasminogen activators				

*Further characteristics not provided because of limited experience in humans.

occurs slowly in vivo.⁵⁰ It is administered by intravenous bolus injection.⁶³ Deacylation occurs in the circulation, but the complex manifests no fibrin specificity.⁶⁴ Its half-life in the circulation is approximately 100 minutes. Because SK is the major component of APSAC, the drug is immunogenic and has a side-effect profile similar to that for SK. Similar induction of anti-SK antibodies⁵⁶ occurs, precluding repeated administration. Its fibrinolytic properties are virtually identical to the fibrinolytic properties of SK. The recommended dose in patients with acute MI is 30 U, given as an intravenous bolus. The nadir in plasma fibrinogen and α_2 -antiplasmin is comparable to that seen with 1.5 million U of SK.⁵⁰

Urokinase

UK, an endogenous trypsin-like enzyme, is a direct plasminogen activator. It is present in urine and occurs in two forms in blood and tissue: a high-molecular-weight form and a

low-molecular-weight form.⁶⁵ Its precursor is scu-PA, which is enzymatically inactive. Cleavage of scu-PA by plasmin yields high-molecular-weight UK, a two-chain, disulfide-linked molecule that lacks fibrin specificity and indiscriminantly activates circulating and fibrin-bound plasminogen, with associated depletion of α_2 -antiplasmin. It degrades fibrinogen and other plasma proteins and induces a systemic lytic state comparable to that seen with SK.

UK has a plasma half-life of approximately 15 minutes. Primary clearance is in the liver, with a small fraction (3% to 5%) cleared by the kidney.⁵⁴ UK has been used commonly in patients undergoing interventional procedures for coronary or peripheral vascular disease and in patients with pulmonary embolism. It is nonimmunogenic and can be administered as an intravenous bolus⁶⁶ or by infusion. The recommended dose for acute MI is a bolus of 1.5 million U followed by 1.5 million U given over 90 minutes.

Relatively Fibrin-Selective Agents

Tissue Plasminogen Activator

t-PA is an endogenous serine protease synthesized and secreted by human vascular endothelium and numerous other types of cells. When t-PA was isolated from a human (Bowes) melanoma cell line,⁶⁷ definitive evaluation of its biochemical and pharmaceutical features became possible. It was first given to patients with acute MI in 1984.⁶⁸ The cloning and expression of the human t-PA gene in *Escherichia coli* in 1983 by Pennica and colleagues⁶⁹ and the development of recombinant t-PA led to administration of t-PA to patients.⁷⁰

The plasma half-life of t-PA is only 5 minutes. Fibrinolytic activity persists on and within clots for 7 hours, however.⁷¹ t-PA is metabolized by the liver. It is inhibited in plasma by PAI-1 and other inhibitors. PAI-1, the “fast-acting inhibitor,” was characterized in the early 1980s.⁷²⁻⁷⁴ Infused t-PA rapidly saturates circulating PAI-1, and subsequently, circulating free t-PA complexes more slowly with inhibitors such as C-1 esterase inhibitor and α_2 -antiplasmin.^{74,75}

An important advantage of t-PA compared with SK is its affinity for fibrin-bound plasminogen through sites in the NH₂-terminal (heavy) chain.⁵⁰ In the absence of fibrin, t-PA is a weak activator of plasminogen. When fibrin is present, however, activation of plasminogen associated with it is rapid and intense. Clinically, conventional doses of t-PA induce some degradation of circulating fibrinogen (to approximately 50% of baseline) and some elevation of concentrations of fibrinogen degradation products. The relative fibrin specificity of t-PA accounts for the more rapid clot lysis seen with t-PA compared with SK.⁷⁶ Because the specificity for fibrin is not absolute, however, doses used clinically elicit degradation of circulating fibrinogen, albeit less than that seen with SK.⁷⁷

In contrast to SK, t-PA is not associated with immunogenicity. Its modest effects on circulating plasminogen do not lead to the degree of hyperplasminemia seen with non-fibrin-specific agents such as SK, and the overall risk of hemorrhage is less.

t-PA is available commercially as alteplase, which is primarily single-chain t-PA. Duteplase, a primarily double-chain t-PA with a different primary structure and different properties, was used in the ISIS-3 study, but is not commercially available. The two agents differ considerably with respect to risk of toxicity and probably differ in therapeutic efficacy.^{50,78-80}

In early clinical trials, the intravenous dose of t-PA was 60 mg in the first hour, with an initial 6-mg bolus, followed by 20 mg/hr for the next 2 hours. The total dose, 100 mg, was selected in part because higher doses had been associated with intracerebral hemorrhage (1.9% incidence with 150 mg administered over 3 hours).⁸¹ Neuhaus and coworkers⁸² introduced “front-loaded” dosing (i.e., 15-mg bolus with 50 mg given by infusion over the first 30 minutes, followed by 35 mg over the next 60 minutes). This regimen was associated with a 91% patency rate at 90 minutes, and it has now been approved by the U.S. Food and Drug Administration.

Third-Generation Fibrinolytic Agents

Numerous agents, sometimes referred to as third-generation agents, are designed to modify pharmacokinetics. Modifications are designed to prolong the half-life, increase fibrinolytic activity, increase fibrin selectivity, or exhibit other potentially advantageous properties. Deletion and substitution

mutants of naturally occurring plasminogen activators, chimeric activators (i.e., with components of UK and t-PA), and molecules containing homing antibodies to fibrin or platelet domains and receptors are being explored. Some examples follow.

Staphylokinase

The profibrinolytic properties of staphylokinase, a protein elaborated by strains of *Staphylococcus aureus*, have been recognized for more than 40 years.⁸³ Results in early studies in animals were not promising,^{84,85} and enthusiasm for this agent soon waned. A recombinant DNA-synthesized variety (STAR) has been developed. Compared with SK, it is more powerful and fibrin selective.⁸⁶ STAR, similar to SK, is not an enzyme. It forms an active proteolytic complex in 1:1 stoichiometry with plasminogen. Although immunogenic, it is a remarkably fibrin-selective fibrinolytic agent.⁸⁷ Its thrombolytic potency with platelet-rich arterial thrombi is impressive.⁸⁸ Compared with SK, STAR induces more frequent and more persistent arterial recanalization. In a pilot study, Collen and Van de Werf⁸⁹ showed successful coronary recanalization in four of five patients with evolving acute MI with 10 mg of intravenous recombinant staphylokinase. Plasma fibrinogen and α_2 -antiplasmin were not significantly decreased, and allergic reactions did not occur. Neutralizing antibodies to STAR were detected in plasma consistently within 14 to 35 days, however. Variants with less immunogenicity are being pursued (2004 D Collen, personal communication).

Tissue Plasminogen Activator Mutants

Hundreds of deletion, insertion, substitution, and combination mutants of wild-type t-PA have been synthesized. One, reteplase, initially called r-PA (also known as BM 06.022), has been studied in clinical trials and marketed as Retavase. Reteplase lacks the kringle 1 domain, resulting in a prolonged half-life and facilitating bolus administration.⁹⁰ It induces coronary recanalization rapidly in dogs,⁹¹ and has elicited early vessel patency in initial clinical studies. Early reocclusion has been encountered, however, implying the potential need for a double-bolus dosing regimen.^{92,93} It is not as fibrin-selective as wild-type t-PA.

Mutants of t-PA with prolonged half-lives have often exhibited reduced thrombolytic efficacy.⁹⁴ Generally, they have not seemed to be superior to wild-type t-PA.⁹⁵ One exception is a so-called triple mutant of t-PA, referred to as TNK t-PA (tenecteplase).⁹⁵ The acronym refers to the three amino acid substitutions that differentiate TNK t-PA from wild-type t-PA. They result in reduced inhibition of the plasminogen activator by PAI-1, prolongation of half life as a result of decreased uptake by the reticuloendothelial system mediated by mannose receptors, and consequent efficacy after bolus injection. TNK t-PA seems to induce reperfusion more rapidly than t-PA in patients treated within 3 hours after onset of symptoms.⁹⁶

Mortality Benefit of Pharmacologic Reperfusion: Clinical Trials of Coronary Thrombolysis

Early Observations

Recanalization trials performed in the late 1970s and early 1980s provided vital information by angiographically documenting relief of thrombotic coronary occlusion induced by

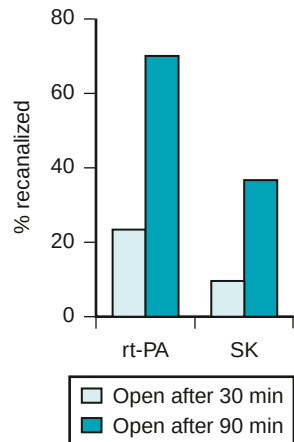


Figure 12-3. Recanalization rates from the TIMI phase I trial. At 90 minutes, recanalization with recombinant tissue plasminogen activator (rt-PA) is twice that seen with streptokinase (SK). (From Chesebro JH, Knatterud G, Roberts R, et al: *Thrombolysis In Myocardial Infarction (TIMI) trial, phase I: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase*. *Circulation* 1987;76:143.)

plasminogen activators. Initially, coronary thrombolysis was performed with intracoronary administration of plasminogen activators. This approach showed the feasibility of clot lysis and induction of recanalization.^{3,4} Rentrop and colleagues,^{97,98} using intracoronary SK, showed improved cardiac function and alleviation of chest pain accompanying recanalization compared with intracoronary nitroglycerin alone or conventional therapy. The Western Washington randomized trial⁹⁹ substantiated the efficacy of intracoronary SK in lysing coronary thrombi, with favorable effects on mortality. High rates of recanalization with intravenously administered t-PA were observed soon thereafter.^{68,100,101}

Intracoronary administration of SK seemed to be more capable of inducing prompt recanalization than SK administered intravenously.¹⁰² Logistic constraints on the availability of immediate cardiac catheterization, time delays, increased costs, and increased risk limited enthusiasm, however, for intracoronary administration of plasminogen activators as primary therapy for patients with acute MI. The appeal of the intravenous route was considerable. Nevertheless, observations in a study in which intracoronary SK was administered after PCI and stenting with apparently increased myocardial perfusion compared with the perfusion seen in the absence of SK may rekindle interest in the intracoronary administration of fibrinolytic drugs.¹⁰³

The TIMI phase I trial compared intravenous t-PA (80 mg over 3 hours) with intravenous SK (1.5 million U over 1 hour).¹⁰⁴ After 90 minutes, twice as many occluded arteries had been opened by t-PA (62%) as by SK (31%) (Fig. 12-3). The superiority of t-PA was evident, regardless of the interval between symptom onset and treatment. t-PA induced more rapid and more frequent clot lysis in the infarct-affected artery.

Patency Trials

Patency trials delineate angiographically defined patency at specified intervals after treatment. Prompt treatment seemed to maximize benefit in the multicenter GISSI-1 mortality trial in 1986.⁶² Patency trials are characterized by an unavoidable lack

of certainty, however, regarding the actual incidence of thrombotic occlusion before therapy, and the inclusion of patients with spontaneous thrombolysis. Nevertheless, such trials were helpful in comparing diverse agents with respect to overall patency. Angiography was required because noninvasive criteria of reperfusion, including relief of chest pain, ECG changes, early washout of enzymes, and arrhythmias, did not reflect actual incidences of recanalization.¹⁰⁵

It soon became clear that the extent and persistence of restoration of flow required to salvage ischemic myocardium were pivotal. Angiographic classifications based on the transit of contrast media through an infarct-related occluded vessel after treatment with plasminogen activators provided useful indices. One set of criteria employed frequently was established in the TIMI phase I trial in 1985 (Table 12-2).¹⁰⁶ It classified coronary flow from TIMI grade 0 (no flow) to TIMI grade 3 (brisk flow of contrast material). TIMI grade 1 (minimal flow of contrast material) and TIMI grade 2 (delayed flow of contrast material) were seen in patients with residual stenosis, coronary vasospasm, ongoing thrombosis, and the no-reflow phenomenon, in which forward flow is restricted, despite a patent vessel, by microvascular stasis downstream as a result of leukocyte and platelet plugging, vasoconstriction, or tissue and cellular edema.

Myocardial contrast echocardiography has been used also to assess the adequacy of restored perfusion. In 39 patients with acute anterior MI in whom recanalization was induced by percutaneous transluminal coronary angioplasty (PTCA) or thrombolysis, subsequent delivery of microbubbles into the coronary circulation followed by two-dimensional surface echocardiography identified nine patients in whom microcirculatory reflow was absent despite coronary patency.¹⁰⁷ Compared with the remainder of the study group, these patients exhibited significantly reduced segmental and global left ventricular function indicative of suboptimal myocardial salvage.

Most early patency trials employed angiographic end points to delineate patency 90 minutes after the administration of a thrombolytic agent. Patients with TIMI grade 2 or TIMI grade 3 were considered together in delineating overall patency incidence. Even when no thrombolytic agent is given, patency rates range from 9% to 29% in the 0- to 90-minute interval.^{100,104,108-112} Considerable “catch up” occurs (i.e., patency attributable to endogenous fibrinolysis), as judged from results of arteriography performed later. Patency rates range from 36%¹¹³ to 78%¹¹⁴ 3 to 21 days after MI in patients not treated with plasminogen activators.^{115,116}

Despite the higher patency rates seen with t-PA compared with SK, results of early megatrials (GISSI-1, ISIS-2)^{60,62} comparing the two agents did not show differences in mortality. The apparent lack of coupling between patency and mortality in these early trials fueled speculation that benefits did not depend on early opening of an infarct-occluded artery, regardless of how quickly coronary recanalization was achieved. Although an infarct-related occluded artery rendered patent late may confer some benefits unrelated to salvage of jeopardized myocardium, such as altered ventricular remodeling and improved electrical stability,^{117,118} the reduction of mortality of patients treated with thrombolytic agents depends primarily on the rapidity and persistence of recanalization. A striking 50% reduction in mortality rates occurred for patients treated within 1 hour of symptom onset in the GISSI-1⁶⁰ and ISIS-2⁶² trials, with the benefit less striking but still evident in patients treated within 3 to

Table 12-2. Angiographic Definitions of Perfusion from the TIMI Phase I Trial

Grade 0 (no perfusion)	There is no antegrade flow beyond the point of occlusion
Grade 1 (penetration without perfusion)	Contrast material passes beyond area of obstruction, but “hangs up” and fails to opacify the entire coronary bed distal to the obstruction for the duration of the cineangiographic filming sequence
Grade 2 (partial perfusion)	Contrast material passes across the obstruction and opacifies the coronary bed distal to the obstruction. Rate of entry of contrast material into the vessel distal to the obstruction, its rate of clearance from the distal bed, or both are perceptibly slower than entry into or clearance from comparable areas not perfused by the previously occluded vessel, such as the opposite coronary artery or the coronary bed proximal to the obstruction
Grade 3 (complete perfusion)	Antegrade flow into the bed distal to obstruction occurs as promptly as antegrade flow into the bed proximal to the obstruction, and clearance of contrast material from the involved bed occurs as rapidly as clearance from an uninvolved bed in the same vessel or the opposite artery

From Chesebro JH, Knatterud G, Roberts R, et al: Thrombolysis and Myocardial Infarction (TIMI) trial, phase I: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase. *Circulation* 1987; 76:143.

4 hours. A 1% mortality rate was seen in the MITI project³¹ for patients with documented MI treated with t-PA within 70 minutes of the onset of symptoms. In many patients, no late scintigraphic evidence of irreversible injury was observed, consistent with extensive and perhaps complete myocardial salvage. The failure to recognize the dependence of mortality reduction on early patency in the megatrials previously mentioned probably reflects the late time to treatment (and obviation of benefit) for many patients, and the failure to employ the adequate conjunctive anticoagulation needed to sustain initially induced patency.

The magnitude of restoration of flow seems to be a major determinant of benefit. *Patency* may be an inadequate term to describe the full impact of any given reperfusion therapy: TIMI grade 2 and TIMI grade 3 flow have different implications. Patients with delayed transit of contrast material in the infarct-affected artery (TIMI grade 2 flow) may not be exhibiting optimal or adequate recanalization. The TEAM-2 study analyzed data with respect to flow in patients treated with intravenous APSAC or SK.¹¹⁹ When TIMI flow grades were considered with respect to enzymatic and ECG markers of infarct size, no statistically significant difference was seen for TIMI flow grades 0, 1, or 2. Better outcomes were seen, however, with TIMI grade 3 flow.

In a retrospective analysis of four multicenter German studies (907 patients), TIMI grade 2 flow was associated with a mortality similar to that of patients with persistently infarct-occluded vessels.¹²⁰ The in-hospital mortality rate of patients with TIMI grades 0 and 1 was 7.1%. With TIMI grade 2, it was similar (6.6%). With TIMI grade 3, the mortality rate was significantly lower (2.7%). The GUSTO-I angiographic study provided another comparison. Lack of patency (TIMI grade 0 or 1) was associated with the highest mortality rate (8.9%). Traditionally defined patency (TIMI grades 2 and 3) was associated with a lower mortality rate (5.7%; $P = .004$).¹²¹ The mortality for patients with TIMI grade 2 flow was 7.4%, and even lower (4.4%) for patients with TIMI grade 3 flow ($P = .08$).

Front-loaded regimens of t-PA seem to be superior in terms of induction of TIMI grade 3 flow compared with other agents. The GUSTO-I angiographic trial directly compared SK, t-PA, and the combination of t-PA and SK (Table 12-3).¹²¹ Front-loaded t-PA was associated with complete reperfusion at 90 minutes (TIMI grade 3) in 54% of patients. With SK alone, complete reperfusion occurred in less than 32% of patients (29% with subcutaneous

heparin and 32% with intravenous heparin). In patients given t-PA and SK, reperfusion occurred in 38%. Similar rates of complete reperfusion at 60 minutes had been seen in earlier trials, with patency and TIMI grade 3 flow ranging from 54% to 62%^{29,82,122} with front-loaded t-PA compared with 40% with intravenous APSAC²⁹ and 40% with the standard dose of t-PA.¹²²

Patency trials have consistently shown more rapid and more complete reperfusion of infarct-occluded coronary arteries with the clot-selective agent t-PA than with other agents alone or agents in combination. Enhanced reperfusion coupled with conjunctive anticoagulation and other strategies designed to sustain reperfusion are the pivotal determinants of the efficacy of coronary recanalization in improving survival of patients treated with plasminogen activators.

One straightforward intervention would undoubtedly decrease mortality and increase the efficacy of coronary thrombolysis markedly. Fresh clots lyse much more rapidly than older ones in which fibrin cross-linking has proceeded.¹²³ Intervention within 30 to 60 minutes is likely to be particularly beneficial because more myocardium would remain viable and amenable to salvage, and because clot lysis would be much more rapid and complete. The rapidity with which patients are treated should be maximized. Current American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend the “earliest possible application of therapy,” and refer to therapy with fibrinolytic agents in the setting of STEMI with symptoms within 12 hours and ECG changes of 0.1 mV in two contiguous leads or new left bundle branch block as a class 1a recommendation.

Left Ventricular Function and Pharmacologic Induction of Reperfusion

Left ventricular contractile function as an end point in trials of coronary thrombolysis requires exceptionally careful analysis. Early placebo-controlled trials of coronary thrombolysis in which left ventricular ejection fraction was a primary end point showed variable but generally consistent group improvement in left ventricular function and indices of infarct size (e.g., enzymatic, scintigraphic) in patients treated with thrombolytic agents.^{99,114,124-130} Similar results were seen with global and regional measures of ventricular function.^{124,129} Improvement in ejection fraction has generally been greatest in groups of patients with anterior infarction, consistent

Table 12-3. Results of the GUSTO-1 Angiographic Study: Patency and Reocclusion of the Infarct-Occluded Artery According to Treatment Group

Variable	Patients with Feature/Patients Examined (%)			
	Streptokinase + Subcutaneous Heparin	Streptokinase + Intravenous Heparin	Accelerated t-PA	t-PA + Streptokinase
Patency				
Open vessels, TIMI grades 2 and 3 combined				
At 90 min	159/293 (54)	170/283 (60)	236/292 (81) ^{††}	218/299 (73) [†]
At 180 min	77/106 (73)	72/97 (74)	71/93 (76)	77/91 (85)
At 24 hr	64/83 (77)	74/92 (80)	89/104 (86)	87/93 (94) [‡]
At 5-7 days	67/93 (72)	81/96 (84)	70/83 (84) ^{†§}	71/89 (80)
Complete reperfusion, TIMI grade 3				
At 90 min	85/293 (29)	91/283 (32)	157/292 (54) ^{†**}	114/299 (38)
At 180 min	37/106 (35)	40/97 (41)	40/93 (43)	48/91 (53)
At 24 hr	42/83 (51)	38/92 (41)	47/104 (45)	56/93 (60)
At 5-7 days	47/93 (51)	56/96 (58)	48/83 (58)	49/89 (55)
Reocclusion				
From TIMI grade 2 at 90 min to grade 0 or 1 at follow-up	3/56 (5.4)	6/58 (10.3)	2/64 (3.1)	4/72 (5.6)
From TIMI grade 3 at 90 min to grade 0 or 1 at follow-up	4/54 (7.4)	1/69 (1.4)	9/121 (7.4)	4/92 (4.3)
Overall reocclusion [¶]	7/110 (6.4)	7/127 (5.5)	11/185 (5.9)	8/164 (4.9)

^{*}*P* = .032 for the comparison of this group with the group given t-PA with streptokinase.

[†]*P* < .001 for the comparison of this group with the groups given streptokinase with subcutaneous or intravenous heparin.

[‡]*P* < .001 for the comparison of this group with the group given streptokinase with subcutaneous heparin.

[§]*P* = .032 for the comparison of this group with the group given streptokinase with subcutaneous heparin.

^{**}*P* < .001 for the comparison of this group with the group given t-PA with streptokinase.

[¶]Overall patency rates (TIMI 2 and 3 flow) at 90 minutes and complete reperfusion rates (TIMI 3 flow only) at 90 minutes are superior with the regimen of accelerated t-PA and intravenous heparin, with similar reocclusion rates in all four groups.

t-PA, tissue plasminogen activator.

From GUSTO Angiographic Investigators: The effects of tissue plasminogen activator, streptokinase, or both on coronary artery patency, ventricular function, and survival after acute myocardial infarction. *N Engl J Med* 1993; 329:1618.

with the large amount of left ventricular muscle supplied by the left anterior descending coronary artery. Patients with inferior infarction have shown improved regional and global left ventricular function as well.^{127,131} Analysis of results in the ISAM study indicated that the patency of an infarct-occluded artery at 1 month was associated with good left ventricular function regardless of treatment (active or placebo) and the vessel involved.¹³²

A key observation was made by Van de Werf,¹³³ who recognized that effective thrombolysis enhances survival of patients with severely reduced left ventricular function who would have otherwise died. Lower ejection fractions are observed in the entire group of treated patients. In essence, the low ejection fractions in survivors with severe insults account for the apparent paradox that becomes prominent when large reductions in early mortality are achieved. This paradox has been called the *ventricular function–mortality paradox*. When it is considered along with methodologic limitations, it becomes clear that, contrary to speculation by some authors,¹³⁴ assessment of ventricular

function in groups is an ambiguous end point for comparing different agents or delineating the efficacy of specific conjunctive and adjunctive regimens. Conversely, sequential measurement of regional ventricular function in individual patients provides a more valid measure of benefit conferred by early and sustained recanalization.

Despite such limitations, correlations between patency and improved function have been striking. In more than 1200 patients enrolled in the five phases of the TAMI trials, TIMI grade 2 flow was associated with a higher incidence of recurrent ischemia and congestive heart failure, and with reduced improvement in global and regional left ventricular function compared with TIMI grade 3 flow.¹³⁵ When patients were evaluated according to TIMI flow grades regardless of the treatment used, patients with TIMI grade 3 had more preservation of regional wall motion, lower end-systolic volume indices, and higher left ventricular ejection fraction values than patients with TIMI flow grades 0, 1, and 2 (Table 12-4) as judged from 90-minute and 5- to 7-day angiography. The results are consistent

Table 12-4. Association between Patency Grade and Measures of Left Ventricular Function from the GUSTO Trial

Variable*	TIMI 0	TIMI 1	TIMI 2	TIMI 3
At 90 min	<i>n</i> = 233	<i>n</i> = 84	<i>n</i> = 275	<i>n</i> = 370
Ejection fraction (%)	55 ± 15	55 ± 15	56 ± 15	62 ± 14 [‡]
ESVI (mL/m ²)	31 ± 17	33 ± 21	29 ± 14	26 ± 14 [‡]
Wall motion (SD/chord)	-2.8 ± 1.3	-2.7 ± 1.4	-2.6 ± 1.4	-2.2 ± 1.5 [‡]
Abnormal chords (no.)	26 ± 17	26 ± 19	27 ± 19	18 ± 17 [‡]
Preserved RWM (% of group)	11	17	19 [§]	31 [‡]
At 5-7 days	<i>n</i> = 171	<i>n</i> = 63	<i>n</i> = 212	<i>n</i> = 284
Ejection fraction (%)	56 ± 14	54 ± 12	56 ± 14	61 ± 14 [‡]
ESVI (mL/m ²)	32 ± 16	34 ± 13	30 ± 13	26 ± 14 [‡]
Wall motion (SD/chord)	-2.5 ± 1.2	-2.7 ± 1.2	-2.3 ± 1.4	-1.8 ± 1.7 [‡]
Abnormal chords (no.)	23 ± 18	25 ± 19	22 ± 18	15 ± 16 [‡]
Preserved RWM (% of group)	18	22	27 ^{**}	39 ^{†¶}

*Compared with the totals of patients in the analyses at 90 minutes and at 5-7 days presented in Table 12-3, there are five fewer patients in the analysis at 90 minutes and three fewer in the analysis at 5-7 days presented in this table because the infarct-related arteries were not identifiable. ± refers to mean ± SD. Wall motion is expressed as the mean magnitude of depressed infarct zone chords; wall motion was considered preserved if all infarct zone chords were normal. Chords in the infarct zone were considered abnormal if they were >2 SD below the norm. All parameters measured are closer to normal with TIMI grade 3 flow compared with TIMI grades 0-2.

[‡]*P* < .001 for the comparison of this group with the groups with TIMI grades 0 and 1.

[‡]*P* < .001 for the comparison of this group with the group with TIMI grade 2.

[§]*P* = .026 for the comparison of this group with the groups with TIMI grades 0 and 1.

^{**}*P* = .034 for the comparison of this group with the groups with TIMI grades 0 and 1.

^{†¶}*P* = .007 for the comparison of this group with the group with TIMI grade 2.

ESVI, end-systolic volume index; RWM, regional wall motion.

From GUSTO Angiographic Investigators: The effects of tissue plasminogen activator, streptokinase, or both on coronary artery patency, ventricular function, and survival after acute myocardial infarction. *N Engl J Med* 1993; 329:1618.

with the fact that myocardial necrosis is virtually complete in 4 to 6 hours.¹¹⁷ The investigators underscore the critical importance of the rapidity and completeness of recanalization.

The TAMI-6 trial evaluated effects of late myocardial reperfusion (6 to 24 hours) induced by thrombolysis with intravenous t-PA (standard dose with a weight-adjusted regimen) or PTCA in patients with acute MI.¹³⁶ Compared with placebo-treated patients, patients subjected to late intervention exhibited no difference in ejection fraction or infarct zone regional wall motion at 1 or 6 months. Compared with t-PA, placebo was associated with a significantly greater end-diastolic volume at 6-month follow-up (*P* = .006). Late thrombolysis or angioplasty exerted no benefit in terms of systolic function despite some prevention of cavity dilation in patients treated with thrombolytic agents. The observations are consistent with the view that early and complete recanalization salvages myocardium, improves systolic function, and reduces mortality.

Pivotal Placebo-Controlled Trials

Results of early, placebo-controlled trials showed consistent reduction of mortality despite differences among them with respect to entry criteria, thrombolytic agents, "conventional care," and adjunctive therapy. In 1986, the landmark GISSI-1⁶² trial showed a reduction in the overall 21-day mortality rate from 13% to 10.7% for 11,806 patients treated with intravenous SK rather than the usual treatment at that time. The trial documented a 47% reduction in mortality rates for patients treated

with SK within 1 hour of symptom onset. Later studies of t-PA (ASSET, ECSG-5) showed analogous mortality reductions compared with placebo.^{114,137} Beneficial effects on survival with APSAC were seen in the AIMS trial,¹³⁸ with a 47% reduction in the 30-day mortality rate for the treatment group leading to early termination of this placebo-controlled trial.

The largest of all the early placebo-controlled trials was ISIS-2.⁶⁰ This trial randomly assigned 17,187 patients with acute MI to treatment with intravenous SK, oral aspirin, both, or neither. The 2 × 2 factorial design substantiated a reduction of mortality for patients treated with SK. The effects of aspirin alone were comparable. In retrospect, it seems clear that aspirin was reducing mortality in a subset of patients with unstable angina lumped with MI patients in this study, which failed to include a qualifying ECG as an entry criterion. The enrollment window from the onset of symptoms was 24 hours. As in GISSI-1, maximal benefit was seen in patients treated early (<4 hours from symptom onset). The smaller reduction in the 5-week mortality for patients treated in the 5- to 24-hour interval (*P* = .004) may have reflected prevention of MI in some patients with unstable angina or misidentification of the time of onset of MI in view of the omission of a qualifying ECG. Mortality reduction for patients treated in the interval 12 to 24 hours after symptom onset was not significant.

Time to treatment has been evaluated in the LATE study, in which 5711 patients presenting with acute MI that occurred 6 to 24 hours earlier were randomly assigned to intravenous t-PA

or placebo.¹³⁹ Treatment within 12 hours of symptom onset was associated with a 26% reduction of mortality for patients given t-PA. In patients treated from 12 to 24 hours, no benefit was evident. The EMERAS¹⁴⁰ study compared intravenous SK with placebo in 4534 patients treated within 6 to 24 hours of symptom onset. In the 12- to 24-hour group, no benefit was shown, but some benefit (not significant) was implicated in the 6- to 12-hour group. This result may have reflected some misclassification of the actual time of onset of infarction or consequences of interruption of stuttering infarcts.

The apparently greater benefit seen with t-PA compared with SK in the LATE and EMERAS trials may reflect more effective lysis by t-PA of aged thrombi. Alternatively, more rapid lysis by t-PA than with SK may be responsible. A meta-analysis of more than 50,000 patients suggested that mortality can be reduced in patients treated within, but not beyond, 12 hours.¹⁴¹ The most compelling evidence indicates that the benefits of fibrinolytic induction of recanalization are minimal if it is not accomplished early, optimally within a few hours after onset of symptoms.

Mortality in Direct Comparison Trials

In 1992, the GISSI-2¹⁴² trial reported no difference in the mortality rates of 12,490 patients treated with intravenous SK compared with standard-dose t-PA (alteplase, single-chain t-PA). In contrast to most smaller trials in the United States, patients were not given protocol-mandated intravenous heparin; patients in the heparin arm were given 12,500 U subcutaneously beginning 12 hours after the onset of infusion of the fibrinolytic drug. The overall mortality of 8.8%, although lower than that seen earlier in GISSI-1, was considerably higher than the mortality rate in the pooled data (5.6%) from numerous trials with t-PA. Neither SK nor t-PA seemed to have been tested under conditions in which benefit could be optimal. The lack of intravenous heparin and the late time to treatment seem to contribute to this phenomenon. ISIS-3¹⁴³ compared SK with t-PA (duteplase, double-chain t-PA) and APSAC in 41,299 patients. As in GISSI-2, ISIS-3 employed subcutaneous heparin (in 50% of the patients) at a dose of 12,500 U begun 4 hours after enrollment. No difference in mortality could be ascribed to any of the strategies. Combined results in the GISSI-2 trial for the overall 35-day mortality rate showed identical, high (10%) values for patients treated with SK and patients treated with t-PA.¹⁴³

Viewed superficially, the results of these megatrials seem to conflict with the results of mechanistic trials that had clearly linked coronary recanalization with improved survival. The lack of adequate anticoagulation seems to be one major factor that contributed to high mortality rates and a lack of difference between t-PA and SK. The subcutaneous heparin regimen used does not lead to adequate anticoagulation in virtually any patient in the first 24 hours because of binding of heparin to endothelial cell binding sites and slow absorption.¹⁴⁴

The need for administration of heparin with t-PA has been underscored by results in HART.¹⁴⁵ The investigators randomly assigned 205 patients with acute MI to treatment with t-PA, aspirin, and intravenous heparin or t-PA and aspirin alone. Although 90-minute patency is the same (79%) with t-PA with and without heparin, as shown in the TAMI-3 trial,¹⁴⁶ the patency rates between 7 hours and 24 hours in HART were 82% in the heparin group and only 52% in the aspirin group ($P < .0001$). A high incidence of reocclusion occurred when heparin was omitted. Analysis of the level of anticoagulation showed that patients

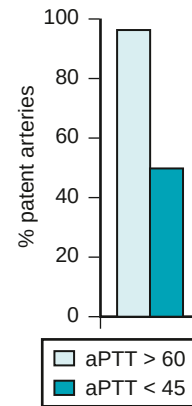


Figure 12-4. Correlation between the level of anticoagulation and patency in the HART trial. Dramatically improved patency rates are seen when recombinant tissue plasminogen activator is combined with sufficient heparin to prolong the activated partial thromboplastin time (aPTT) to greater than 60 seconds. (Hsia J, Kleiman N, Aguirre F, et al; HART Investigators: Heparin-induced prolongation of partial thromboplastin time after thrombolysis: relation to coronary artery patency. *J Am Coll Cardiol* 1992;20:31-35.)

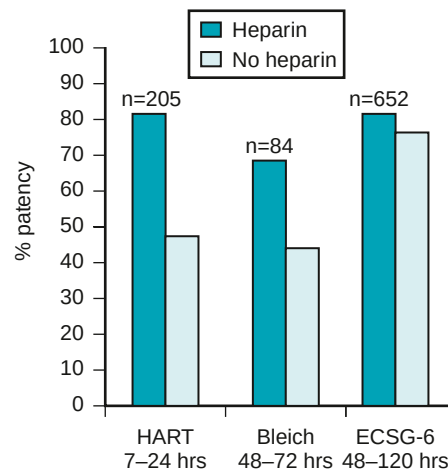


Figure 12-5. Patency trials comparing intravenous recombinant tissue plasminogen activator with and without intravenous heparin. All three trials show improved patency rates with conjunctive heparin. (Data from references 145, 149, and 150.)

with activated partial thromboplastin times (aPTTs) longer than 60 seconds had patency rates of 95%, in contrast to the dramatically lower late patency rate of 45% for patients with aPTTs less than 45 seconds (Fig. 12-4).¹⁴⁷

Analogous results were obtained by the European Cooperative Study Group.¹⁴⁸ The patency rate was higher for patients treated with t-PA and heparin and highest for patients with optimal anticoagulation. The same result was seen by Bleich and colleagues¹⁴⁹ and in the ECSG-6 study.¹⁵⁰ A consistent increase in persistence of coronary patency (from 7 to 120 hours after treatment) in patients undergoing coronary thrombolysis with t-PA accompanied coadministration of heparin, as shown in Figure 12-5. In view of the inadequate rapidity and magnitude of anticoagulation induced by the subcutaneous heparin dosage used in GISSI-2/International trial^{142,151} and ISIS-3,¹⁴³ the high

Table 12-5. Major Clinical Outcomes from the GUSTO-1 Trial

Outcome	Streptokinase + Subcutaneous Heparin (n = 9796)	Streptokinase + Intravenous Heparin (n = 10,377)	Accelerated t-PA + Intravenous Heparin (n = 10,344)*	Both Thrombolytic Agents + Intravenous Heparin (n = 10,323)	P Value, Accelerated t-PA ver- sus Both Streptokinase Groups
Mortality, 24-hr	2.8 [†]	2.9	2.3	2.8	.005
Mortality, 30-day	7.2	7.4	6.3	7.0	.001
Or nonfatal stroke	7.9	8.2	7.2	7.9	.006
Or nonfatal hemor- rhagic stroke	7.4	7.6	6.6	7.4	.004
Or nonfatal dis- abling stroke	7.7	7.9	6.9	7.6	.006

*There are significant reductions in mortality and the combined end point of mortality plus stroke (including intracranial bleeding) seen in the accelerated t-PA group. The outcomes are similar for the other three treatment groups.

[†]All values are percentages of patients responding.

t-PA, tissue plasminogen activator.

From GUSTO Investigators: An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 1993; 329:676.

mortality rate and lack of fibrinolytic drug-dependent differences in ISIS-3¹⁴³ and the GISSI-2/International trials^{142,151} are probably attributable to a design that led to substandard rates and rapidity of coronary recanalization and to a failure to maintain patency (particularly in the t-PA group), rather than to a lack of dependence of benefit and survival on early recanalization.

Because of allegations regarding the efficacy of combinations of fibrinolytic agents,¹⁵²⁻¹⁵⁴ and the need to delineate the relative merits of conjunctive anticoagulation, the GUSTO-I trial was implemented to compare four different regimens in 41,021 patients: SK with subcutaneous heparin, SK with intravenous heparin, front-loaded (also called accelerated) t-PA with intravenous heparin, and a combination of SK and t-PA with intravenous heparin.³⁰ The 30-day mortality was lowest with front-loaded t-PA and intravenous heparin (6.3%) and significantly less than that with combination therapy (7%), SK and subcutaneous heparin (7.2%), and SK and intravenous heparin (7.4%) (Table 12-5). Reduction of mortality directly depended on the rapidity and adequacy of recanalization.¹²¹ Front-loaded t-PA was associated with fewer allergic reactions, less hypotension, less overall bleeding, and a lower incidence of recurrent ischemia, reinfarction, and diverse cardiac complications than the other regimens.³⁰ The incidence of reocclusion was no higher than that with the other regimens.¹²¹ Overall, front-loaded t-PA led to more rapid and complete recanalization and an increase in the combined end point of survival without a stroke, equivalent to 10 lives saved per 1000 patients treated compared with either SK regimen.

Fibrinolysis, Reperfusion, and the Importance of Early Treatment

The fundamental principle that benefits of coronary thrombolysis directly depend on rapid and sustained induction of infarct-related artery patency implies several considerations for optimizing results.¹⁵⁵ Among these considerations are optimal dosage regimens with highly fibrin-selective agents, novel agents resistant to inhibitors targeted to clots, optimal

antiplatelet and anticoagulant agents and regimens, and coupling later mechanical interventions to thrombolysis in patients with inadequate infarct-occluded artery luminal dimensions. No approach is more important, more powerful, more readily achieved, or more underused than the reduction of the time to treatment after onset of symptoms in patients with early, evolving acute MI. Advantages of this approach include the enhanced myocardial salvage that can be anticipated when recanalization is induced before the bulk of jeopardized ischemic myocardium is blighted,¹⁵⁶ and the increased rapidity and extent of lysis that can be anticipated with fresh clots compared with more mature thrombi already undergoing cross-linking of fibrin¹²³ and consequent occupancy of lysine-binding sites that otherwise serve to bind plasminogen to fibrin.

The MITI phase I pilot study¹⁵⁷ documented an average 73-minute delay from recognition of acute MI (documented by transmission of ECG data by cellular telephone) to in-hospital treatment with coronary thrombolysis, even with highly skilled paramedical personnel. Subsequently, randomized trials were performed to identify the potential benefits of reducing this delay by implementation of prehospital coronary thrombolysis compared with in-hospital treatment.^{31,158,159}

The importance of early treatment with fibrinolytic drugs has led to a European practice of prehospital fibrinolysis. Despite the theoretical appeal of this approach and favorable results with low mortality in several small studies, results of more recent studies of prehospital fibrinolysis without subsequent mandatory PCI compared with primary PCI are not compelling in support of this practice. Examples include the results of the Leipzig study,¹⁶⁰ which showed superiority of primary PCI compared with administration of 50% of conventional doses of TNK combined with abciximab reflected by resolution of ST segment elevation within 90 minutes; results in the SWEDES reperfusion trial,¹⁶¹ in which prehospital administration of lytic agents without mandatory subsequent PCI was shown to be inferior to primary PCI despite a briefer interval between the onset of symptoms and initiation of treatment as reflected by resolution

of ST segment elevation and TIMI flow grade at angiography 5 to 7 days later; and analogous results in a more recent registry study,¹⁶² in which lower 30-day and 1-year mortality was evident in patients treated with primary PCI compared with prehospital lysis without PCI regardless of whether symptoms persisted for less than or more than 2 hours before the onset of treatment, and despite the fact that prehospital lysis led to more favorable results than in-hospital lysis.

The CAPTIM study¹⁶³ did not detect differences in benefit with prehospital lysis compared with primary PCI, but subsequent analysis suggested that prehospital lysis was more favorable, although not significantly ($P = .058$), when performed within 2 hours after onset of symptoms compared with primary PCI. The ASSENT 3-plus study,¹⁶⁴ in which TNK was studied with unfractionated heparin compared with enoxaparin as prehospital regimens, showed better safety with unfractionated heparin with very low overall rates of the primary end points in both groups. Taken together, available data indicate that a pivotal component of favorable outcomes is the rapidity of treatment and restoration of patency of the infarct-related artery. Despite the theoretical advantage of prehospital thrombolysis consistent with this determinant, objective information in aggregate is consistent with the superiority of primary PCI to a strategy of prehospital thrombolysis in most instances. Although European practice frequently entails prehospital thrombolysis, conventional care in the United States relies more completely on PCI.

Conjunctive Therapy

The activation of circulating platelets and the blood coagulation system in patients with acute MI is a result of complex phenomena.⁴⁶ Administration of plasminogen activators paradoxically contributes to these reactions. All available thrombolytic agents exhibit at least some nonspecificity, resulting in plasminemia with consequent activation of the coagulation cascade because of proteolytic cleavage of factors XII, X, and V and activation of factor X to Xa.^{44,45,165} Thrombin is generated in vivo, reflected by elevated concentrations in plasma of fibrinopeptide A, a cleavage product from fibrinogen elaborated by thrombin. Thrombin also activates platelets.

Suppression of coagulation and activation of platelets is necessary as conjunctive therapy to accelerate coronary recanalization, optimize its extent, and prevent reocclusion.¹⁶⁵ We have used the term *adjunctive therapy* in a restricted sense to refer to measures designed to reduce myocardial injury through mechanisms independent of the mode of recanalization and without directly influencing recanalization. Examples include methods used to reduce myocardial oxygen requirements or attenuate cellular injury.

Platelet-Targeted Conjunctive Therapy

Platelets can promote thrombosis by providing surfaces favoring the assembly of prothrombinase, activation of factor XII, and cross-linking of fibrin mediated by factor XIII. Platelets also can inhibit thrombolysis by the release of PAI-1 and α_2 -antiplasmin. Inhibition of platelet activation should potentiate clot lysis. At least five pathways exist through which activation of platelets can occur.

Aspirin improved survival when used in conjunction with SK in the large ISIS-2 trial.⁶⁰ It is an established conjunctive agent that is usually given at an initial dose of 162 mg (chewable

aspirin) as soon as possible when thrombolysis is planned, followed by daily doses of 162 to 325 mg.

Platelet activation is inhibited by aspirin through the blockade of cyclooxygenase and synthesis of thromboxane. Inhibition is incomplete, and other mechanisms can still activate platelets. A more complete inhibition can be induced by blocking the glycoprotein (GP) IIb/IIIa receptor on the platelet surface; the receptor provides the fibrinogen binding site that is required for platelet aggregation. Monoclonal antibodies directed at this receptor offer a promising approach to the blockade of platelet aggregation, which is implicated in the early thrombotic reocclusion associated with platelet-rich thrombi relatively resistant to lysis with plasminogen activators.^{47,166-168}

Monoclonal antibodies to GP IIb/IIIa enhance lysis of platelet-rich thrombi¹⁶⁸⁻¹⁷⁰ and reduce reocclusion^{168,171} when administered in combination with t-PA to laboratory animals. In clinical studies, a humanized murine monoclonal antibody 7E3 Fab (abciximab) has proven promising. In the TAMI-8 pilot study,¹⁷² 7E3 Fab was administered 3 hours after t-PA, heparin, and aspirin. Fewer episodes of recurrent ischemia and higher patency rates resulted. Analogous, favorable results have been obtained after PTCA.^{173,174} GP IIb/IIIa blockade has emerged as a valuable conjunctive measure for patients treated with PCI, but its value in association with thrombolytic agents is compromised by excess bleeding and its clearly deleterious consequences.⁴⁶ In the CLARITY TIMI-28 trial,¹⁷⁵ in which a 300-mg loading dose of clopidogrel was compared with placebo in patients treated with fibrinolytic drugs followed by mandatory angiography within 2 to 8 days and "open-label" clopidogrel subsequently, results with clopidogrel were more favorable. Significantly more patients exhibited occlusion of the infarct-related artery at angiography or death ($P = .01$) in the placebo-treated group (21.7%) compared with the clopidogrel group (15%). There was no difference in the incidence of mortality or the incidence of bleeding. Use of antiplatelet drugs in the adenosine diphosphate (ADP) antagonism class may be beneficial in association with administration of fibrinolytic agents.

Thrombin-Targeted Conjunctive Therapy Unfractionated Heparin

Prevention and amelioration of the generation and activation of thrombin are important determinants of the success of coronary recanalization.¹⁷⁶ Intravenous heparin is the most widely used conjunctive agent for this purpose. Heparin acts on thrombin indirectly, however, by complexing with antithrombin III, forming a bulky moiety that is ineffective in inhibiting clot-bound thrombin.^{165,177,178} Nevertheless, its antithrombin effects improve the rate of patency induced by fibrinolytic agents. Conjunctive antithrombin agents are particularly important with second-generation fibrinolytic agents because they elicit more modest elevations of circulating fibrinogen degradation products, moieties with some intrinsic anticoagulant and antiplatelet properties. Even with non-fibrin-selective agents, heparin is beneficial, however.¹²¹

The benefits of intravenous heparin (including low-molecular-weight heparin [LMWH]) in mechanistic trials are evident from the recanalization and patency rates delineated angiographically. Mortality data are also consistent with its beneficial effects.¹⁷⁹ In the GUSTO-I angiographic study, intravenous heparin induced greater early patency than subcutaneous heparin, even with the nonselective agent SK (see Table 12-3).¹²¹

Alternatives to Unfractionated Heparin

Several studies have addressed the potential benefit of agents other than unfractionated heparin in combination with fibrinolytic drugs. In the ASSENT 3 trial,¹⁸⁰ in which TNK plus LMWH was compared with half-dose TNK plus a bivalirudin, a low dose unfractionated heparin and TNK+ weight-adjusted unfractionated heparin LMWH seemed to be the superior conjunctive agent with respect to the combination of efficacy and safety. Although unfractionated heparin plus a bivalirudin exhibited the lowest incidence of the combined end point of 30-day mortality, reinfarction, and refractory ischemia, the regimen was associated with a greater incidence of bleeding, especially in elderly patients. The ASSENT 3-plus trial,¹⁶⁴ in which 1639 patients were studied after treatment with TNK plus enoxaparin compared with unfractionated heparin, showed superiority of enoxaparin ($P = .08$), but no difference in the combined end point of safety plus efficacy. There was a significant increase in intracranial hemorrhage (2.2% versus 1%; $P = .047$) associated with administration of the LMWH, especially in elderly patients.

In the EXTRACT TIMI-25 study,¹⁸¹ in which 20,479 patients were enrolled and treated with either TNK (80% of patients) or SK (20% of patients) combined with unfractionated heparin or enoxaparin, the combined end point of death or MI within 30 days was significantly lower with the LMWH enoxaparin ($P < .001$), with an odds ratio (OR) of 0.83 and a confidence interval (CI) of 0.77 to 0.90. There was an increased incidence of overall episodes of bleeding, but not of intracranial hemorrhage with enoxaparin, and the incidence of urgently required target vessel revascularization was lower with enoxaparin. In this study, enoxaparin dosage was reduced with respect to advanced age and other criteria, perhaps accounting in part for the favorable results.

In the OASIS VI study¹⁸² of fondaparinux, in which 12,092 patients were treated with fibrinolytic drugs or PCI combined with heparin during the procedure compared with unfractionated heparin or placebo in patients treated with SK or r-PA, results with fondaparinux were better (11.2% versus 9.7%) with respect to the incidence of the primary end point of death or MI within 30 days in patients who were not treated with PCI. Less bleeding was encountered in the patients treated with fondaparinux. The reason for administration of heparin during PCI in OASIS VI¹⁸² was that the results in the OASIS V study¹⁸³ showed an unacceptable incidence of thrombus formation on guidewires without the addition of heparin to fondaparinux. Results of OASIS VI¹⁸² suggest that fondaparinux is a reasonable alternative as a conjunctive agent compared with unfractionated heparin for patients treated with thrombolytic drugs.

Hirudin

Intrinsic limitations of heparin as a pharmaceutical, particularly its dependence on antithrombin III for activity, were an impetus to the development of direct-acting antithrombins. Such agents are likely to induce more complete inhibition of thrombin. The most initially studied example is hirudin, a protein isolated originally from the medicinal leech (*Hirudo medicinalis*) and subsequently synthesized through recombinant technology. Hirudin binds directly to thrombin, inhibiting its catalytic and anion binding sites.^{178,179,184-187} In animals, hirudin exerted more favorable synergistic effects with respect to accelerating thrombolysis and sustaining patency in thrombotically occluded

canine coronary arteries compared with aspirin, heparin, and a GP IIb/IIIa receptor antagonist.¹⁸⁸

Results of three clinical trials¹⁸⁹⁻¹⁹¹ employing hirudin in patients with acute MI or unstable angina led to a critical reappraisal of dosage and the optimal approach to balancing safety and efficacy.¹⁹¹ The GUSTO IIA trial¹⁸⁹ compared intravenous heparin titrated to aPTT values of 60 to 90 seconds with intravenous hirudin at a fixed dose (0.6 mg/kg bolus and 0.2 mg/kg/hr infusion) without aPTT adjustment in patients with chest pain and ECG changes consistent with acute MI or unstable angina. This trial was designed to enroll 12,000 patients, but was terminated prematurely after 2564 patients had been studied because of an unacceptably high incidence of intracranial hemorrhage in all treatment groups. The TIMI-9A trial¹⁹⁰ employed the same dose of intravenous hirudin and compared it with aPTT-adjusted (60 to 90 seconds) intravenous heparin combined with front-loaded t-PA or SK (the choice was made at the treating physician's discretion) in patients with acute MI. TIMI-9A also was terminated early because of an unacceptably high incidence of intracranial and other major hemorrhage in the heparin and hirudin groups. The high incidence of complications was particularly profound in the patients treated with SK plus hirudin.

The randomized multicenter German pilot study HIT-III¹⁹¹ compared a different dosage and type of recombinant hirudin with heparin in combination with front-loaded t-PA (alteplase) in patients with acute MI. In all treatment groups, dosage of the antithrombin was adjusted to maintain aPTTs within a range of 2.5 to 3 times baseline values. HIT-III¹⁹¹ had to be terminated early because of an unacceptably high incidence of intracranial bleeding that was confined to the group treated with t-PA plus hirudin (3.4%). No intracranial bleeding occurred in the group treated with t-PA plus heparin.

The increased incidence of catastrophic bleeding encountered in these three studies might have resulted from the prolonged duration of infusion of antithrombin agents (48 to 120 hours); features of the patients studied, including advanced age (in view of the markedly low clearance of hirudin in elderly patients); high doses of the antithrombin agents associated with late bleeding as a result of adjustments based on body weight and aPTT values; and other factors that are discussed later. Regardless of the reason, the lesson to be learned is that therapeutic efficacy and safety depend on optimal dosing, as yet undefined, and its appropriate individualization. The results do not justify denigration of the value of conjunctive therapy.¹⁹² The TIMI-9B trial has been reconfigured to employ a lower dose and duration of infusion of hirudin (bolus of 0.1 mg/kg and infusion of 0.1 mg/kg/hr) and heparin (1000 U/hr without weight adjustment) plus titration of both agents to maintain aPTTs between 55 and 85 seconds.

Other direct-acting antithrombin agents, such as bivalirudin (Hirulog), have been employed in the setting of PCI with promising results.¹⁹³⁻¹⁹⁶ Definitive evaluations of bivalirudin in association with fibrinolytic drugs are unavailable. The HERO-2 study¹⁹⁷ examined the use of bivalirudin or unfractionated heparin in conjunction with intravenous SK on 1-month mortality. There was no significant difference in the primary end point, although the bivalirudin group had a lower rate of reinfarction at 96 hours. Additional direct-acting antithrombins include argatroban, D-phenylalanyl-L-arginyl-chloromethylketone (P-PACK), and other chloromethylketones.¹⁹⁸⁻²⁰¹

Table 12-6. Combined Incidence of Ischemic and Hemorrhagic Strokes in the GISSI/International Trial

Condition	Fibrinolytic Drug		Odds Ratio	Confidence Interval (95%)	P Value (chi-square)
	t-PA	SK			
With heparin	64/5, 170 (1.2%)	53/5, 191 (1%)	1.22	(0.77-1.67)	.3
Without heparin	74/5, 202 (1.4%)*	45/5, 205 (0.9%)	1.65	(1.04-2.26)	.007
Total	138/10, 372 (1.3%)	98/10, 396 (0.9%)	1.40	(1.04-1.76)	.0004

*The stroke rate with t-PA and subcutaneous heparin is similar to the stroke rate with SK. There is a higher incidence of stroke in the t-PA group without subcutaneous heparin.

SK, streptokinase; t-PA, tissue plasminogen activator.

From Sobel BE, Collen D: Strokes, statistics and sophistry in trials of thrombolysis for acute myocardial infarction. *Am J Cardiol* 1993; 71:425.

Intracranial Hemorrhage and Stroke

Hemorrhage, particularly intracranial bleeding, is the major risk associated with the use of thrombolytic agents. Hemorrhage occurs through conversion of ischemic strokes to hemorrhagic ones, and by inducing a modestly higher frequency of de novo hemorrhagic strokes in patients treated with fibrinolytic drugs compared with anticoagulants alone. For patients with infarction who were treated with placebo in the early thrombolytic trials, overall early stroke incidence was approximately 1%.²⁰² With fibrinolytic drugs, stroke incidence is 1.2% to 1.5%, with hemorrhagic stroke accounting for 0.3% to 0.7%. The risk of intracranial bleeding with t-PA is greater than with SK: 0.4% versus 0.3% in the GISSI-2 International trials^{142,151} and 0.7% versus 0.5% in GUSTO-I.³⁰

Patients with infarction are at risk for emboli from carotid plaques, emboli from mural thrombi in the left ventricle, ischemic strokes that can be rendered hemorrhagic by anticoagulants or plasminogen activators, and possibly occult susceptibility to proteolysis of cerebral vessels with unsuspected pathology, such as abnormal cerebrovascular integrity as a result of an aneurysm or β -amyloid deposition (i.e., congophilic angiopathy). Patients may be prone to complications attributable to an endogenous hypercoagulable state or procoagulant effects of plasminogen activators, particularly fibrin-specific agents administered without adequate anticoagulation with intravenous heparin.²⁰² Even before thrombolysis became part of the therapeutic armamentarium, the overall incidence of early stroke of all types accompanying acute MI ranged from 1.7% to 3.2%.²⁰³⁻²⁰⁵ In the GUSTO-I trial,³⁰ the risk of any stroke (including intracranial bleeding) was 1.55% for patients treated with front-loaded t-PA and intravenous heparin and 1.4% for patients treated with SK and intravenous heparin.

As shown by pooling data from numerous early placebo-controlled trials of fibrinolytic agents enrolling tens of thousands of patients, the incidences of stroke were similar with and without plasminogen activators.²⁰⁶ The incidence of stroke overall was higher before thrombolysis was widely used than it is now.²⁰⁷ Coronary thrombolysis exerts only a minimal or no adverse effect on the overall incidence of stroke despite increasing the frequency of intracranial bleeds from the approximately 0.1%²⁰⁷ seen with anticoagulants alone to 0.3% to 0.7%. The increase in intracranial bleeds associated with plasminogen activators seems to be small and more than offset by a reduction

in the incidence of thromboembolic stroke and the decrease in mortality.²⁰⁶

After the GISSI-2/International trials^{142,151} and ISIS-3,¹⁴³ much debate surrounded the incidence of stroke in relation to specific thrombolytic agents (i.e., single-chain t-PA [alteplase], double-chain t-PA [duteplase], and SK). Close examination of the results of the GISSI/International trials showed a significant increase of all-cause stroke in patients given t-PA (alteplase) without subcutaneous heparin compared with patients given subcutaneous heparin (1.4% versus 1.2%).²⁰² The incidence of intracranial hemorrhage was similar when t-PA was compared with SK (0.4% versus 0.3%). The difference in the combined incidence of ischemic and hemorrhagic stroke with t-PA (1.32%) compared with SK (0.9%) seems to be attributable largely to an increase in thromboembolic rather than hemorrhagic events. Because the late use of subcutaneous heparin failed to induce adequate anticoagulation, the increase in ischemic strokes is not surprising in the context of the procoagulant effects and fibrin-selective properties of t-PA. This interpretation is consistent with the lack of difference in the incidence of stroke with SK with or without subcutaneous heparin (1% versus 0.9%),²⁰² as summarized in Table 12-6.

Conversely, the difference in the total incidence of stroke seen with double-chain t-PA (duteplase) and SK in the ISIS-3 trial¹⁴³ was attributable largely to hemorrhagic rather than ischemic stroke (0.7% with duteplase versus 0.2% with SK). The dose of duteplase used in ISIS-3 (0.6 MU/kg) corresponds functionally, with respect to plasmin-generating potential, to a dose of 150 mg of single-chain t-PA (alteplase).^{202,208} It was precisely this dose of alteplase that led to inordinately high intracranial hemorrhage rates (1.5%) in the pilot phase of the TIMI trial.²⁰⁹ The imposition of stricter recruitment criteria and a lower total dose of t-PA (alteplase, 100 mg) in the TIMI trial resulted in a reduction of the hemorrhagic stroke incidence to 0.6%.²⁰⁹

The excess incidence of stroke with t-PA in the GISSI/International trials cannot be lumped with the excess in ISIS-3. In GISSI-2, it reflected primarily a lack of adequate anticoagulation. In ISIS-3, it reflected excessive dosing of the anomalous double-chain t-PA used. A summary of data from these two trials is presented in Table 12-7. Because of the disparate design of these two large studies and the consequent mechanistic differences, meta-analysis²¹⁰ of these trials is inappropriate in delineating the overall risk of patients given t-PA or SK.

Several factors may have contributed to the unexpectedly high incidence of adverse effects in these trials.^{192,211} The

Table 12-7. Overall Incidence of Stroke in the GISSI/International and ISIS-3 Trials

Clinical Event in Hospital	Study	Fibrinolytic Agent Allocated		Odds Ratio	Confidence Interval (95%)
		t-PA	SK		
Total stroke	GISSI/International	136/10,372 (1.32%)	98/10,396 (0.9%)	1.40	(1.04-1.76)
	ISIS-3	188/13,569 (1.4%)	141/13,607 (1%)	1.34	(1.05-1.63)
	Both	324/23,991 (1.4%)	239/24,003 (1%)	1.36	(1.13-1.59)
Cerebral hemorrhage*	GISSI/International	44/10,372 (0.4%)	30/10,396 (0.3%)	1.47	(0.79-2.16)
	ISIS-3	89/13,569 (0.7%)	32/13,607 (0.2%)	2.80	(2.21-3.40)
	Both	133/23,941 (0.6%)	62/24,003 (0.3%)	2.16	(1.51-2.81)
Nonhemorrhagic or undefined stroke	GISSI/International	92/10,372 (0.9%)	63/10,396 (0.7%)	1.36	(0.93-1.79)
	ISIS-3	99/13,569 (0.7%)	109/13,607 (0.8%)	0.91	(0.66-1.16)
	Both	191/23,941 (0.8%)	177/24,003 (0.7%)	1.08	(0.86-1.30)

*The increased incidence of intracranial stroke with alteplase in ISIS-3 results from an inordinate increase in intracranial hemorrhage. In the GISSI/International trial, the increased stroke rate with alteplase reflects higher rates of nonhemorrhagic stroke.

SK, streptokinase; t-PA, tissue plasminogen activator.

From Sobel BE, Collen D: Strokes, statistics and sophistry in trials of thrombolysis for acute myocardial infarction. *Am J Cardiol* 1993; 71:426.

consistency of the results with hirudin suggests that the dosage was probably excessive. The higher rates of intracranial bleeds with t-PA and heparin in GUSTO-IIA than in GUSTO-I may reflect the higher doses and more prolonged administration of heparin (GUSTO-IIA, 70 to 120 hours; GUSTO-I, ≥ 48 hours at the physician's discretion) and the broader interval for enrollment (12 hours compared with 6 hours after symptom onset in GUSTO-I). The duration of heparin infusion may be particularly culpable in view of the late (average 31 hours) occurrence of intracranial bleeds in GUSTO-IIA. The benefits of continuation of heparin beyond 24 hours have not been established.^{192,212} Similar considerations apply to TIMI-9A, in which enrollment was up to 12 hours after symptom onset, and heparin was given at higher doses and for longer than in the GUSTO-I trial. HIT-III limited enrollment to within 6 hours of symptom onset and used a heparin dose similar to that used in GUSTO-I; this may explain the anticipated low overall occurrence of stroke (1.3%) in patients treated with t-PA and heparin and the absence of intracranial bleeds.

These results underscore the need to focus on the treatment of patients with acute MI as early as possible (perhaps only within 6 hours after symptom onset in the absence of extenuating circumstances) and to use heparin in regimens shown to be safe and effective in GUSTO-I. An intravenous bolus of 5000 U should be followed by 1000 U/hr and continued for 24 to 48 hours, unless circumstances dictate otherwise. Target aPTT values of 55 to 85 seconds are appropriate.

Although the relative risk reduction for death conferred by treatment with plasminogen activators is greatest in elderly patients, an age greater than 65 years, weight less than 70 kg, and female gender correlate with an increased risk of intracranial bleeding.^{213,214} Elevated blood pressure is another risk factor,¹⁸⁶ perhaps because prolonged, uncontrolled hypertension induces vasculopathy, rendering cerebral vessels susceptible to the adverse effects of proteolytic agents. The risk of intracranial bleeding increases with systolic blood pressures greater than

150 mm Hg and is particularly high in patients with systolic blood pressures exceeding 175 mm Hg (1.6% intracranial bleeding rate; $P = .001$).¹⁴¹ Older, diminutive, and severely hypertensive patients are at high risk.

Consideration of these factors is needed to select specific treatment modalities prudently for individual patients. Overall, effective regimens for coronary thrombolysis have improved outcomes in aggregate with respect to mortality, nonfatal disabling stroke, and intracranial bleeding, as shown by the GUSTO-I results in Table 12-5, in which front-loaded t-PA with intravenous heparin, SK with intravenous heparin, and combined t-PA and SK with heparin are compared.³⁰

Patient Selection, Complications, and Considerations Pertinent to Specific Groups

Most patients presenting with acute MI are managed initially by primary care physicians, including internists, family practitioners, and emergency physicians.²¹⁵ Sophistication regarding patient selection for treatment options is essential.

The risk of hemorrhage (exclusive of intracranial hemorrhage) was greater in early mechanistic clinical trials in which early and repeated angiography was undertaken more universally than it is today. The incidence of bleeding associated with access sites ranged from 12% to 50% compared with 1% in studies in which angiography was not implemented.²¹⁶ With the availability of refined, small-gauge catheters, modern angiography, avoidance of unnecessary femoral vein puncture, and expertise of experienced angiographers, the risks of early angiography are probably similar to the risks associated with deferred angiography after infarction (TAMI-5)^{152,217} and elective angiography in patients without recent infarction.

Much debate has surrounded the incidence of major "spontaneous" (nonaccess site) bleeding in gastrointestinal,

retroperitoneal, pulmonary, or genitourinary sites relative to the agents used and the use of conjunctive anticoagulation. GUSTO-I³⁰ results show low rates with SK and with front-loaded t-PA (t-PA and intravenous heparin, 0.4%; SK and subcutaneous heparin, 0.3%; SK and intravenous heparin, 0.4%).

Risks associated with immunologically mediated side effects related to some thrombolytic agents include anaphylaxis and other, less serious allergic reactions, such as fever, chills, arthralgias, anaphylactoid reactions, and vasculitis. Such complications occur particularly with SK and agents containing the SK moiety, such as APSAC. Anaphylaxis occurred in 0.6% of patients treated with SK in GUSTO-I.³⁰ It may be under-reported, however, because of the difficulty of diagnosis in the setting of acute MI, when severe hypotension or shock may be attributed erroneously to other causes.

Hypotension occurs commonly with SK, with an average decrease in systolic blood pressure of 35 mm Hg and transient reductions to less than 90 mm Hg in 38% of patients.⁵⁹ It probably reflects activation of the kinin system by plasmin, decreased viscosity of blood secondary to proteolysis, and perhaps negative inotropic effects induced indirectly. Hypotension is much less common in patients treated with fibrin-selective agents. In GUSTO-I, front-loaded t-PA and intravenous heparin was the regimen associated with the lowest mortality and with a significantly lower incidence of mild allergic reactions, anaphylaxis, congestive heart failure, cardiogenic shock, sustained hypotension, atrioventricular block, sustained ventricular tachycardia, ventricular fibrillation, asystole, and atrial fibrillation or flutter.³⁰

Paradoxically, patients who are at the highest risk for complications from coronary thrombolysis may be the patients who can benefit most from treatment. Among all patients presenting with acute MI, approximately 50% are eligible for treatment with thrombolytic agents on the basis of current criteria.²¹⁸ Approximately 20% are treated.²¹⁵ Mortality in patients considered to be ineligible for treatment is fivefold greater than in patients who are treated.²¹⁹ Efforts have been made to determine whether eligibility criteria should be less strict than the criteria employed for other reasons (investigative considerations) in early trials.

Criteria developed by an ACC/AHA Task Force²²⁰ in 1990 are shown in Table 12-8. In contrast to the extensive list of absolute contraindications promulgated, in GUSTO-I,³⁰ the only absolute criteria for exclusion were previous stroke, active bleeding, recent trauma, recent major surgery, and noncompressible vascular puncture sites. Patients with a systolic blood pressure of 180 mm Hg or greater that was unresponsive to therapy were considered to have a relative contraindication. Diabetic patients with hemorrhagic retinopathy were not excluded, and an age limit was not invoked in GUSTO-I. Nevertheless, the rate and profile of complications in this very large trial were acceptable in view of the use of highly effective thrombolytic regimens and conjunctive anticoagulation.

Patients requiring cardiopulmonary resuscitation (CPR) of less than 10 minutes' duration do not seem to be at high risk for additional complications when treated with thrombolytic drugs. Clinical judgment, taking into account the extent of thoracic trauma and neurologic injury sustained, is more helpful than criteria based solely on the duration of CPR.²²¹

Treating physicians must rely on common sense and clinical acumen to anticipate best the risk-benefit ratio for an individual

Table 12-8. Absolute and Relative Contraindications to Coronary Thrombolysis as Proposed by the American College of Cardiology/American Heart Association Task Force

Absolute Contraindications

Active internal bleeding
Suspected aortic dissection
Prolonged or traumatic cardiopulmonary resuscitation
Recent head trauma or known intracranial neoplasm
Diabetic hemorrhagic retinopathy or other hemorrhagic ophthalmic condition
Pregnancy
Previous allergic reaction to thrombolytic agent (streptokinase or APSAC)
Recorded blood pressure >200/120 mm Hg
History of cerebrovascular accident known to be hemorrhagic

Relative Contraindications*

Recent trauma or surgery >2 wk; trauma or surgery more recent than 2 wk, which could be a source of rebleeding, is an absolute contraindication
History of chronic severe hypertension with or without drug therapy
Active peptic ulcer
History of cerebrovascular accident
Known bleeding diathesis or current use of anticoagulants
Significant liver dysfunction
Prior exposure to streptokinase or APSAC; this contraindication is particularly important in the initial 6- to 9-mo period after streptokinase or APSAC administration, and applies to reuse of any streptokinase-containing agent, but does not apply to rt-PA or urokinase

*Risk-benefit analysis in the presence of relative contraindications should be individualized.

APSAC, anisoylated plasminogen streptokinase activator complex; rt-PA, recombinant tissue plasminogen activator.

From ACC/AHA Task Force: Guidelines for the early management of patients with acute myocardial infarction. *Circulation* 1990; 82:683.

patient. An 80-year-old woman with an acute inferior MI of 8 hours' duration and with an admitting blood pressure of 200/120 mm Hg would not likely be a good candidate for thrombolytic drugs. Conversely, a young diabetic patient with a large anterior MI of 90 minutes' duration and with a history of retinopathy that has been well controlled with laser therapy is likely to be a good candidate.

Elderly Patients

Most of the early mechanistic studies of coronary thrombolysis and large trials excluded patients older than 75 years. The incidence of mortality from MI is high for elderly patients, as are risks of bleeding with thrombolytic drugs. Although less than 20% of U.S. citizens are 65 years old or older, 80% of all deaths from acute MI occur in this group.²²² The risk of hemorrhagic

complications with treatment increases with age, as does the risk of all-cause mortality. Nevertheless, subgroup analysis^{218,222,223} shows unequivocally that the relative benefit seen with coronary thrombolysis is greatest for elderly patients. For patients older than 75 years in the ISIS-2/International t-PA/SK trials,^{142,151} mortality reduction was far greater than for younger patients.^{218,223} Generally, and in elderly patients, the enhanced survival benefit of PCI compared with administration of thrombolytic drugs declines as the delay of implementation of PCI compared with the onset of pharmacologic treatment increases.²²⁴

Women

Women have a poor prognosis compared with men after acute MI.^{225,226} Compared with men, rates of induction of coronary patency with thrombolytic drugs are comparable in women, as are the effects of treatment on left ventricular function. Nevertheless, mortality is higher.^{227,228} When adjustments are made for age and comorbidities (e.g., diabetes, hypertension, hypercholesterolemia), the adverse odds ratio (OR) declines (gender alone, 1.7695% CI; adjusted, 1.31 95% CI).²²⁸

The risk of hemorrhagic stroke seems to be higher for women than men with MI treated with plasminogen activators. In GISSI-2, the incidence of hemorrhagic stroke was 0.3% for men and 0.6% for women, with no difference in the incidence of ischemic stroke (0.5% for both).²¹⁴ Similar data are available from the International t-PA/Streptokinase mortality trial,¹⁵¹ with women having a 1% hemorrhagic stroke rate compared with 0.3% for men, a disparity that persists despite adjustments for age and body weight.

Menstruation and pregnancy are potential contraindications to therapeutic thrombolysis. Traditionally, women of childbearing age have been excluded from thrombolytic drug trials. It seems to be safe to treat women of childbearing age who are not pregnant, however, because menstrual bleeding is related more to sloughing of tissue than active bleeding.²²⁷ Pregnancy has been considered by some investigators to be an absolute contraindication to coronary thrombolysis because of the potential risks of fetal or placental hemorrhage and the known incidence of coronary spasm.²²⁷ Apparently massive infarction may warrant treatment if emergency direct angioplasty is not promptly available.

Patients with Congestive Heart Failure or Cardiogenic Shock

In patients presenting with severe congestive heart failure, particularly patients with cardiogenic shock, the risks of coronary thrombolysis are likely to be increased because of biochemical derangements secondary to liver and other organ failure. Improved survival has not been shown. Hospital mortality rates for patients presenting in Killip class IV heart failure in the GISSI-1 trial were no different for SK than for placebo (69.9% and 70.1%). Reduction of mortality may be absent in part because of low rates of adequate recanalization.²²⁹ Results in the SHOCK trial indicate that patients who cannot be treated with PCI immediately should be treated with fibrinolytic drugs and supportive measures such as intra-aortic balloon counterpulsation, and transferred immediately to a facility in which PCI can be performed.

Retrospective analysis suggests that successful reperfusion with PCI contributed to improved survival of patients presenting

with acute MI complicated by cardiogenic shock.²³⁰ If available, direct PCI seems to be the best option. In its absence, thrombolysis should be considered. Efforts to enhance survival by diminishing cytokine-driven expression of nitric oxide have not been shown to be beneficial.²³¹ There is no convincing evidence that any adjunctive pharmacologic measure in addition to restoration of patency of the infarct-related artery enhances survival in patients with cardiogenic shock.

Bundle Branch Block

Patients presenting with symptoms of acute MI may not have diagnostic ECG evidence of acute myocardial injury because of right or left bundle branch block. Nonetheless, these patients often have extensive infarction and may derive benefit from coronary thrombolysis. Current AHA/ACC guidelines underscore the importance of new left bundle branch block with angina as an indication for thrombolysis. Meta-analysis of nine large placebo-controlled trials showed increased survival for more than 2000 patients presenting with bundle branch block with the use of plasminogen activators compared with placebo.¹⁴⁶ The mortality rate for treated patients was 18.7% compared with 23.6% for patients allocated to placebo ($P < .01$).

Treatment of Hemorrhage

In patients treated with thrombolytic drugs, anticoagulants, or both, minor bleeding occurs, frequently at vascular puncture and access sites. Manual compression for 30 minutes or until the bleeding stops is usually effective. In the case of uncontrolled, life-threatening, systemic or intracranial bleeding, stronger measures are needed. Thrombolytic, antiplatelet (e.g., aspirin), and antithrombin (e.g., heparin) agents should be discontinued, and reversal of heparin with protamine (1 mg of protamine per 100 U of heparin) should be considered. Diabetic patients who have been exposed to protamine through injections of NPH insulin are at risk for severe allergic reactions and hypotension if intravenous protamine is given at these doses, and they require special consideration. Packed red blood cells and crystalloid should be administered to maintain the hematocrit greater than 25%.

If the patient has been treated recently with a thrombolytic agent, and the concentration of fibrinogen levels is low or clotting factors are depleted, administration of cryoprecipitate (10 U) or fresh frozen plasma (2 to 4 U) may be required, despite the associated risk of viral hepatitis and human immunodeficiency virus infections. ϵ -aminocaproic acid (Amicar), an antifibrinolytic agent that competes with plasminogen for lysine binding sites on fibrin, should be reserved for patients with refractory bleeding unresponsive to other measures because it can precipitate thrombosis. If used, ϵ -aminocaproic acid should be given in a loading dose of 5 g intravenously, followed by 0.5 to 1 g/hr until bleeding has stopped.²³² A general approach to treatment of hemorrhage after the use of thrombolytic agents^{217,232} has been reviewed elsewhere and is presented in Figure 12-6.²³²

Bleeding in patients given direct-acting antithrombins such as hirudin instead of heparin as the conjunctive agent may present a particular problem.²³³ Fresh frozen plasma may normalize laboratory values, but fail to stop the bleeding. Administration of prothrombin complex concentrate (25 to 30 U/kg) or recombinant coagulation factor VIIa (35 to 120 μ g/kg) may be useful, although risks of thrombosis are substantial.

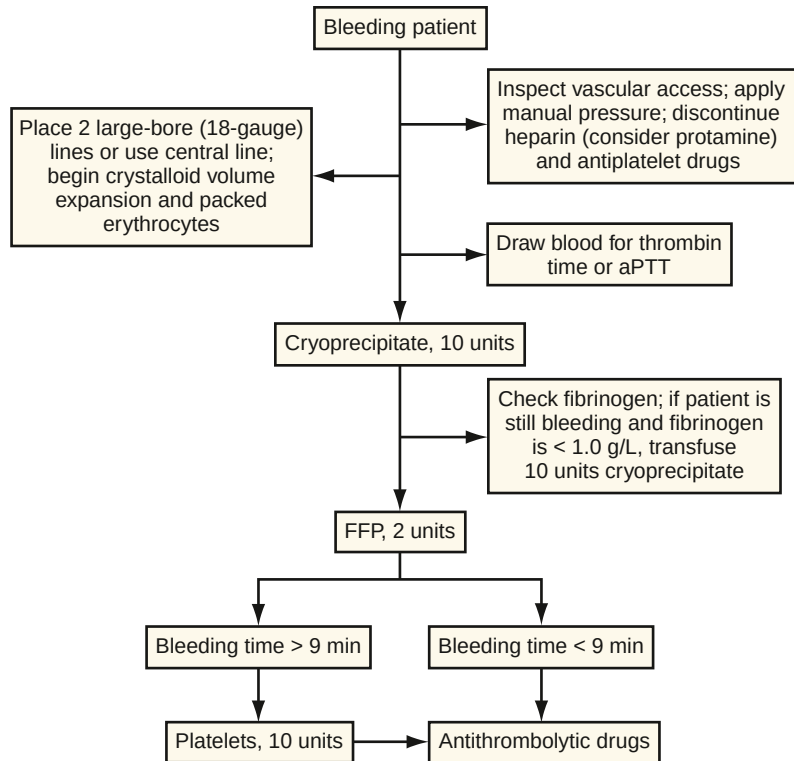


Figure 12-6. Schematic representation of the strategy for management of serious bleeding in patients treated with plasminogen activators. aPTT, activated partial thromboplastin time; FFP, fresh frozen plasma. (From Sane DC, Califf RM, Topol EJ, et al: Bleeding during thrombolytic therapy for acute myocardial infarction: mechanisms and management. *Ann Intern Med* 1989;111:1015.)

Evolution of Coronary Revascularization from Thrombolysis to Percutaneous Coronary Intervention

Much of the progress in coronary thrombolysis and particularly the principles that became established through its use contributed to the foundation for use of PCI for primary treatment of patients with acute coronary syndromes. Although these two modalities have often been contrasted, they are, in reality, simply two approaches that can be used either independently or in a sequential fashion for achieving the desired objective of prompt recanalization of the infarct-related artery, sustained recanalization, and complete recanalization, all of which contribute to the ultimate efficacy of the intervention. PCI has undergone profound evolution since its inception as coronary angioplasty more than 5 decades ago. On the basis of some early studies in which angioplasty was used in association with coronary thrombolysis, it had been thought that PCI was hazardous under these circumstances. Technical progress has largely obviated that concern, however, and the superiority of PCI as an initial intervention in centers that can support it on a 24-hour-a-day basis has become clear.

Surgical Alternative

An alternative way of inducing revascularization for treatment of patients with STEMI is coronary artery bypass graft surgery. Historically, this intervention was preferred, especially in patients with cardiogenic shock before the advent of PTCA and subsequently PCI. In current practice, coronary artery bypass graft surgery is not the favored form of induction of

revascularization through mechanical means because of the high risk entailed with coronary surgery under emergency conditions compared with that associated with elective coronary surgery, and because of time constraints that make it difficult for surgical revascularization to be implemented before completion of the evolving infarct. Based in part on results with emergency coronary artery bypass graft surgery compared with PCI in randomized patient assignment trials and registry data as noted subsequently, the consensus is that primary PCI is the preferred modality for induction of revascularization in the treatment of patients with STEMI.

Feasibility of Early Percutaneous Coronary Intervention for Treatment of ST Segment Elevation Myocardial Infarction

In 1964, Dotter and Judkins²³⁴ conceived of inducing angioplasty of the coronary arteries by sequentially introducing a series of rigid dilation catheters of increasing diameter to compress the stenotic lesion. Ten years later, Gruentzig and Kumpe²³⁵ showed the utility of replacing the rigid catheters with an inflatable dilation balloon in vivo. After meticulous study and refinement, Gruentzig and colleagues²³⁶ performed the first coronary balloon angioplasty in a patient in 1977, providing the foundation for PCI. Despite profound expansion of its indications over time, and treatment of even more complex coronary anatomy and lesions including those responsible for STEMI, success rates now exceed 98%. By 2004, an estimated 664,000 PCI procedures were performed in the United States, constituting a 325% increase in annual implementation compared with that in 1987.²³⁷

Early in the evolution of PCI, its feasibility in addition to fibrinolysis was explored in the setting of acute MI.²³⁸ Partly because of the primitive and unwieldy nature of angioplasty available at

that time, early strategies involving catheter-based techniques focused on the direct infusion of the fibrinolytic agent into the infarct-related artery.^{70,102,239,240} With the advent of superior fibrinolytic agents and the extant logistical difficulties of catheter-based interventions at that time, early attempts with primary PCI languished. First-line therapy for STEMI in the late 1980s was coronary thrombolysis. Nevertheless, limitations of stand-alone fibrinolytic therapy led to a rekindled interest in the combination of clot lysis and subsequent balloon angioplasty.

Experience with fibrinolysis alone showed that in approximately 15% of patients recanalization fails. In almost 50%, restoration of flow in the infarct-related artery is suboptimal. In 10% of patients in whom recanalization is successful, subsequent early infarction occurs.²⁴¹ In influential early studies including the TIMI IIA and TIMI IIB trials, in which strategies of PCI were performed with balloon angioplasty after thrombolysis, no clinical benefit was observed with either immediate or delayed PCI compared with conservative therapy. Immediate PCI led to a much higher incidence of bleeding and emergency coronary artery bypass graft surgery.^{242,243}

Despite the discouraging results of these early trials of combination therapy, several investigators explored the possibility that early balloon angioplasty would be a safe and perhaps more effective alternative to stand-alone fibrinolysis.²⁴⁴ Early results by O'Neill and coworkers²⁴⁵ in comparisons of angioplasty versus intracoronary SK showed that balloon angioplasty was superior in improving ventricular function and reducing residual stenosis in the setting of acute MI. Over the next 15 years, multiple trials directly comparing stand-alone fibrinolysis with primary PCI were performed, eventually validating the utility of primary PCI and its superiority compared with thrombolysis in inducing more complete and more frequent recanalization of the infarct-related artery.²⁴⁶

Primary Percutaneous Coronary Intervention for Treatment of ST Segment Elevation Myocardial Infarction

Limitations of fibrinolytic therapy include the risk of bleeding and particularly intracranial hemorrhage, especially in patients with recent surgery, previous cerebral vascular insults or head or facial trauma, intracranial neoplasm, aortic dissection, or occult β -amyloid angiopathy. Uncontrolled hypertension is a prominent risk factor for intracranial bleeding.^{247,248} The risks of intracranial hemorrhage with fibrinolysis are particularly high in patients older than 75 years despite the fact that treatment is associated with a lower hospital mortality compared with placebo.²⁴⁹

As investigators of coronary thrombolysis learned, benefit is greatest when the agents are administered within 2 hours after the onset of symptoms.^{31,250} Efficacy of lysis diminishes as clots age; this may contribute to the higher mortality in patients treated later after the onset of symptoms.²⁵¹ Fibrinolytic therapy restores normal flow in less than 65% of treated patients, and reocclusion hours to days after treatment resulting in reinfarction is common.

As PCI evolved, a trial of early PCI with intracoronary SK comprising 56 patients showed improved preservation of left

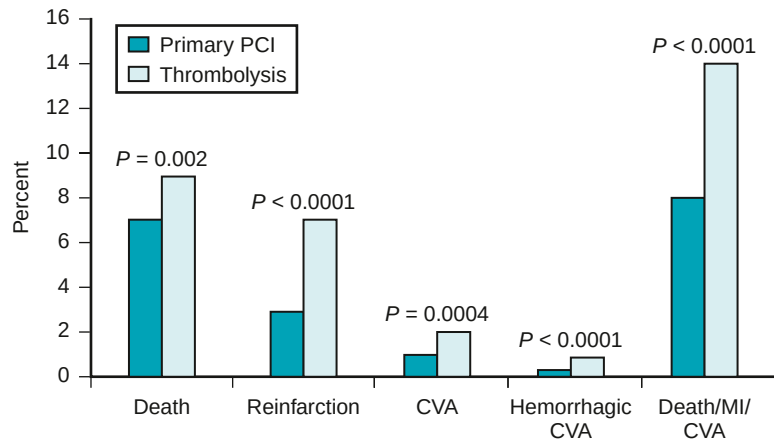
ventricular function compared with treatment with intravenous SK alone.²⁴⁵ Similar results were obtained in a trial with a slightly larger sample ($N = 156$) of patients.²⁵² In 1993, PAMI, a multicenter randomized trial, compared primary PCI with intravenous t-PA in 395 patients. Although this study found no difference in the primary end point of post-treatment radionuclide left ventricular function, it showed a trend of decreased hospital mortality with primary PCI (6.5% versus 2.6%; $P = .06$), significantly decreased in-hospital and 6-month incidence of death and reinfarction, and a decreased incidence of intracranial hemorrhage (0% versus 2%).²⁵³

Despite the favorable results with PCI in this early trial, primary PCI was not widely adopted immediately as a treatment strategy for patients with STEMI,¹⁷ partly because of the substantial resources required for offering primary PCI around the clock and the relative scarcity of experienced operators able to perform emergency PCI in a high-risk setting. Numerous studies comparing fibrinolytic therapy with primary PCI were performed throughout the late 1990s and early 2000s. The GUSTO-IIb trial randomly assigned 1138 patients to either primary PCI or fibrinolytic therapy with “accelerated” administration of t-PA. With respect to the primary end point, a composite outcome of death, nonfatal MI, and disabling stroke at 30 days, primary PCI was found to be superior to fibrinolytic therapy. The study did not show a reduction in mortality, however, comparable to that seen in the earlier PAMI trial. In subgroup analysis, none of the individualized end points met statistical significance, although all showed trends in favor of primary PCI. The benefit of primary PCI seemed to be short-lived because the composite end point in favor of PCI did not remain significant at 6 months (13.3% versus 15.7%; $P =$ nonsignificant).²⁵⁴

Presently, more than 90% of patients presenting to the hospital with STEMI are considered to be eligible for treatment with primary PCI. PCI results in induction of TIMI 3 grade flow in more than 90% of infarct-related arteries when stents and thrombectomy can be employed if indicated. With stenting, the acute reocclusion rate is less than 5%.²⁵⁵ As stents became available, Schomig and associates²⁵⁶ compared primary PCI with the use of adjunctive GP IIb/IIIa inhibition with fibrinolytic therapy in 140 patients. The primary end point was myocardial salvage as measured by serial nuclear scintigraphy with a secondary end point being composite of death, reinfarction, or stroke at 6 months. Myocardial salvage was greater with primary PCI (salvage index 0.57 versus 0.21; $P < .01$). Evaluation of the 6-month end point strongly supported the use of primary PCI (8.5% versus 23.2%; $P = .02$).²⁵⁶ Results in other studies performed after stents had been developed showed similar benefits.²⁵⁷⁻²⁵⁹

Trials of primary PCI compared with thrombolysis were reviewed by Keeley and colleagues²⁴⁶ in 2003 (Fig. 12-7). The authors evaluated the results of 23 trials involving 7739 patients. Most of the patients (76%) randomly assigned to the thrombolytic arms of these trials were treated with fibrin-specific thrombolytic agents. Primary PCI was superior with respect to short-term mortality (7% versus 9%; $P = .0002$), reinfarction (3% versus 7%; $P < .0001$), and stroke (1% versus 2%; $P = .004$). With long-term follow-up, the benefits of primary PCI remained robust with substantial reduction in mortality ($P = .0019$), nonfatal reinfarction ($P < .0001$), and recurrent ischemia ($P < .0001$). Adjunctive stenting in primary PCI was used in 12 of the 23 trials. The ACC/AHA guidelines in 2004 for the care of patients

Figure 12-7. Short-term outcomes after primary percutaneous coronary intervention (PCI) compared with thrombolysis in the treatment of ST segment elevation myocardial infarction as judged from a meta-analysis of 7739 patients. CVA, cerebrovascular accident; MI, myocardial infarction. (Data from Keeley EC, Boura JA, Grines CL: Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet* 2003;361:13-20.)



with STEMI referred to PCI as a class I recommendation with the highest level of supporting evidence.²⁴⁷

The preponderance of evidence favoring primary PCI was gathered in trials directly comparing it with thrombolysis. Patients who are ineligible for treatment with fibrinolytic drugs seem to benefit from primary PCI as well. Evaluating data from the Second National Registry of Myocardial Infarction (NORMI), Grzybowski and coworkers²⁶⁰ analyzed results from more than 19,000 patients with STEMI who had contraindications to the use of thrombolytic agents; 4705 of these patients underwent immediate primary PCI. The remaining patients were treated medically without attempts at revascularization. As judged from analyses of matched patients characterized with propensity scores, a significant effect was evident on mortality reduction favoring primary PCI (OR 0.64; 95% CI 0.56 to 0.75). The investigators concluded that primary PCI should be strongly considered for patients who have contraindications to fibrinolysis.²⁶⁰

Efforts to Overcome Limitations Discovered in Early Trials of Primary Percutaneous Coronary Intervention

All of the trials included in the meta-analysis by Keeley and colleagues²⁴⁶ were conducted in centers with considerable experience with primary PCI. The patients had been randomly assigned in circumstances in which PCI could be performed with minimal delay. Despite the benefit seen for primary PCI over fibrinolysis, several registries did not confirm the benefit seen in these trials in part because of difference in the circumstances surrounding treatment.^{261,262}

The current ACC/AHA guidelines indicate that PCI should be performed in conditions conforming as closely as possible to the conditions in the clinical trials in which it was shown to be superior to fibrinolysis. Specifically, primary PCI should be performed when patients present with an admission to balloon time of 90 minutes or less by skilled operators who perform more than 75 PCI procedures per year; the procedure should be done in hospitals that perform more than 36 PCI procedures for STEMI annually and have cardiothoracic surgery capability.²⁴⁷ Fulfilling these requirements is not feasible in more than a few

hospitals; in one survey, less than 25% of hospitals in the United States have the needed capabilities.²⁶³

To increase the availability of primary PCI, various strategies have evolved to reduce delay by rapidly bringing patients to hospitals with PCI capability or performing the procedure in smaller hospitals without cardiac surgery capabilities. The PRAGUE-2 trial of 850 patients showed safety and feasibility of rapid transport of patients without antecedent thrombolysis to larger centers for performance of primary PCI, although the decrease in mortality was not statistically significant (6.8% versus 10%; $P = .12$).²⁶⁴ These results presaged the results in the larger DANAMI-2 trial, in which coordinated transport of patients was implemented to PCI centers dispersed throughout Denmark. In this trial, 1572 patients were randomly assigned to treatment with either fibrinolysis or primary PCI. Patients presenting to hospitals without PCI capability were transported immediately by ambulance to the nearest PCI center. The primary end point was the composite of death, reinfarction, or stroke at 1 month. Transport for PCI was superior to fibrinolysis for patients in aggregate presenting to referring hospitals (mortality being 8.5% versus 14.2%; $P = .002$).²⁶⁵

The results from these two trials led some authors to suggest that integrated transport systems involving the bypass of closer non-PCI hospitals should be implemented modeled on the "level 1 trauma center" precedent in place in the United States. The average distance for transport to a PCI center in DANAMI-2 was 35 miles with a very short average transport time (32 minutes; interquartile range 20 to 45 minutes), ensuring a short symptom onset-to-balloon time of 224 minutes for patients requiring transport to a PCI center. Because of the larger geographic distances outside of the densely populated areas of western Europe or the American Atlantic seaboard, and the increase in the direct costs of a regional rapid transport initiative, the implementation of a DANAMI-2 system has not been widespread. Sporadic efforts have been undertaken, however, with good results in the United States.²⁶⁶ The average door-to-balloon time for patients who were initially transported for primary PCI in NORMI was 180 minutes, and only 4.2% were transported in less than 90 minutes.²⁶⁷ When short transfer times are feasible, and primary PCI can be performed without a delay of more than 60 minutes compared with when the patient could have been treated with a fibrinolytic drug, transfer is reasonable.

An alternative to rapid transport of patients for primary PCI is performance of PCI in hospitals that lack cardiac surgery capabilities. In the C-PORT trial, Aversano and colleagues²⁶⁸ conducted a study of 451 patients in rural Massachusetts and Maryland in which patients were randomly assigned to undergo PCI or fibrinolysis at hospitals without cardiac surgery capabilities. Before the study, the 11 centers participating were required to implement a program designed to develop a PCI approach consistent with modifications of the ACC/AHA guidelines. Some modifications, such as those requiring the operators to perform a minimum of only 50 cases per year, differed from the formal guidelines. Other requirements, such as new standards for nursing and catheterization laboratory technicians, were employed by the investigators to ensure quality and safety. The study's primary end point was the composite of death, reinfarction, or stroke at 6 months. In the PCI arm, no patients required emergency cardiac surgery secondary to a complication. Patients who underwent PCI fared better than patients treated with a fibrinolytic drug (12.4% versus 19.9%; $P = .03$).²⁶⁸ The high event rates in both arms of the study have made implementation of the strategy characterized controversial.

The capacity to perform primary PCI without surgical backup has been adopted only on an erratic basis in the United States. The ACC/AHA guidelines recommend primary PCI with the absence of on-site surgery with only a class IIb recommendation. Caveats include the hospital personnel and operators being experienced, and the presence of an established plan for rapid transport to a surgical center if a complication should occur.

In concert, the observations reviewed indicate that primary PCI is the preferred strategy for patients presenting with STEMI as long as the procedure can be implemented promptly (generally considered to be <90 minutes from presentation by experienced operators at experienced facilities). This strategy was given the highest recommendation with the strongest level of evidence by the writing committee of the ACC/AHA in the latest iteration of the consensus guidelines published in 2004.²⁴⁷

Ancillary Therapy for Primary Percutaneous Coronary Intervention

Coinciding with the evolution of sophisticated techniques and technology enhancing the efficacy of primary PCI was the evolution of medical therapy used concomitantly with PCI. The goal of such conjunctive medical therapy is to enhance safety (i.e., minimize hemorrhagic risk and safely inhibit the coagulation system to prevent abrupt thrombotic vessel closure before, during, and in the early interval after PCI). Anticoagulants are agents used to inhibit directly or indirectly individual or multiple plasma proteins in the coagulation cascade. Antiplatelet therapies either prevent platelet activation by antagonizing substances that activate platelets (including ADP, cyclooxygenase, and thrombin) or inhibit platelet aggregation by neutralizing surface antigens that are responsible for platelet-fibrinogen-platelet cross-linking. Effective conjunctive medical therapy should inhibit the plasma protein-based coagulation system and the activation and aggregation of platelets. Adjunctive medical therapy differs from conjunctive therapy and is designed to limit the consequences of myocardial ischemia, enhance myocardial healing, and confer tissue protection.

Orally Active Antiplatelet Agents

Aspirin

Aspirin is an irreversible inhibitor of the cyclooxygenase pathway pivotal in the cascade of platelet activation. Unless they are allergic to aspirin, patients presenting with STEMI should be given 162 to 325 mg of aspirin as early as possible and should continue on aspirin indefinitely. ISIS-2 showed a significant decrease in 35-day mortality (11.1% versus 9.2%; $P < .001$) for patients randomly assigned to aspirin compared with placebo.⁶⁰ In the setting of PCI, aspirin decreases the incidence of periprocedural Q wave MI compared with placebo (6.9% versus 1.6%; $P = .013$).²⁶⁹

Platelet Adenosine Diphosphate Receptor Inhibitors

Results in multiple large trials have established that platelet ADP receptor antagonism with P2Y₁₂ receptor inhibitors is beneficial in the setting of elective PCI and PCI for acute coronary syndromes.²⁷⁰⁻²⁷² The CLARITY trial studied 1863 patients undergoing PCI after mandated angiography in the CLARITY-TIMI 28, a randomized, double-blind, placebo-controlled trial of clopidogrel in patients given fibrinolytic drugs for treatment of STEMI. Results showed that patients given 300 mg initially and 75 mg daily of clopidogrel along with a fibrinolytic drug at presentation to the hospital and who subsequently underwent PCI had lower mortality and incidence of reinfarction or stroke at 30 days (6.2% versus 3.6%; $P = .008$) compared with patients not treated with clopidogrel.²⁷³

Clopidogrel undergoes processing in the liver yielding an active metabolite. Its effect on platelet inhibition may not occur for 12 hours with a load of 300 mg. A 600-mg load has been shown to be more effective in rapidly inhibiting platelet aggregation and improving clinical outcomes in patients with acute coronary syndromes,²⁷⁴ although no further benefit is seen with an increased load of 900 mg.²⁷⁵ The use of clopidogrel before PCI without antecedent fibrinolysis has not been studied in large numbers of patients. Nonetheless, it seems likely that patients who are to undergo primary PCI should be given a loading dose of 600 mg immediately (i.e., in the emergency department) and 75 mg daily thereafter. Two other platelet ADP receptor inhibitors—ASD 6140 and prasugrel—are currently undergoing evaluation in phase III studies under conditions in which patients with acute coronary syndromes are undergoing PCI.

Intravenously Administered Agents

Glycoprotein IIb/IIIa Inhibitors

The only compound in the class of GP IIb/IIIa inhibitors that has been studied in large clinical trials in the setting of primary PCI is abciximab. Abciximab is a chimeric antibody to the GP IIb/IIIa receptor that strongly and irreversibly binds to the receptor. In five trials involving 3666 patients, of which only 1843 patients were enrolled in the abciximab arms,²⁷⁶⁻²⁸⁰ none had power adequate enough to delineate a cardiovascular mortality effect. Patients given abciximab had higher pre-PCI, infarct-related artery patency rates, better 6-month left ventricular ejection fraction, and less need for urgent target vessel revascularization. Controversy still exists regarding the timing of the administration of this agent. Some trials have shown that starting abciximab upstream (in the emergency department) before transport of the patient to the catheterization laboratory improves infarct-related artery patency before definitive revascularization. This benefit has not been reflected by significant differences in 1-year outcomes, however.²⁸¹

Eptifibatide and tirofiban are two other commercially available intravenous GP IIb/IIIa inhibitors available in the United States. Although proven to be effective in the setting of non-STEMI and unstable angina pectoris, definitive studies on outcomes in the setting of STEMI have yet to be performed. Eptifibatide increases the incidence of infarct-related artery patency at angiography when administered before transport of the patient to the catheterization laboratory.²⁸²

Platelet Adenosine Diphosphate Receptor Inhibitors

Cangrelor is an investigational intravenously administered small molecule that is an ADP receptor antagonist that is metabolized by vascular endothelium. Its pharmacokinetics are unique. It has a rapid onset of action, measured in minutes, with a half-life in blood of 3 to 5 minutes and a platelet inhibitory effect of only 50 to 70 minutes' duration after discontinuation. Its advantages over an alternative platelet ADP inhibitor, clopidogrel, include more complete and more rapid inhibition of platelet ADP receptors and potentially lower bleeding risk given the short duration of effect. The CHAMPION-PCI trial is a phase III investigation of the use of cangrelor compared with clopidogrel in 9000 patients undergoing PCI for treatment of acute coronary syndromes, including STEMI.

Intravenously Administered Antithrombotic Therapy

The initiation of the coagulation cascade results ultimately in the formation of thrombin that subsequently converts fibrinogen to fibrin and activates platelets mediated via surface receptors specific for thrombin. Antithrombotic agents include numerous compounds that inhibit the proteins involved in the coagulation cascade, activation of platelets, or both at one or many loci.

Unfractionated Heparin

Despite 40 years of history of the use of unfractionated heparin in treatment of patients with STEMI, little data inform the rationale for its use when primary PCI is to be undertaken. The use of unfractionated heparin plus aspirin as conjunctive therapy is inferior compared with their combination with abciximab, the first platelet GP IIb/IIIa antagonist that became available. When used as conjunctive therapy in combination with GP IIb/IIIa inhibitors, unfractionated heparin should be given as a bolus in a weight-adjusted dose of 50 to 70 U/kg to target an activated coagulation time of 200 seconds.²⁸³

Low-Molecular-Weight Heparins

Compared with unfractionated heparin, LMWH is easier to administer because subcutaneous depot injections with weight-adjusted dosing is effective. Additionally, the anticoagulant effects are more predictable, and use of LMWH does not require frequent partial thromboplastin time testing for monitoring. LMWH has been studied most thoroughly in patients with STEMI with respect to utility as conjunctive therapy with thrombolysis. No large clinical trials have directly compared any of the antithrombins in patients scheduled to undergo primary PCI. There have been some alarming reports of catheter-induced and guidewire-induced thrombosis in patients who were given LMWH as conjunctive antithrombotic therapy for scheduled PCI²⁸⁴ or primary PCI for treatment of STEMI.²⁸⁵

LMWH cannot be strongly recommended based on the limited data available compared with unfractionated heparin when used in conjunction with GP IIb/IIIa inhibitors in the setting of

primary PCI. The ACC/AHA guidelines discourage the use of LMWH for treatment of STEMI in patients older than 75 years or with renal insufficiency.

Direct Thrombin Inhibitors and Pentasaccharides

Bivalirudin is a bivalent direct thrombin inhibitor that is given intravenously, usually with a bolus load and continuous infusion. As is the case with LMWH, it is unnecessary to follow partial thromboplastin times for monitoring. The only currently approved indication for use of bivalirudin is in the setting of PCI in low-risk patients^{286,287} or as conjunctive therapy with thrombolysis for patients with an allergy to heparin or with heparin-induced thrombocytopenia. Bivalirudin has been shown to be equivalent to heparin alone as a conjunctive agent for thrombolysis.²⁸⁸ The ACUITY trial randomly assigned 13,819 patients with high-risk acute coronary syndromes (except STEMI) to bivalirudin or unfractionated heparin plus a GP IIb/IIIa inhibitor. The primary end point of this noninferiority trial was combined efficacy with respect to mortality, reinfarction, or stroke and a safety end point of bleeding. There were no significant differences with respect to the primary end point, and bivalirudin caused significantly less bleeding (3% versus 5.7%; $P < .001$).²⁸⁹

Fondaparinux is a synthetic factor Xa (indirect acting requiring interaction with antithrombin III) inhibitor that is given once daily in a fixed dose without the need for monitoring. Although fondaparinux was proven to be effective in patients who are given thrombolytic drugs in reducing mortality and the incidence of reinfarction compared with conjunctive therapy with heparin, it was found to be inferior to heparin in patients undergoing primary PCI.¹⁸² Because of previous reports of catheter-associated and wire-associated thrombosis when fondaparinux alone was used as conjunctive therapy for PCI, unfractionated heparin was used as conjunctive therapy for PCI that was performed after the index event in this trial. In regions and systems in which most patients with STEMI eventually undergo PCI, either during or after the index event, fondaparinux cannot be recommended as conjunctive therapy either for primary PCI or for use with fibrinolytic agents.

Pharmacoinvasive Strategy for Ensuring Rapid Infarct-Related Artery Patency

The available approaches for urgent treatment of STEMI—fibrinolytics and primary PCI—have been described often as competing strategies. Although numerous trials directly comparing the two have been performed over the last 2 decades, the two approaches are not mutually exclusive. In an editorial in 2003, we used the term *pharmacoinvasive therapy* to describe various iterations of the combination of fibrinolysis and PCI.²⁹⁰

As noted earlier, the most significant factor determining infarct size and risk of mortality in patients with STEMI is the time to induction of patency of the infarct-related artery after the onset of ischemia. Primary PCI (without antecedent fibrinolysis) with a brief door-to-balloon time of less than 90 minutes has proven to be the single approach to reperfusion with the fewest complications and the most preservation of left ventricular function with minimization of the incidence of major adverse events.²⁴⁶ The infrastructure required is not available at many

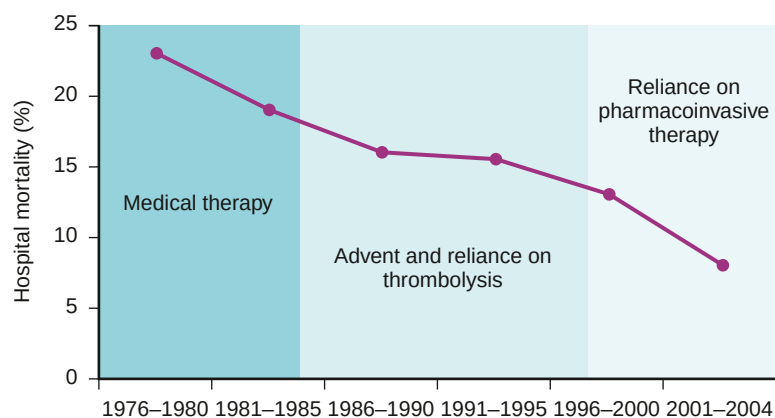


Figure 12-8. Hospital mortality over time. The reliance on pharmacoinvasive therapy entails the rational use of the combination of percutaneous coronary intervention with thrombolysis.

medical facilities, however; this, combined with long transport times and distances in many areas, precludes widespread use of this therapy.

In terms of sheer numbers, fibrinolytic therapy is still the de facto predominant strategy used for treatment of STEMI in the United States and worldwide. Limitations in terms of the capability of fibrinolysis to restore fully or at least maintain infarct-related artery patency compared with PCI result, however, in more than 80% of patients in the United States undergoing cardiac catheterization after fibrinolysis.²⁹¹ Results of more recent trials show the benefit of delayed PCI after thrombolysis.^{292,293} A pharmacoinvasive strategy that encompasses both is attractive. Application of the combined approach should be based on a rational process focusing on consideration of factors such as time to treatment and the clinical status of an individual patient. Such considerations can maximize the advantages of each of the two strategies—the widespread availability of fibrinolysis and the definitive revascularization of an infarct-related artery with PCI—while the balance is maintained with respect to the risk-benefit equation and minimizing harm to patients.

We and many others have adopted an evolving pharmacoinvasive strategy since the late 1990s, which has periodically changed over the years to incorporate methods and practices based on knowledge gained in the latest trials of treatment of patients with STEMI. Analysis of results in more recent registries suggests that wider adoption of a pharmacoinvasive approach can lead to remarkably low mortality for patients with STEMI (Fig. 12-8).

Given the mounting evidence supporting the practice, we believe that all patients with STEMI—whether or not they are treated with fibrinolytic agents—should undergo coronary angiography and mechanical revascularization if necessary as judged from the anatomy uncovered. Our proposed approach is depicted in Figures 12-9, 12-10, and 12-11. The timing to coronary angiography and intervention is predicated on the clinical status of the patient at the time when reperfusion would be expected after administration of fibrinolytic drugs. The practice of routinely performing PCI for patients immediately after fibrinolysis (so-called facilitated PCI) is not recommended based on results in the ASSENT-4 trial (Fig. 12-12), which was stopped prematurely because of an excess incidence of events in the active arm of the trial.²⁹⁴ As judged from all the data available, however, we believe that all PCI-eligible patients who present to a hospital without PCI capabilities should be transported

immediately to a PCI-capable hospital, either immediately after administration of fibrinolytic drugs or immediately on presentation if transfer times can be anticipated to be short enough to ensure an initial hospitalization door-to-balloon time of less than 90 minutes.

Rescue Percutaneous Coronary Intervention

Many patients treated with modern fibrinolytic drugs manifest prompt reperfusion with normalization of coronary blood flow in the infarct-related artery accompanied by complete resolution of symptoms and ECG changes. Contingency therapy for patients who do not manifest prompt reperfusion has been controversial, however. Until more recently, there has been widespread hesitation to “rescue” patients with failed fibrinolytic therapy because of a perceived increased hazard of major hemorrhage as observed in earlier trials of obligatory PCI after thrombolytic/fibrinolytic therapy.^{242,243} Many investigators advocated reinstallation of fibrinolytic drugs or medical therapy alone and no invasive intervention to modify evolution of the infarct.

Preliminary evidence supporting the strategy of rescue PCI for patients without fibrinolytic drug-induced reperfusion came from the MERLIN trial. It included 307 patients randomly assigned to either conservative therapy, including repeat fibrinolysis, or immediate angiography with or without PCI. Although there was only a numerical trend favoring rescue PCI for the primary end point of 30-day mortality (9.8% versus 11%; $P = .70$), rescue PCI was superior to conservative treatment with respect to the combined secondary end point of death, reinfarction, stroke, heart failure, and urgent revascularization.²⁹⁵ The benefit was driven mostly by a decreased incidence of urgent revascularization that remained robust at 6-month, 1-year, and 3-year follow-up.²⁹⁶

These results were corroborated by results in the larger REACT trial comprising 427 British patients. Results in the REACT trial showed lower mortality in patients undergoing rescue PCI compared with the combined medical therapy or repeat thrombolysis treatment groups (hazard ratio 0.48, 95% CI 0.23 to 0.99).²⁹⁷ A meta-analysis of results from trials addressing rescue PCI when PTCA was prominent and after stents became available was published in 2007. Its results indicated less heart failure and reinfarction in patients who had undergone rescue PCI and a strong trend toward lower mortality (Fig. 12-13) in the trials with stenting.²⁹⁸

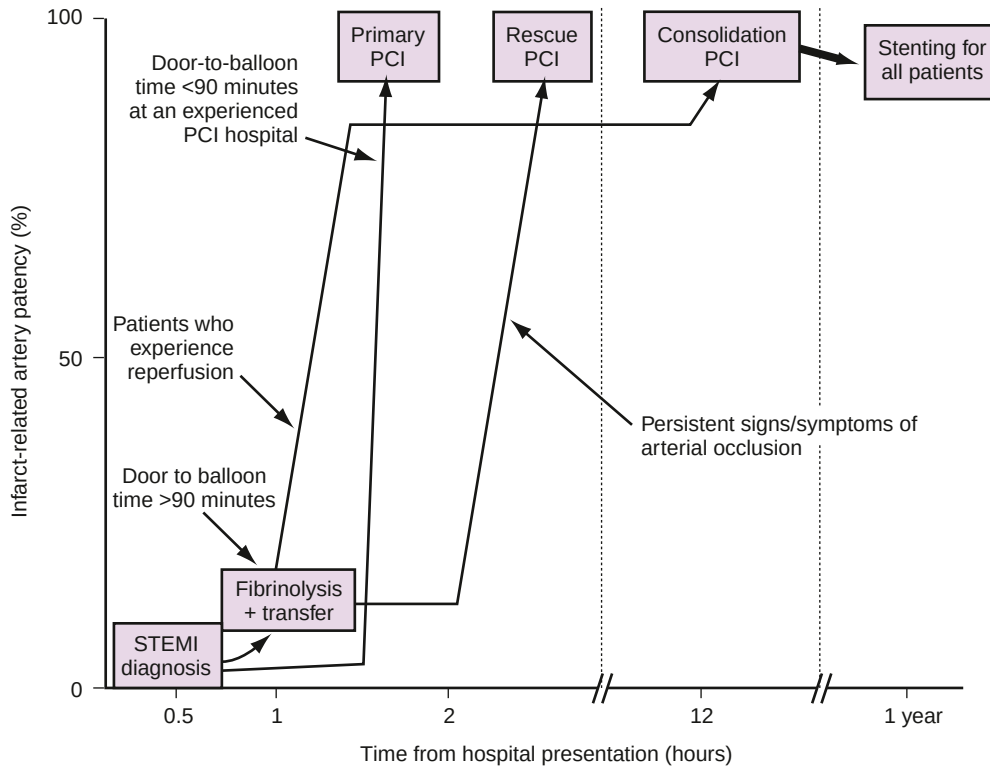


Figure 12-9. Overview of pharmacoinvasive therapy.

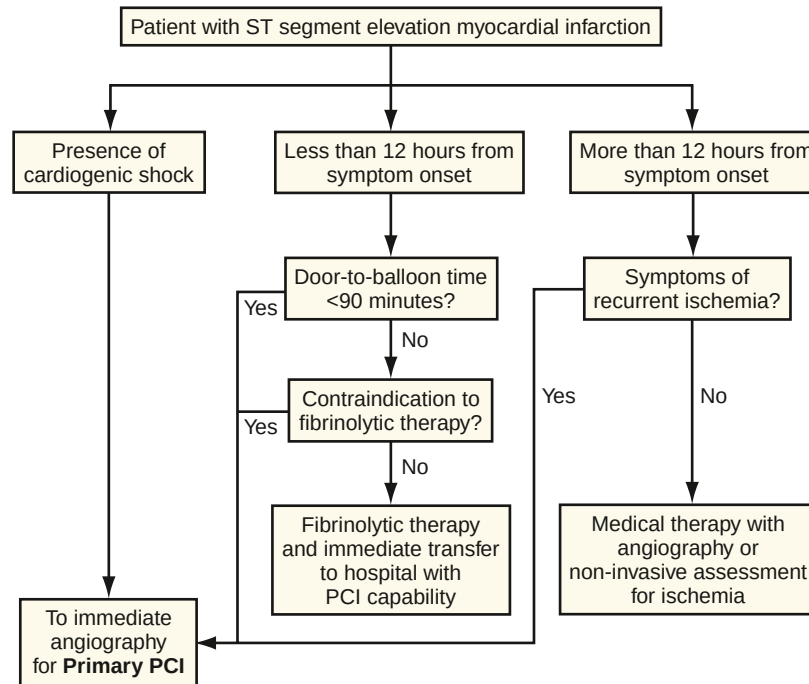


Figure 12-10. Initial pharmacoinvasive management. PCI, percutaneous coronary intervention.

If a patient who has been given fibrinolytic drugs presents to a hospital with PCI capabilities with ongoing signs or symptoms of ischemia, manifested as persistent angina, unresolved (<70%) ST segment elevation²⁹⁹ on an arrival ECG, or hemodynamic or electrical instability, the patient should be transported

immediately to the cardiac catheterization laboratory for prompt angiography and possible intervention. Conjunctive therapy in this setting is controversial. Patients will likely have been given antithrombotic agents (with the possible exception of patients who had been treated with SK) with either unfractionated

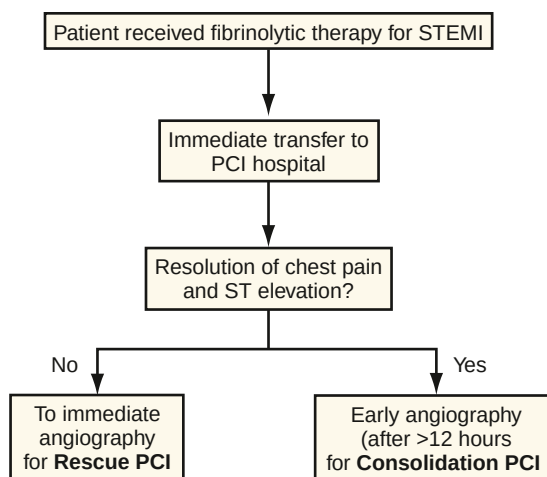


Figure 12-11. Pharmacoinvasive management after fibrinolysis. PCI, percutaneous coronary intervention; STEMI, ST segment elevation myocardial infarction.

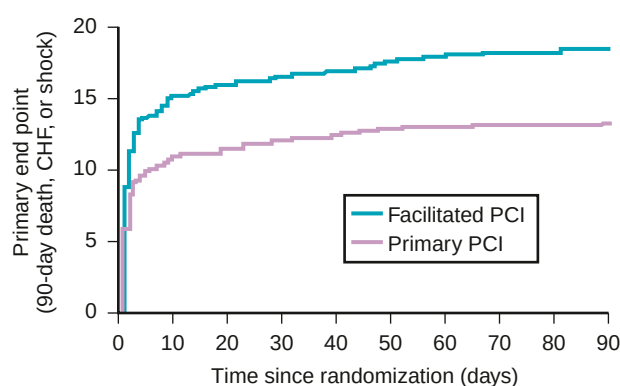


Figure 12-12. ASSENT-4 PCI. $P = .0042$ for the two curves, log-rank test. CHF, congestive heart failure; PCI, percutaneous coronary intervention. (Data from Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction [ASSENT-4 PCI]: randomised trial. *Lancet* 2006;367:569-578.)

heparin or LMWH. Additionally, aspirin and clopidogrel are likely to have been given. The controversy focuses on whether to add intravenous GP IIb/IIIa inhibitors to enhance inhibition of platelet aggregation in the face of a potential increase in the risk of bleeding in a patient with an ongoing fibrinolytic state.¹⁸⁰ Our recommendation is to add this therapy in the catheterization laboratory only if massive coronary thrombosis is seen on angiography. Otherwise, PCI should be performed without administration of additional antiplatelet agents.

Consolidation Percutaneous Coronary Intervention

As noted previously, intravenous thrombolysis can increase the risks of coronary angiography and intervention by affecting hemostasis. Thrombolysis and treatment with unfractionated heparin can paradoxically increase platelet activation in this setting.^{300,301} Patients are at increased risks of bleeding and thrombosis if they undergo instrumentation soon after thrombolysis.

Studies of PCI after resolution of the lytic state have shown, however, that PCI induced at this time is safer with less bleeding and lower thrombotic risk.^{242,302} Coronary angiography followed by revascularization was proven to be superior in patients with spontaneous or inducible ischemia in the Danish trial by Madsen and associates.³⁰³ They found that this intervention resulted in a lower incidence of reinfarction and decreased subsequent hospital admissions for unstable angina (10.5% versus 5.6%; $P = .038$ and 29.5% versus 17.9%; $P < .0002$) in contrast to medical treatment alone. Previous guidelines recommended that only patients who have symptomatic or inducible ischemia after thrombolysis undergo angiography and possible PCI. Because PCI early after thrombolysis can establish recanalization when lysis has failed and can consolidate benefit when it has succeeded, we prefer to refer to it as consolidating PCI and support its use.

Under conditions in which coronary stenting and advanced conjunctive therapy are available, the approach may differ. Improved efficacy and safety and a reduction in the incidence of urgent revascularization and reinfarction have been seen in patients undergoing consolidating PCI. Collet and associates³⁰⁴ reported results from the three major trials addressing this issue in a meta-analysis involving a 832 patients. Consolidation PCI was associated with a strong trend of decreasing mortality (OR 0.55, $P = .07$) and significantly lower risk for the combined end point of death and reinfarction (13.2% versus 7.5%; $P = .0067$) without a significant increase of the risk of major hemorrhage or stroke. All three of these recent trials showed similar and a consistent extent of benefit (Fig. 12-14). These results differed markedly from the results in earlier trials of consolidation PCI when PCI meant PCTA. We believe that all patients treated with thrombolytic drugs should undergo angiography early (12 hours is optimal) after initial treatment.

Data from OAT have called into question the practice of “routine” PCI in stable patients presenting at least 3 days after their index event. The patients studied had to have at least one high-risk characteristic, such as diminished left ventricular function or proximal vessel occlusion. Only 20% of the patients in the trial had been treated with antecedent thrombolytic drugs, and none had undergone primary PCI. The patients were not randomly assigned until after angiography. The trial showed no differences in mortality, the incidence of reinfarction, or subsequent heart failure in the routine PCI group compared with the medical therapy group (Fig. 12-15).³⁰⁵

Patients given thrombolytic drugs who experience prompt reperfusion often have residual stenosis in the infarct-related artery. Such patients would not have been randomly assigned in OAT. Results from this trial do not obviate our recommendation for performing consolidating PCI.

Facilitated Percutaneous Coronary Intervention and ASSENT-4

The performance of PCI as soon as possible after thrombolysis has been termed *facilitated PCI*.³⁰⁶ As noted earlier, invasive instrumentation of patients may not be made easier when a lytic state is present, however, and a lytic state may make PCI more difficult and place the patient at higher risk of complications such as bleeding or thrombosis. For this reason, it would seem that only patients in clinical situations of risk that outweigh the procedural risks should undergo immediate postlysis PCI (rescue PCI).

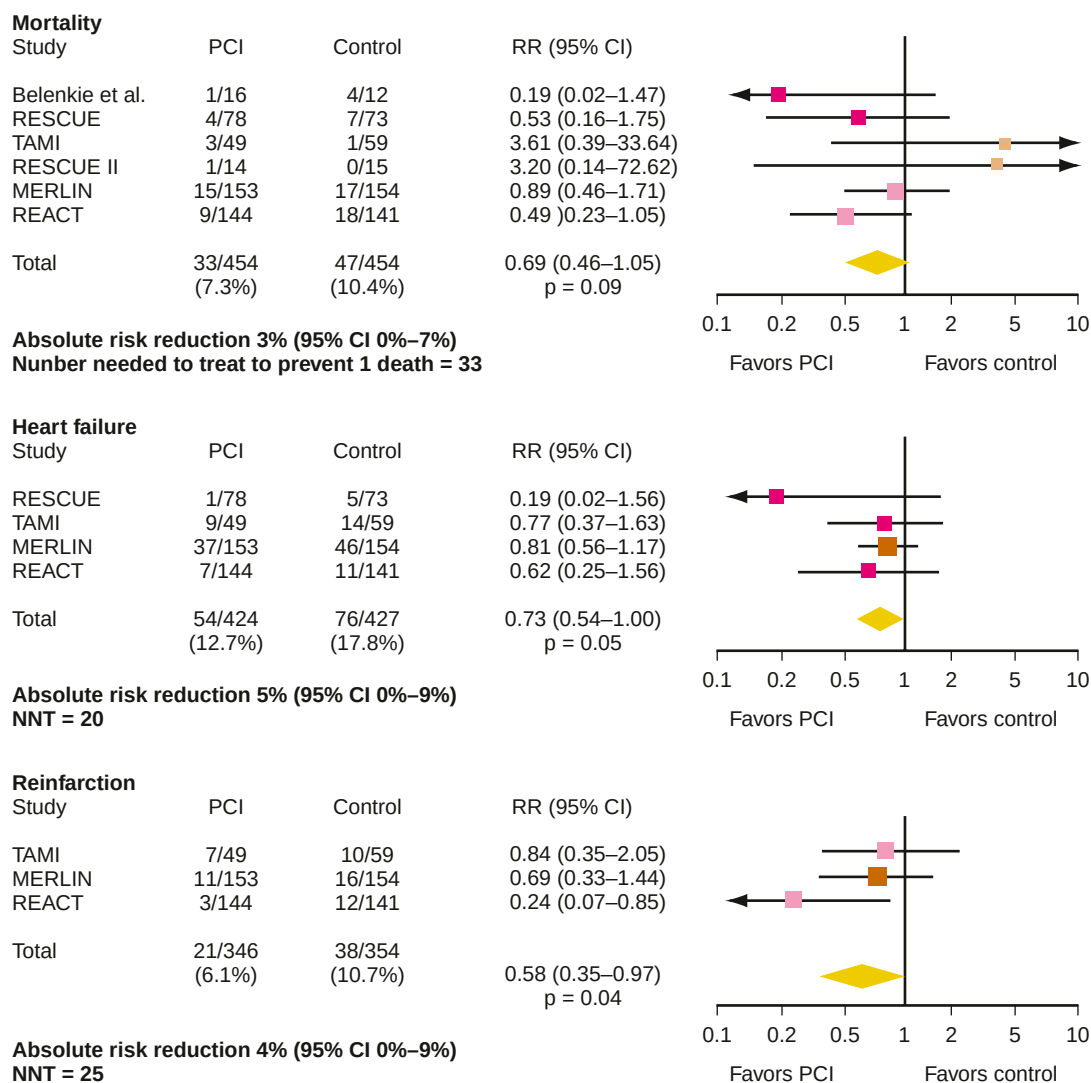


Figure 12-13. Meta-analysis of studies comparing rescue percutaneous coronary intervention (PCI) with medical therapy (including repeat thrombolysis) for failed thrombolysis. PCI seems to be superior. CI, confidence interval; NNT, number needed to treat; RR, relative risk. (Data from Wijeyesundera HC, Vijayaraghavan R, Nallamothu BK, et al: Rescue angioplasty or repeat fibrinolysis after failed fibrinolytic therapy for ST-segment myocardial infarction: a meta-analysis of randomized trials. *J Am Coll Cardiol* 2007;49:422-430.)

The possible use of a combination of half-dose thrombolytic therapy and GP IIb/IIIa inhibitors was anticipated to improve outcomes in patients with STEMI. Encouraging results of the combination from GUSTO V and ASSENT III showed a lower incidence of complications secondary to ischemia and better infarct-related artery flow at follow-up angiography.^{180,307} There was an increased incidence of nonintracranial bleeding, however, especially in elderly patients, which may limit the applicability of the combination. Given the investigators' observation that patients with better pre-PCI infarct-related artery flow had better outcomes, many investigators have been led to believe that the combination would be ideal for pre-PCI pharmacotherapy in all patients.

Facilitated PCI has been examined in two more recent trials. Because of a slow rate of enrollment, the ADVANCE AMI trial was stopped prematurely after only 148 of a planned total of more than 5500 patients had been randomly assigned. This trial

investigated the use of half-dose fibrinolytic therapy in combination with eptifibatide. Despite the low numbers, the study showed increased bleeding risks with the combination and better coronary flow, similar to the patterns of results in previous studies.³⁰⁸ ASSENT IV randomly assigned patients to either primary PCI or PCI "facilitated" by fibrinolytic therapy given immediately before transfer of patients to the catheterization laboratory (Table 12-9). After only 1600 of the planned 4000 patients had been enrolled, the study was stopped prematurely by the data safety monitoring board because of increased in-hospital mortality in the facilitated PCI arm (6% versus 3%; $P = .0105$). The incidences of stroke, reinfarction, and urgent target vessel revascularization were unexpectedly higher as well in the treatment arm.²⁹⁴

Routine use of fibrinolytic therapy immediately before PCI cannot be recommended. Investigation of "facilitated PCI" is still incomplete. The FINESSE study is currently enrolling patients into three arms—primary PCI, half-dose fibrinolytic

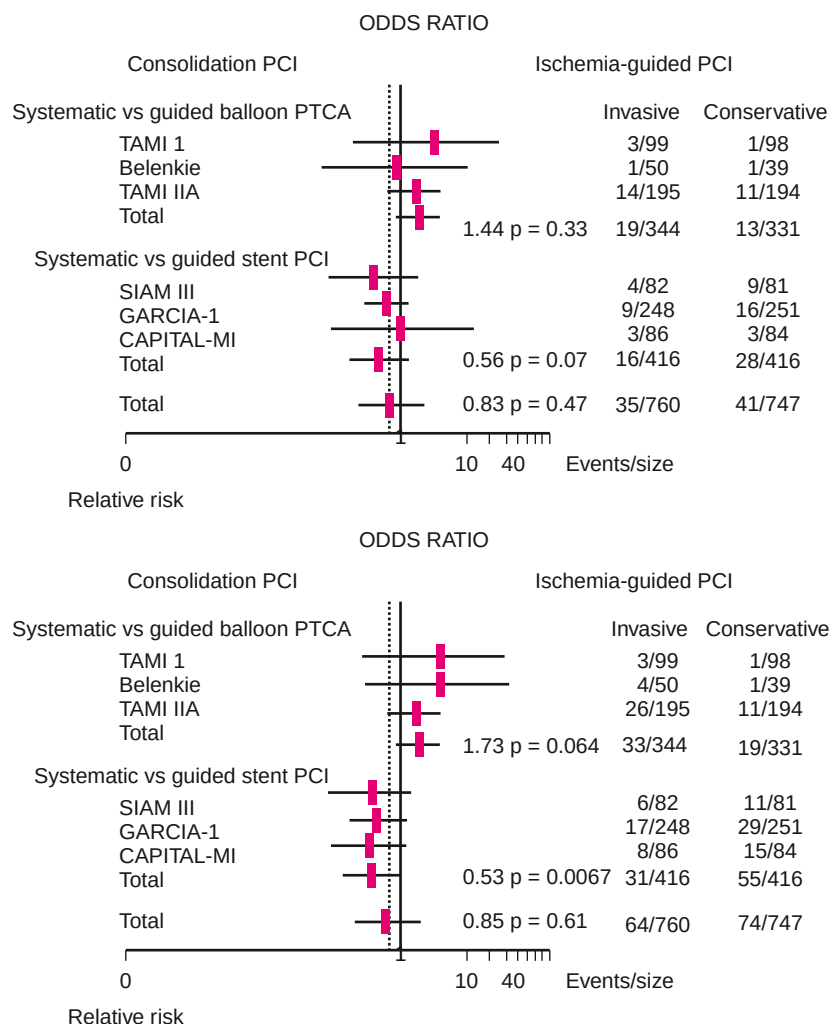


Figure 12-14. Meta-analysis of trials of consolidation percutaneous coronary intervention (PCI) compared with ischemia-guided PCI after thrombolysis. There was a nonsignificant trend for less mortality with consolidation PCI after the advent of stenting. There was lower mortality and less reinfarction with consolidation PCI. PTCA, percutaneous transluminal coronary angioplasty. (Data from Collet JP, Montalescot G, Le MM, et al: Percutaneous coronary intervention after fibrinolysis: a multiple meta-analyses approach according to the type of strategy. *J Am Coll Cardiol* 2006;48:1326-1335.)

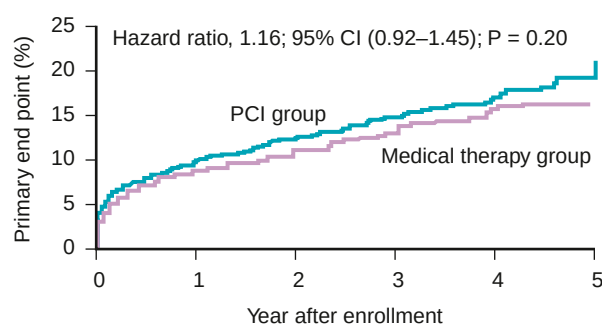


Figure 12-15. Kaplan-Meier curves for the primary end point of death, reinfarction, or congestive heart failure in OAT. CI, confidence interval; PCI, percutaneous coronary intervention. (Data from Hochman JS, Lamas GA, Buller CE, et al: Coronary intervention for persistent occlusion after myocardial infarction. *N Engl J Med* 2006;355:2395-2407.)

drug administration plus abciximab, or early administration of abciximab alone before PCI.

Special Considerations

Elderly Patients

Although primary PCI is highly recommended in ACC/AHA clinical guidelines for the treatment of STEMI, data on which the recommendation is based are sparse. Completed trials have included few patients older than 75 years, and many clinical studies have considered advanced age as an exclusion criterion.³⁰⁹ Risks associated with thrombolysis are greater in elderly patients, who exhibit higher incidences of bleeding, intracranial hemorrhage, heart failure, and cardiogenic shock. The frequencies of comorbidities such as cancer and lung disease are also increased. Determinants of complications related to thrombolysis include age older than 75 years as a factor as powerful as

Table 12-9. Results within 90 Days of Randomization in ASSENT-4

	Tenecteplase and PCI (n = 829)	PCI alone (n = 838)	P
Mortality	7%	5%	NS
Congestive heart failure	12%	9%	NS
Shock	6%	5%	NS
Reinfarction	6%	4%	.0279
Repeat target vessel revascularization	7%	3%	.0041
Rehospitalization for congestive heart failure	2%	1%	NS
Rehospitalization for shock	0%	<1%	NS
Rehospitalization for another cardiac reason	10%	11%	NS

NS, nonsignificant; PCI, percutaneous coronary intervention.

Data from Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): randomised trial. *Lancet* 2006; 367:569.

uncontrolled hypertension or low body weight.^{310,311} Results in some studies have indicated a 10-fold increased risk of adverse events and mortality in very elderly patients (>85 years old).³¹² In national registries, many elderly patients who might otherwise be eligible for thrombolysis are treated instead with a medical regimen devoid of fibrinolytic drugs to circumvent the increased risk.

Subset analyses in large multicenter trials have addressed the issue of primary PCI compared with thrombolysis in patients older than 75 years. Trends were evident in favor of primary PCI with respect to short-term mortality, as were significant decreases in the combined end point of death, recurrent MI, or stroke.^{253,254,313} Results in relatively small trials focusing on elderly patients have shown similar trends with respect to decreased mortality and significantly less reinfarction, urgent revascularization, and stroke.³¹⁴⁻³¹⁶ Registries of patients who may not have been eligible for inclusion in clinical trials have identified a substantial benefit favoring primary PCI in elderly patients with respect to mortality favoring primary PCI compared with thrombolysis (OR 0.62, CI 0.36 to 0.96) after adjustment for baseline differences.³¹⁷ A risk-benefit ratio favoring primary PCI in elderly patients has led to recommendations that it be the primary treatment for elderly patients with STEMI at hospitals that meet the same time to treatment and experience criteria as those applicable to the general population. Because of the greater frequency of comorbidities and increased risk of hemorrhage in elderly patients, conjunctive therapy must be judiciously employed with appropriate dose adjustments for weight and renal function. Decisions regarding interventions must be made in the context of careful consideration of factors such as the quality of life and the impact of comorbidities on outcomes and life expectancy.

Cardiogenic Shock

Patients who develop cardiogenic shock associated with MI are at extremely high risk of in-hospital mortality with data from registries documenting mortality ranging from 45% to 60%.³¹⁸⁻³²⁰ Patients with nonmechanical causes of cardiogenic shock, such as acute severe mitral regurgitation or ventricular septal rupture, exhibit better survival when PCI has been implemented as judged from registry data.³¹⁹ The SHOCK trial showed definitively that patients younger than 75 years with myocardial infarction who undergo PCI have lower mortality than that in patients treated conservatively with medical therapy, including thrombolysis. Patients randomly assigned to the PCI arm of this trial had a 9% absolute risk reduction in short-term mortality and a significant reduction in 6-month mortality (50.3% versus 63.1%; $P = .027$).

Although benefit did not pertain to patients older than 75 years as judged from subset analysis, the small number of elderly patients ($n = 56$) in the study limited power for its detection. Data from registries have shown that elderly patients with shock experience comparable benefit from PCI compared with that seen in the overall population, albeit with a “frame shift” in mortality to a higher range (i.e., 70% to 80%).^{318,321} ACC/AHA guidelines designate PCI for treatment of cardiogenic shock as a class 2 recommendation with the highest level of evidence for patients younger than 75 years. For elderly patients, the designation is class IIa with the caveat that patients should be carefully selected.

Conclusion

Results obtained in studies of coronary thrombolysis established the principle that reperfusion, induced without the need for surgical intervention, improved survival in patients with STEMI. It remains an appropriate approach in settings in which primary PCI cannot be pursued expeditiously. Achieving optimal results with primary PCI depends on inducing revascularization of the infarct-related artery within 90 minutes after presentation of the patient to the hospital. Implementation of primary PCI is appropriate for patients presenting to an interventional center or patients who can be transported to one via helicopter or ambulance within 30 minutes. For patients presenting to institutions that cannot meet these criteria, patients who have no contraindication to thrombolysis should be treated with full doses of fibrinolytic drugs, aspirin, clopidogrel, and heparin.

Thrombolysis is unsuccessful or associated with reinfarction in 30% of patients with STEMI. When thrombolysis fails, the best strategy is induction of reperfusion with PCI. Patients in whom thrombolysis has not induced revascularization should be transferred immediately to an interventional cardiology center. Prompt PCI can be implemented if ischemia persists or recurs in the first 24 hours after the onset of infarction.

In patients who have undergone attempted thrombolysis and transfer, angiography and PCI should be performed immediately if revascularization has not been accomplished or recurrent infarction is imminent or in progress as judged from ST segment elevation or ongoing chest pain. Immediate PCI should not be performed routinely in patients in whom thrombolysis has been successful—an intervention referred to generally as facilitated PCI. Instead, we believe the recommendations of the European PCI Guidelines are most appropriate. They suggest “early, but nonemergency PCI” under these circumstances for

patients with either STEMI or non-ST segment elevated MI: they endorse performance of PCI within 12 to 24 hours after presentation of the patient to the interventional cardiology center to define coronary anatomy and prevent recurrent infarction in susceptible patients who have undergone successful PCI for treatment of STEMI.

In settings in which primary PCI can be implemented consistent with the criteria outlined in the text, it should be the therapeutic modality of choice; we endorse the 2005 ACC/AHA PCI Guidelines, which hold that a volume/outcome relationship applies to PCI in general and primary PCI in particular. Operators should meet specific volume requirements to increase the likelihood that quality would be optimal 24 hours a day, 7 days a week. The volume requirements noted are more than 11 primary PCI procedures annually for the operator, more than 36 primary PCI procedures annually for the institution, and more than 75 general PCI procedures annually for the operator.

Appropriate adjunctive and conjunctive therapy should be implemented, including administration of aspirin, clopidogrel, and heparin for all patients with STEMI. The use of unfractionated heparin as opposed to LMWH depends on the clinical situation, with advanced age, the presence of renal failure, and planned primary PCI rather than fibrinolysis supporting its use. The use of intravenously administered β blockers depends also on the clinical circumstances, with factors likely to precipitate hemodynamic instability, such as advanced age, militating against their use. Generally, the use of statins, orally administered β blockers, and angiotensin-converting enzyme inhibitors in the first 24 hours after the onset of STEMI is appropriate.

With prompt revascularization as the linchpin of therapy for STEMI, 30-day mortality is 2% in clinical trials and is 5% to 10% in clinical practice. The major risk factor for mortality after STEMI is the development of cardiogenic shock. Even in the setting of successful, early infarct artery revascularization, a patient with cardiogenic shock has a mortality risk of 30% or greater (with an increasingly greater risk with advanced age). Because the incidence of cardiogenic shock varies widely from institution to institution, caution must be exercised with respect to the use of absolute mortality as a comparator for programmatic success. Comparisons of the efficacy of diverse programs and the extent to which they meet best practice standards should be based on risk-adjusted mortality and surrogate markers of quality (e.g., time to open artery).

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Adjunctive Pharmacologic Therapies in Acute Myocardial Infarction

CHAPTER 13

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Aspirin	Free Radical Scavengers
Thienopyridines	Morphine
β -Adrenergic Blockers	Glycemic Control and Insulin
Nitrates	3-Hydroxy-3-methylglutaryl Coenzyme A Reductase Inhibitors or Statins
Angiotensin-Converting Enzyme Inhibitors and Other Renin-Angiotensin-Aldosterone System Inhibitors	Anticoagulants
Calcium Channel Blockers	Antioxidants, Vitamins, and Natural Supplements
Magnesium	Conclusion
Lidocaine	

ADJUNCTIVE PHARMACOLOGIC therapies play an important role in the management of patients with acute myocardial infarction (MI). It became increasingly clear 2 decades ago that primary management of patients with acute MI should be aimed at the occlusive coronary thrombus,¹ and should include early reperfusion therapy with thrombolytic agents or mechanical devices.^{2,3} Because not all patients could be reperfused within 2 hours of onset of coronary thrombosis,⁴ however, the goal of early and complete reperfusion could not be achieved in everyone.^{5,6} Late reperfusion is associated with myocardial stunning or persistent left ventricular dysfunction,^{7,8} and early but incomplete reperfusion might be harmful.⁶

Evidence accrued during the last 2 decades supports the use of adjunctive pharmacologic therapies in addition to therapies used to reperfuse directly the infarct-related artery and tissue (i.e., conjunctive) for managing acute MI patients.⁹⁻¹² These adjunctive therapies should be considered as alternative therapy for patients in whom thrombolytics are contraindicated, for widening the time window for reperfusion when therapy cannot be instituted early, for reducing reperfusion injury in patients given late reperfusion therapy, and for achieving complete reperfusion. The ultimate goal of therapy for acute MI, whether primary or adjunctive, is to preserve myocardium and myocardial geometry and function, decreasing cardiovascular morbidity and mortality. Specifically, the aims of adjunctive therapy are to limit consequences of ischemia or infarction, optimize healing, and reduce adverse and recurrent events.

The scope of post-MI adjunctive therapy has expanded as a result of evidence accrued over the last decade related to the following five main factors: (1) the redefinition of acute coronary syndromes to include unstable angina, non-ST segment elevation MI (NSTEMI), and ST segment elevation MI (STEMI)¹³⁻¹⁵; (2) the implementation of troponin as the preferred novel biomarker of necrosis¹⁶; (3) the implementation of novel therapeutic strategies for limiting adverse remodeling during and after

healing post-MI¹⁷⁻²⁵; (4) recognition that MI is the central event in the cardiovascular disease continuum extending from risk factors and coronary atherosclerosis to heart failure and death²⁶; and (5) recognition of the higher risk of elderly patients with MI.^{27,28}

Acute coronary syndromes result from plaque disruption leading to thrombus formation.²⁹ Most patients with STEMI have an occlusive thrombus^{1,30} and develop a Q wave MI (previously termed *transmural*), whereas most patients with NSTEMI have a nonocclusive or mural thrombus and develop non-Q wave MI (previously termed *nontransmural* or *subendocardial*).³¹⁻³³ A few patients with ST segment elevation may develop non-Q wave MI, and a few with non-ST segment elevation may develop Q wave MI. More patients present with NSTEMI than STEMI, and NSTEMI can be difficult to differentiate from unstable angina on presentation. Transmural or Q wave MIs, or STEMI, result in more severe ventricular remodeling and dysfunction,^{17,34,35} however, and high mortality and morbidity.³³ Early and successful reperfusion interrupts the “march to necrosis” and transmural extension as a “wavefront” from endocardium to epicardium,³⁶ preserving most epicardial and some subendocardial myocardium and extracellular matrix and limiting ventricular remodeling.¹⁹⁻²¹

In the era before reperfusion, most MI studies focused on STEMI or Q wave MI. Ideally, all STEMI patients should receive immediate pharmacologic or catheter-based reperfusion therapy,⁹⁻¹¹ whereas NSTEMI patients are not considered candidates for immediate catheter-based reperfusion and should have received anti-ischemic, antiplatelet, and antithrombotic therapy, and may subsequently require catheter-based therapy.¹² Patients with new bundle branch block are considered candidates for reperfusion based on fibrinolytic trial data.³⁷

In a national registry of 240,980 patients with acute MI from 1073 hospitals in the United States during 1990-1993, only 35% received thrombolytic therapy.⁴ The patients who were given thrombolytics in the study⁴ also received concomitant

pharmacotherapy with intravenous heparin (96.9%), aspirin (84%), intravenous nitroglycerin (76%), oral β -blockers (36.3%), calcium channel blockers (29.5%), and intravenous β -blockers (17.4%). In the study,⁴ 65% of the patients were not given thrombolytic therapy and were treated entirely with adjunctive pharmacologic therapies.

Use of reperfusion therapy in acute MI and adjunctive therapy after MI have increased over the last decade. In one registry from 1994-2003,³⁸ nearly 90% of STEMI patients received acute reperfusion. In another registry of NSTEMI and STEMI patients receiving acute percutaneous coronary intervention (PCI) during 1999-2004,³⁹ the discharge medications in the two groups were angiotensin-converting enzyme (ACE) inhibitor, 50.3% versus 63%; aspirin, 95.1% versus 95.8%; β -blocker, 83.8% versus 88.6%; statin, 71.1% versus 73.4%; and thienopyridine, 89.6% versus 88.2%. In the national registry of MI during 1994-2003,⁴⁰ there was a steady increase in the use of adjunctive agents such as aspirin, β -blockers, ACE inhibitors, other antiplatelet agents, and antithrombins within the first 24 hours of STEMI (Fig. 13-1).

Published American College of Cardiology and American Heart Association (ACC/AHA) practice guidelines for management of MI⁹⁻¹² provide expert panel recommendations for initial reperfusion and concurrent or subsequent adjunctive therapies based on a ranking of the clinical evidence into class I, with benefit >>> risk ("should" be used); class II, with benefit >> or $\geq$ risk ("reasonable" or "might be reasonable"); and class III, with risk $\geq$ benefit ("should not" be used, "may be harmful"). There are clinical scenarios, however, in which deviations from these guidelines are considered appropriate.^{11,12} Ultimately, therapy should be tailored to the individual patient profile.

Consistent with the updated guidelines,¹⁰⁻¹² unstable angina/NSTEMI¹² is addressed separately in Chapters 8 and 16, whereas STEMI^{10,11} is addressed here. It is useful to time phases of adjunctive

therapy according to temporal changes after MI, as follows: a very early or acute phase, in the first 12 to 24 hours; a subacute phase during healing, over 1 week to between 6 weeks and 6 months depending on infarct size and other factors; and a posthealing phase, after 1.5 to 12 months.^{19,23} Survivors of STEMI represent a special group of patients at double jeopardy for increased morbidity and mortality, and they stand to benefit from adjunctive therapies and comprehensive secondary prevention (Fig. 13-2).⁴¹

Practice pattern studies reveal suboptimal use of medications and invasive strategies in elderly MI patients (STEMI or NSTEMI) and lack of evidence-based data.^{27,28} Contraindications to reperfusion increase with age, and eligible elderly patients with STEMI are more likely to receive conservative than aggressive reperfusion therapy.²⁸ Most first MIs occur in patients older than 65 years; the average age for a first MI is 66 in men and 70 in women.⁴² Adjunctive therapy plays an important role in elderly patients, but close attention to dosing and complications is needed pending more data. Results of studies on novel adjunctive therapies during the healing phase after reperfused STEMI in elderly patients are awaited.

Aspirin

Low-dose aspirin (acetylsalicylic acid) should be prescribed as adjunctive therapy to all acute MI patients who can tolerate it, including patients with STEMI, NSTEMI, and unstable angina. Platelets are important in thrombus formation after plaque rupture.^{29,43} Early thrombus is composed of a white clot consisting of aggregated platelets and a red clot consisting of fibrin and erythrocytes. Platelets are activated by fibrinolysis, and platelet-rich clots are more resistant to fibrinolysis than fibrin and erythrocyte thrombi. Aspirin is an effective antiplatelet agent that inhibits platelet aggregation.

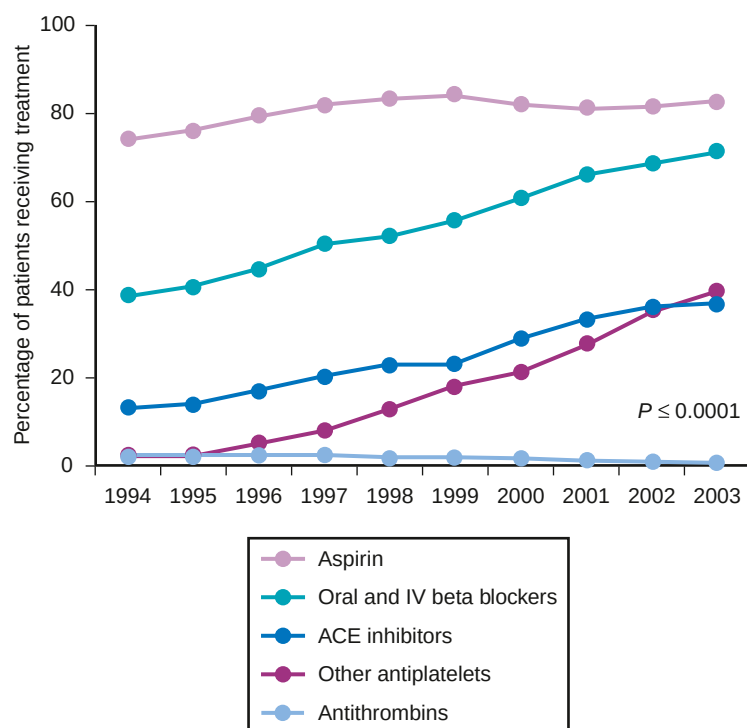


Figure 13-1. Medications received within the first 24 hours. ACE, angiotensin-converting enzyme. (From Gibson CM: *NRMI and current treatment patterns for ST-elevation myocardial infarction*. *Am Heart J* 2004;148:S29-S33.)

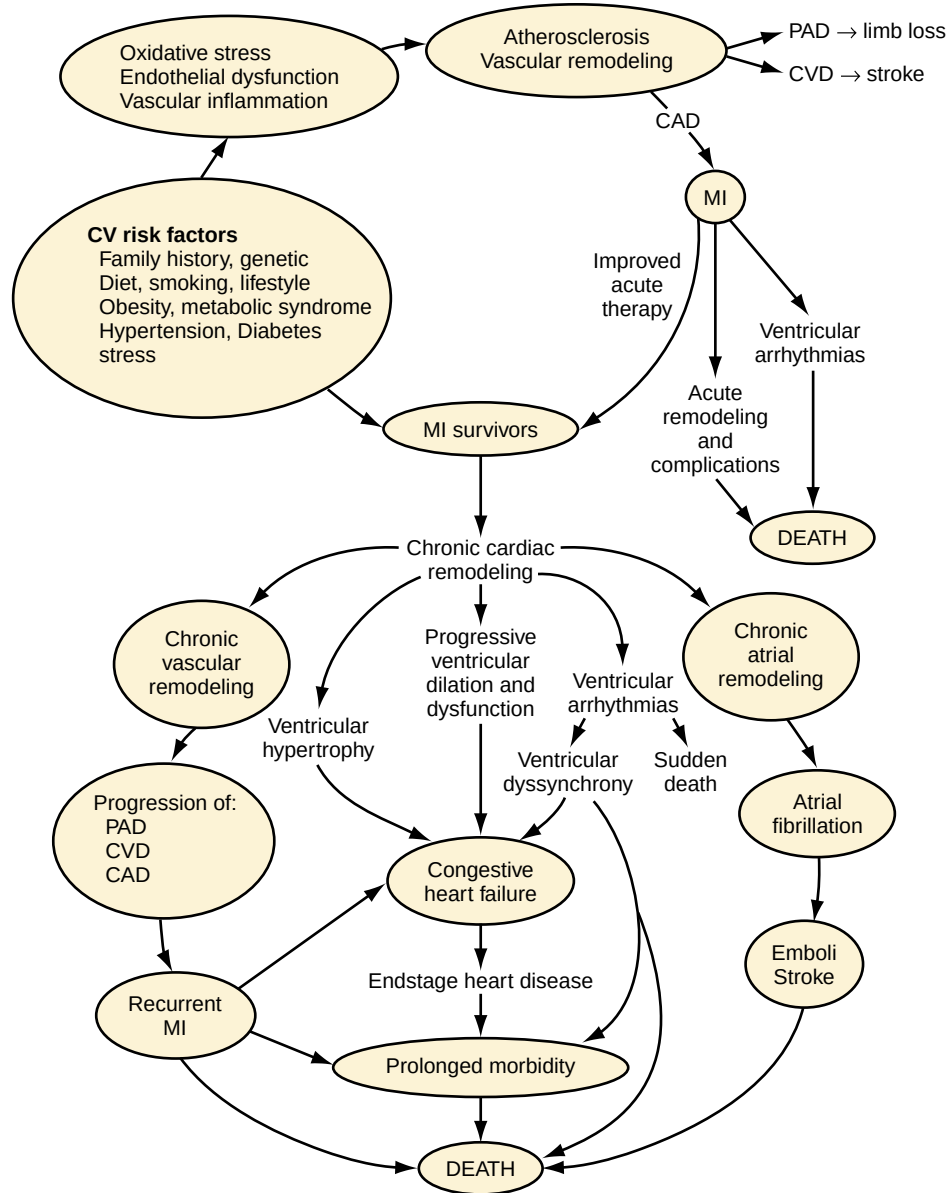


Figure 13-2. Double jeopardy in myocardial infarction (MI) survivors. CAD, coronary artery disease; CV, cardiovascular; CVD, cerebrovascular disease; PAD, peripheral artery disease. (Modified from Jugdutt BI: Valsartan in the treatment of heart attack survivors. *Vasc Health Risk Management* 2006;2:125-138.)

Mode of Action

Taken orally, aspirin is rapidly absorbed in the stomach and small intestine. Aspirin is the only nonsteroidal anti-inflammatory drug (NSAID) to react covalently with the cyclooxygenase (COX) channel of prostaglandin (PG) G/H synthase-1 (now referred to as COX-1 and COX-2) through selective acetylation of serine residues Ser⁵²⁹ in human COX-1⁴⁴ and Ser⁵¹⁶ in human COX-2.⁴⁵ Constitutive COX-1 promotes platelet aggregation, thrombosis, and vasoconstriction, and protects gastrointestinal mucosa (Fig. 13-3).⁴⁶ In contrast, inducible COX-2 is proinflammatory via PGE₂ and antithrombotic and vasodilatory via PGI₂ (prostacyclin) (see Fig. 13-3).⁴⁶

Only a low dose is required to achieve irreversible acetylation of COX-1 in platelets and to block thromboxane A₂ (TXA₂) production and spare PGI₂ synthesis.⁴⁷ Higher doses are not more

effective and might not spare PGI₂.⁴⁷ The effect of aspirin begins within 30 to 40 minutes and lasts for the life of the platelet (7 to 10 days).^{48,49} Nearly complete blockade of TXA₂ can be achieved after 7 to 10 days of a daily dosage of 162 mg or more of aspirin. Side effects with low-dose aspirin, especially buffered tablets, are minimal. The cost is also low.

Dose, Timing, and Benefits

The efficacy of low-dose aspirin in acute STEMI was established in the randomized ISIS-2 trial, which assessed the effects of a 1-hour intravenous infusion of streptokinase (1.5 million U) or oral aspirin (160 mg) or both for 1 month in patients with acute MI presenting within 24 hours of the onset of symptoms.³ By 5 weeks, aspirin reduced nonfatal reinfarction by 50%, nonfatal stroke by 46%, total cardiovascular mortality by 23% (absolute

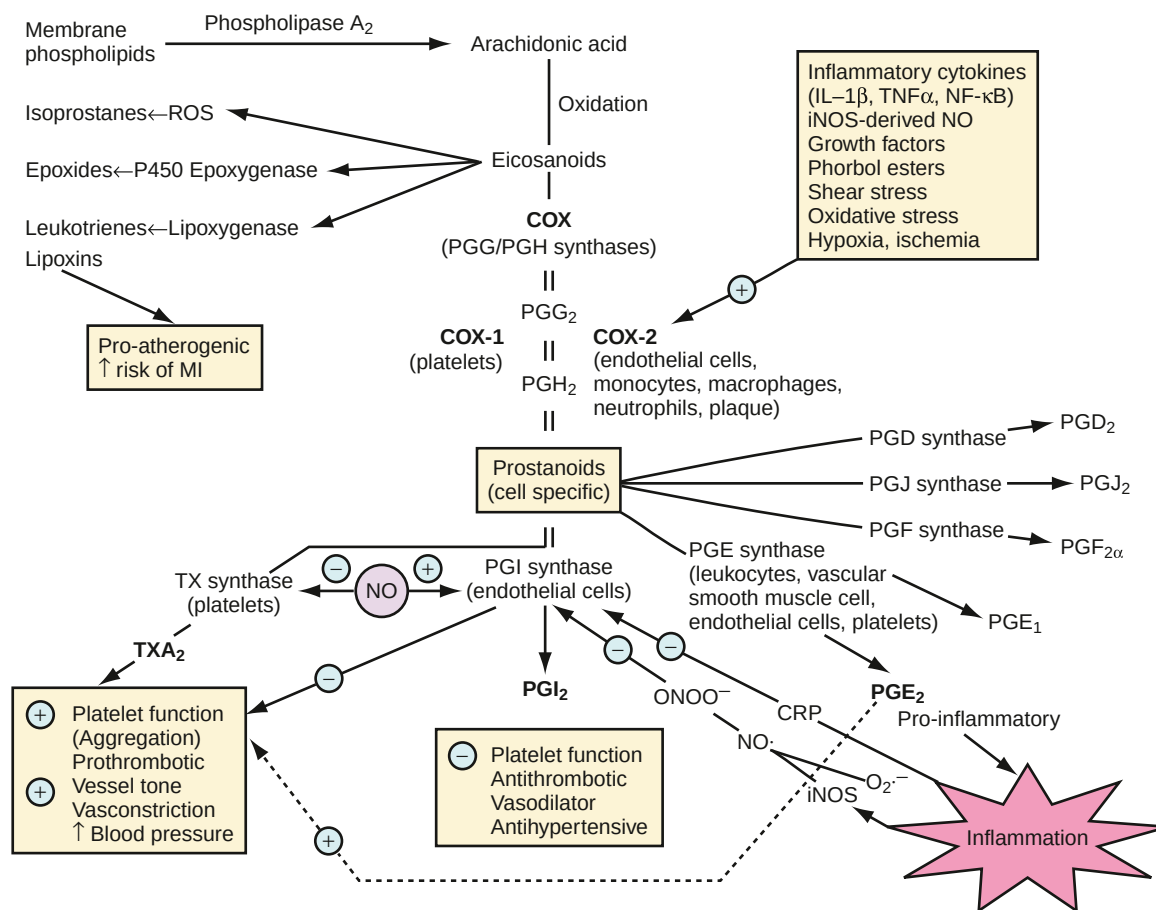


Figure 13-3. Pathways of prostanoide formation and role of cyclooxygenase-2 (COX-2) in vascular pathophysiology. +, stimulation; -, inhibition; CRP, C-reactive protein; IL-1 β , interleukin-1 β ; iNOS, inducible nitric oxide synthase; MI, myocardial infarction; NF- κ B, nuclear factor- κ B; NO, nitric oxide; PG, prostaglandin; ROS, reactive oxygen species; TNF- α , tumor necrosis factor- α ; TX, thromboxane. (Modified from Jugdutt BL: Cyclooxygenase inhibition and adverse remodeling during healing after myocardial infarction. *Circulation* 2007;115:288-291.)

risk reduction of 2.4%), and the risk of any vascular event by 23%. Reduction of cardiovascular mortality was enhanced by the combination of antiplatelet and fibrinolytic therapy, and cardiovascular mortality was decreased by 25% with streptokinase alone and by 42% with streptokinase and aspirin combined (absolute risk reduction of 5.2%), indicating that low-dose aspirin alone was as effective as streptokinase, and the combination produced synergism. Aspirin therapy might reduce the rate of reocclusion.³ Patients taking aspirin had fewer cardiac arrests, but slightly more minor bleeding. Aspirin did not increase the risk of cardiac rupture or bleeding requiring transfusion.

ISIS-2 was not only the largest aspirin trial in STEMI patients, but also the trial with the most robust evidence that aspirin reduces mortality in STEMI patients.³ Mortality reduction was similar in patients treated within 4 hours (by 25%), between 5 and 12 hours (by 21%), and between 13 and 24 hours (by 21%). A subsequent meta-analysis of MI trials using aspirin and the thrombolytics streptokinase and alteplase showed that aspirin reduces coronary reocclusion and recurrent ischemic events.⁵⁰

On presentation, STEMI patients should be started on 162 to 325 mg of aspirin followed by 81 to 162 mg daily indefinitely (Table 13-1).^{10-12,51} Non-enteric-coated aspirin should be used initially and chewed to ensure rapid buccal absorption.^{52,53} Long-term aspirin therapy for secondary and primary prevention has

Table 13-1. Dosing for Oral Antiplatelet Therapy

Drug	Loading Dose (mg)	Maintenance
Aspirin	162-325	75-81 mg or 162 mg daily
Clopidogrel	300-600*	75 mg daily
Prasugrel	60	10 mg daily
Ticlopidine	500	250 mg twice daily

Note: Drugs are listed alphabetically and not in order of preference.

*Depending on interventionalist's preference.

tended to use higher doses,⁵⁴ although a low dose might be equally effective.⁵¹ A meta-analysis of small randomized trials of antiplatelet agents (aspirin, dipyridamole, or sulfinpyrazone, alone or in combination) for secondary prevention in survivors of previous cardiovascular events including acute MI indicated reduction in the risk of nonfatal acute MI by 32%, nonfatal stroke by 27%, total cardiovascular death by 15%, and vascular event by 25%. Aspirin alone was as effective as aspirin combined with another antiplatelet agent.⁵⁵ A lower dose (300 mg daily) was as effective as higher doses (1000 to 1500 mg daily) for secondary prevention. A large U.S. trial on primary prevention showed that a low dose of aspirin (325 mg on alternate days) was highly

effective and decreased the risk of acute MI by 44%.⁵⁶ The resulting recommendation was that 160 mg of aspirin daily be given immediately after acute MI and be considered for primary prevention.

In STEMI patients who have received stents for reperfusion, a higher dose regimen is recommended. Patients with bare metal stents should be given 325 mg of aspirin daily for 1 month; patients with drug-eluting stents should be given 325 mg aspirin daily for 3 to 6 months.⁵⁷ In patients with unstable angina or NSTEMI, aspirin trials show mortality benefit independent of dose, initial timing, and duration of follow-up,⁵⁸⁻⁶¹ and the 2007 ACC/AHA guideline panel recommended decreasing the post-stent aspirin dose from 325 mg to between 162 to 325 mg daily.¹² Aspirin does not prevent restenosis, and its benefits are attributed to prevention of in-stent thrombosis and secondary prevention.⁶² Based on evidence that lower doses of 75 to 150 mg are effective for secondary prevention,^{51,63} a daily dose of 75 to 162 mg indefinitely is recommended for secondary prophylaxis in patients without stents,⁵⁷ and a similar dose is recommended after finishing the higher dose schedule in patients with stents.⁵⁷

The dose range in aspirin recommendations is due to the lack of head-to-head trials comparing the low doses and high doses in patients with acute MI. Although there have been no randomized controlled trials on differing lengths of therapy, STEMI, unstable angina/NSTEMI, and chronic angina guidelines all state that aspirin for secondary prevention should be continued indefinitely.^{10-12,64} Evidence for this recommendation comes from the Antiplatelet Trialists' Collaboration review of 145 randomized controlled trials with aspirin over the long-term in patients with known coronary artery disease, prior stroke, or transient ischemic attack.⁶⁵ There was statistically significant benefit for 2 years, although there was no statistically significant benefit in the third year. There was a 22% reduction in the composite end point of death, nonfatal recurrent infarction, and nonfatal stroke in patients with acute STEMI, patients at risk for STEMI, and patients with documented prior STEMI, with superior benefit in patients with the highest baseline risk.⁶⁵

Adverse Effects

Aspirin can cause gastrointestinal bleeding and intracranial hemorrhage. Long-term or high-dose aspirin and other NSAIDs are associated with increased risk of gastrointestinal bleeding.⁶⁶ Although several studies did not find increased bleeding risk from aspirin dosages of 75 to 325 mg daily,^{51,65,67-69} subset analyses from the nonrandomized CURE and BRAVO trials showed increased risk of bleeding from the low-dose to mid-dose range.^{68,69} Although the Antithrombotic Trialists' Collaboration found no difference in bleeding between aspirin groups given less than 75 mg versus greater than 75 mg daily, there was still a small statistically nonsignificant increase in the risk of bleeding.⁵¹ A meta-analysis of aspirin dosing in cardiovascular prevention and side effects revealed no difference in bleeding risk with daily dose ranging from medium (75 to 162 mg) to low (<75 mg).⁶⁷ Collective evidence supports low-dose aspirin (75 to 81 mg) for long-term use.⁷⁰

Patients unable to tolerate oral medications because of severe nausea can be given a 300-mg aspirin suppository.⁶¹ An absolute contraindication to aspirin is evidence of hypersensitivity to salicylates⁶¹; most such patients manifest the Samter's triad (sensitivity to salicylates, asthma, and nasal polyps).¹² Patients with true allergy to aspirin can be given the thienopyridine

clopidogrel or ticlopidine.¹⁰⁻¹² Aspirin is also contraindicated in patients with bleeding conditions (e.g., retinal hemorrhage, active peptic ulcer, other serious gastrointestinal or urogenital bleeding, hemophilia, and untreated severe hypertension).¹² In patients with prior gastrointestinal bleeding owing to ulcer after long-term use of low-dose aspirin and evidence of healed ulcer and eradication of *Helicobacter pylori*, 100 mg daily of aspirin plus the proton pump inhibitor lansoprazole for 12 months resulted in marked reduction of recurrent bleeding.⁷¹ In another study of patients with ulcer bleeding during aspirin therapy and evidence of healed ulcer and *H. pylori* eradication, comparison of clopidogrel plus the proton pump inhibitor esomeprazole versus low-dose aspirin (75 mg daily) plus a proton pump inhibitor showed the aspirin plus proton pump inhibitor combination to be superior in preventing recurrent ulcer bleeding.⁷²

Based on these results,^{71,72} and evidence of the large benefit of aspirin after MI,⁵¹ aspirin combined with a proton pump inhibitor should be continued if possible, unless the bleeding is life-threatening or cannot be controlled otherwise. It is reasonable to use acetaminophen initially in patients at risk for gastrointestinal bleeding for pain control.⁶⁶ If use of acetaminophen is impossible, it may be reasonable to use a selective COX-2 inhibitor in the short-term pending more long-term clinical data.⁶⁶

The use of selective COX-2 inhibitors (COXIBs) and nonselective NSAIDs has been reviewed elsewhere.^{46,66,73-75} COXIBs in all dosages and nonselective NSAIDs in high doses increase mortality in patients with previous MI and should be avoided.⁷³ Adverse effects of nonselective NSAIDs are attributed to loss of gastrointestinal protection and hemostasis via COX-1 and loss of anti-inflammatory activity via COX-2.⁴⁶ COXIB-induced reduction of PGI₂ and unchecked COX-1 activity result in continued TXA₂ production and increased risk of thrombosis, which may be harmful during acute MI.⁴⁶ COXIB-induced anti-inflammatory effects may be beneficial for progression of atherosclerosis, but harmful during infarct healing.⁴⁶ Suppression of inflammation by COX inhibitors can impair infarct healing after STEMI and lead to infarct thinning, adverse left ventricular remodeling, aneurysm, decreased resistance to rupture, and cardiac rupture,^{46,76-80} suggesting the need for caution.

The U.S. Food and Drug Administration (FDA) issued a warning on the concomitant use of aspirin and the NSAID ibuprofen.⁷⁵ Ibuprofen (but not rofecoxib, acetaminophen, or diclofenac) interferes with aspirin-induced acetylation of COX-1.⁷¹ The FDA also warned that COXIBs increase cardiovascular risk; rofecoxib (Vioxx) was withdrawn, although celecoxib and valdecoxib remain on the market.⁷¹ STEMI patients taking ibuprofen and requiring aspirin either should switch to another NSAID or should take ibuprofen 30 minutes after taking an immediate-release aspirin tablet or 8 hours before taking aspirin.⁷⁵ Data on the concomitant use of enteric-coated aspirin and ibuprofen are lacking.⁷⁵ One study showed, however, that the antiplatelet effect of enteric-coated low-dose aspirin was attenuated by ibuprofen (400 mg daily) given 2, 7, and 12 hours after aspirin.⁷¹

If COXIBs are used for pain control, they should be given "at the lowest possible dose and for the shortest time necessary."⁷¹ In the 2007 guideline update, morphine is recommended for pain control in patients with acute STEMI whether reperfused or not (class I, evidence level C).¹¹ On the basis of evidence that patients taking NSAIDs within the week before MI have an increased risk of death, hypertension, reinfarction, heart failure, myocardial rupture or shock,^{66,73,81-83} NSAIDs and COXIBs

should be stopped in patients who develop acute STEMI (class I, evidence level C), and should not be given to them during hospitalization (class III, evidence level C).^{11,66} Data from a substudy of the ExTRACT TIMI-25 trial showed that STEMI patients taking NSAIDs within 7 days of enrollment were at increased risk of death, reinfarction, heart failure, or shock.⁸³ A stepped-care approach has been recommended and is useful.⁶⁶

The role of other antiplatelet agents, such as prostacyclin analogues, thromboxane antagonists, phosphodiesterase inhibitors, serotonin receptor antagonists, fibrinogen receptor antagonists, monoclonal antibodies directed against glycoprotein (GP) IIb/IIIa, von Willebrand factor inhibitors, thienopyridines, thrombin inhibitors, and nitrates, in treating and preventing acute MI and other acute coronary syndromes continues to be evaluated.⁸⁴

Although aspirin is an effective antiplatelet drug, five points warrant mention. (1) Aspirin does not inhibit platelet degranulation in response to various stimuli or platelet adhesion to damaged endothelium.⁸⁵ (2) Aspirin resistance develops in 40% of patients, mostly women and elderly patients.^{86,87} (3) Patients with PGI₂ polymorphism for GP IIb/IIIa show an enhanced platelet aggregation response to aspirin.⁸⁸ (4) Aspirin has non-platelet effects, such as inhibition of interleukin-6 synthesis in leukocytes⁸⁹ and inhibition of endothelial nitric oxide inhibitors.⁹⁰ (5) Low-dose aspirin inhibits platelet and vascular COX activity.⁹¹

Pericarditis is common after STEMI.⁷⁹ Its timing coincides with the subacute phase during healing.^{19,23} Successful early reperfusion attenuates transmural extension and explains why Dressler's syndrome is rare in the reperfusion era.⁹² Although NSAIDs, such as ibuprofen and indomethacin, and corticosteroids have been effective for pericarditis, they can cause infarct expansion and thinning and cardiac rupture,^{76-79,93-95} and should be avoided or used as a last resort. High-dose aspirin (650 mg every 4 to 6 hours) may be used for pain control.^{10,96,97} Alternatively, colchicine⁹⁸⁻¹⁰⁰ or acetaminophen¹⁰ may be used. Short-term corticosteroids and NSAIDs may be used with extreme caution.^{10,66,83} Ibuprofen should not be used because it attenuates the antiplatelet effect of aspirin⁷¹ and causes infarct thinning.^{76-79,97} Misoprostol may be added for gastric and renal protection when NSAIDs are used.^{101,102} Data on the optimal management of pericarditis occurring in STEMI patients after reperfusion are awaited.

Summary of ACC/AHA Task Force Recommendations for Aspirin in ST Segment Elevation Myocardial Infarction

The ACC/AHA Task Force recommendations for aspirin in STEMI are summarized as follows.^{10,11}

- For convalescence and secondary prevention after STEMI, aspirin (75 to 162 mg daily) should be given indefinitely (class I, evidence level A). Patients with true aspirin allergy should preferably be given clopidogrel (75 mg daily) with ticlopidine (250 mg twice daily) as an alternative (class I, evidence level C). Also for patients with true aspirin allergy, warfarin (Coumadin) therapy (target international normalized ratio [INR] 2.5 to 3.5) is a useful alternative to clopidogrel in patients younger than 75 years old and at low risk of bleeding, provided that the INR can be monitored (class I, evidence level C). Ibuprofen should not be used because it blocks antiplatelet effects of aspirin (class III, evidence level C).

- Aspirin should be given promptly to all patients with suspected STEMI and no evidence of allergy, starting with a dose of 162 (class I, evidence level A) to 325 mg (class I, evidence level C), preferably non-enteric-coated and chewed, regardless of the reperfusion strategy or adjunctive therapies used. A maintenance dose of 75 to 162 mg daily (class I, evidence level A) should be given indefinitely.
- Patients with aspirin allergy or gastrointestinal intolerance should be given a thienopyridine, preferably clopidogrel, 75 mg daily (class I, evidence level C), rather than ticlopidine, 250 mg twice daily. In STEMI patients with planned PCI, clopidogrel should be given and continued for at least 1 month after bare metal stents and for 3 to 12 months after drug-eluting stents (class I, evidence level B).
- STEMI patients who develop pericarditis may be given high-dose aspirin, 650 mg orally every 4 to 6 hours (class I, evidence level B), although 162 to 325 mg is preferred. If aspirin does not control pain, oral colchicine, 0.6 µg every 12 hours (class IIa, evidence level B), or oral acetaminophen, 500 mg every 6 hours (class IIa, evidence level C), may be used. As a last resort, corticosteroids (class IIb, evidence level C) may be used. Except for aspirin, NSAIDs previously recommended (class IIa, evidence level B)¹⁰ should not be given to STEMI patients including during convalescence (class III, evidence level C).¹¹ Nonselective and COX-2-selective NSAIDs should be discontinued after acute STEMI in patients taking them before because of the amplified cardiovascular risk associated with their use (class I, evidence level C).¹¹ Ibuprofen should not be used (class III, evidence level B).¹⁰ If NSAIDs are used, misoprostol, 200 mg every 6 hours, should be added.¹⁰ Because analgesic doses of aspirin provide an antiplatelet effect but also increase the risk of bleeding compared with low-dose aspirin with another analgesic⁵¹ or without,⁷⁰ a proton pump inhibitor may be added to the analgesic dose of aspirin.
- A proton pump inhibitor should be added if patients develop gastrointestinal bleeding while taking aspirin (class I, evidence level B).¹²

Thienopyridines

The thienopyridines, such as clopidogrel and ticlopidine, are antiplatelet drugs and are useful as adjunctive therapy after MI. The rationale is that, despite COX inhibition by aspirin, platelet activation can continue through TXA₂-independent pathways leading to platelet aggregation and thrombin formation. Thienopyridines are recommended by the ACC/AHA management guidelines for STEMI and unstable angina/NSTEMI.¹⁰⁻¹² Clopidogrel is preferred over ticlopidine because it has fewer side effects.^{103,104}

Mode of Action

Thienopyridines block binding of adenosine 5'-diphosphate (ADP) to the low-affinity type 2 purinergic (P2Y₁₂) receptor, inhibiting the binding of fibrinogen to the GP IIb/IIIa complex and preventing its activation, and resulting in inhibition of platelet aggregation (Fig. 13-4).¹⁰⁵ Clopidogrel and ticlopidine do not affect the second type of high-affinity purinergic (P2Y₁) receptor and do not affect COX. They have a more potent antiplatelet effect than aspirin. Both agents can be given orally, preferably after meals for maximal bioavailability. They are prodrugs and are activated in the liver and excreted by the kidneys.

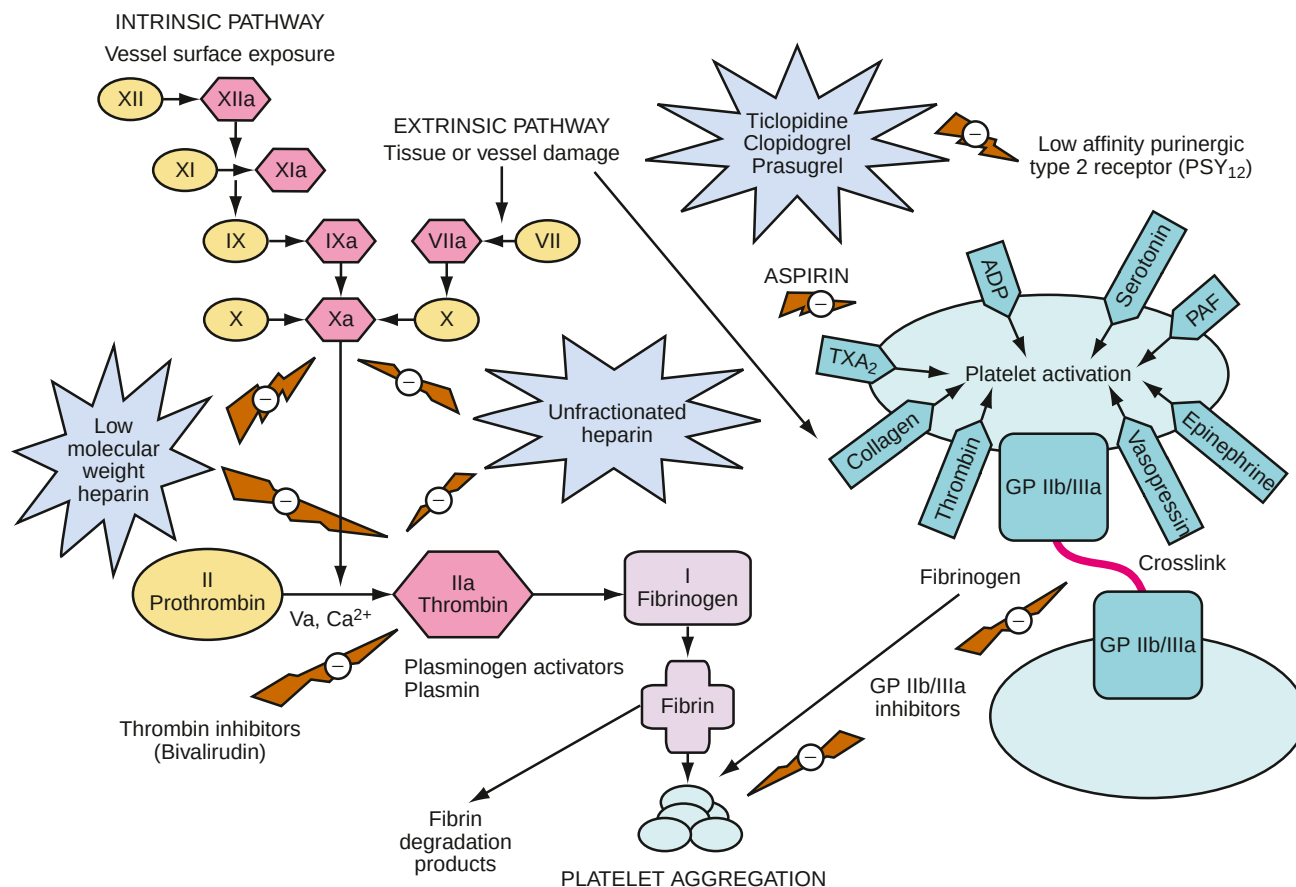


Figure 13-4. Sites of action of antiplatelet and antithrombin agents. Low-molecular-weight heparin produces more potent inhibition of factor Xa than thrombin, whereas unfractionated heparin produces equal inhibition of factor Xa and thrombin. Direct thrombin inhibitors inhibit thrombin, but have little effect on its generation. Thrombin amplifies generation of factors VIIa and Va, enhancing thrombus formation. Thrombin also promotes platelet activation by binding to platelet thrombin receptor. Cross-links, via ligands such as fibrinogen (factor I) to platelet glycoprotein (GP) IIb/IIIa receptors, lead to platelet aggregation. GP IIb/IIIa inhibitors act at these sites. ADP, adenosine triphosphate; PAF, platelet-activating factor; TXA₂, thromboxane A₂.

Clopidogrel and ticlopidine have similar efficacy as aspirin for long-term prevention^{106,107} and may be substituted in patients with aspirin allergy or intolerance.¹² In contrast to aspirin, thienopyridines produce significant inhibition after 2 to 3 days, and may take 4 to 7 days to achieve their full effect.¹⁰⁵ Their platelet-inhibiting effects are long-lasting and persist for 7 to 10 days after therapy is stopped¹⁰⁵; this corresponds to the life span of the platelet.

Dosing, Timing, and Benefits

Pending more data on the optimal loading dose of clopidogrel, 300 mg is used on the first day and followed by 75 mg daily in STEMI patients undergoing PCI and in unstable angina/NSTEMI patients being managed conservatively or undergoing PCI.^{10,12} A dose of 75 mg of clopidogrel is used in patients with aspirin allergy or intolerance.^{10,12} Clopidogrel should not be administered for 5 to 7 days before coronary artery bypass graft (CABG) surgery^{10,12,108} because of increased risk of bleeding with clopidogrel plus aspirin.¹⁰⁸⁻¹¹⁰ Clopidogrel doses of 600 to 900 mg have been studied, and small to moderate size trials have compared 600 mg with 300 mg.^{12,111-113} Ticlopidine (loading dose 500 mg; maintenance dose 250 mg twice daily) is used in patients with allergy to clopidogrel.

Pending more data on optimal timing of clopidogrel in PCI, and based on data from PCI-CURE,¹¹⁴ the ACC/AHA guidelines recommend initiating therapy even if a conservative strategy is planned.¹⁰ The CURE trial showed benefit with clopidogrel started on hospital admission despite the need for cardiac surgery in some patients.¹¹⁵ Clopidogrel also benefited patients with low 0-2 Thrombolysis In Myocardial Infarction (TIMI) risk scores, although the largest benefit in terms of the primary end point of MI, stroke, or death occurred in the highest risk patients.¹¹⁶ Clopidogrel should no longer be considered only for patients undergoing PCI. At hospitals that have rapid access to the cardiac catheterization laboratory, clopidogrel is withheld until there is confirmation of the coronary anatomy and that the patient needs PCI rather than CABG surgery. The loading dose of clopidogrel (300 to 600 mg) is given on the catheterization table just before PCI.¹² This approach is acceptable because of the increased risk of bleeding if the patient were to require urgent CABG surgery.

Based on findings of the PCI-CLARITY study in CLARITY-TIMI 28,¹¹⁷ clopidogrel should be started early (i.e., pretreatment) in cases of STEMI where angiography is delayed by 2 to 8 days because it results in a better outcome without increased risk of major or minor bleeding than when it is given just before

angiography. In the CLARITY-TIMI 28 study,¹¹⁷ the addition of clopidogrel to background aspirin therapy in STEMI patients reduced the risk of clinical events (i.e., death, reinfarction, stroke). Because the patients enrolled in CLARITY^{117,118} were 75 years old or younger, guidance on whether STEMI patients older than 75 years should receive a loading dose of clopidogrel is awaited.

Data on the risks and benefits of performing early versus delayed CABG surgery in STEMI patients receiving clopidogrel are lacking. Evidence from the CRUSADE registry showed no difference, however, in death, reinfarction, or stroke in NSTEMI patients who did versus patients who did not receive clopidogrel and went for early CABG surgery, despite an increase in blood transfusion requirements associated with failure to delay surgery.^{12,108}

Collective evidence indicates that all patients undergoing PCI should receive dual antiplatelet therapy with clopidogrel and aspirin.^{10,12,54,103,114,117-119} The length of clopidogrel therapy varies depending on the type of stent. For bare metal stents, aspirin at a dose of 162 to 325 mg daily plus clopidogrel at a dose of 75 mg daily for 1 month is necessary.^{12,54} Ideally, clopidogrel can be continued for 1 year if the risk for bleeding is low.⁵⁴ Clopidogrel and aspirin may be continued for other reasons. There is controversy regarding the length of clopidogrel therapy with drug-eluting stents. The old PCI guidelines stated that clopidogrel should be given for at least 3 months for sirolimus-eluting stents and at least 6 months for paclitaxel-eluting stents, but ideally therapy should be continued for 1 year if the risk of bleeding is low.¹⁶

STEMI patients who have not undergone revascularization may also benefit from clopidogrel therapy. The COMMIT/CCS-2, in which half of the patients did not undergo revascularization, showed benefit of clopidogrel therapy in STEMI.¹²⁰ Clopidogrel-treated patients in that study had a lower rate of the composite end point (death, reinfarction, stroke) and death (7.5% versus 8.1%), with no excess bleeding. In the CURE trial, NSTEMI patients who did not undergo stenting also benefited from clopidogrel therapy.¹⁰⁹

The optimal length of clopidogrel therapy for secondary prevention in patients with acute coronary syndromes is not well defined.^{12,121,122} For a noninvasive strategy, the ACC/AHA guidelines for unstable angina/NSTEMI recommend clopidogrel for 1 month to 1 year after the event.¹² The advice to extend therapy beyond 1 month is based primarily on data from the CURE trial.¹²³ There is no evidence to support prolonging therapy beyond 1 year, however. Because the 2004 STEMI guidelines¹⁰ do not give advice for patients managed conservatively with thienopyridines, it is reasonable to follow the 2007 unstable angina/NSTEMI guidelines¹² and recommend clopidogrel for at least 1 month and up to 1 year.

Adverse Effects

Ticlopidine therapy is associated with gastrointestinal upset, neutropenia, agranulocytosis, aplastic anemia, and rarely thrombotic thrombocytopenic purpura,^{103,104,124} requiring complete and differential blood counts every 2 weeks for 3 months. Clopidogrel therapy is associated with gastrointestinal upset and a low risk of thrombotic thrombocytopenic purpura but no neutropenia.^{106,125} Advantages of clopidogrel, such as once-daily dosing and no need for repeated laboratory monitoring, make it the preferred thienopyridine for the management of STEMI and NSTEMI and unstable angina.^{10,12,126,127} Typically, neutropenia

from ticlopidine resolves within 1 to 3 weeks after stopping the drug and may rarely be fatal.¹² Plasma exchange is required if thrombotic thrombocytopenic purpura develops.¹²⁴⁻¹²⁶ Ticlopidine is discouraged in patients with renal and hepatic dysfunction.

Although there is evidence that dual antiplatelet therapy with low-dose aspirin and clopidogrel reduces repeat cardiac events,^{109,114,128} the combination of aspirin and clopidogrel was not more effective than aspirin for primary prevention in high-risk patients in the CHARISMA trial.¹²⁹ The primary end point in that study was MI, stroke, or cardiovascular death. There was a moderate benefit in the secondary end point of MI, stroke, cardiovascular death, or hospitalization for unstable angina, transient ischemic attack, or revascularization. Although there was no significant difference in severe bleeding, there was an increased risk of moderate bleeding in the group treated with aspirin plus clopidogrel. Moderate bleeding was defined as nonsevere bleeding requiring transfusion. The study showed that clopidogrel plus aspirin prevented 94 ischemic (secondary) end points at the cost of 93 moderate or severe bleeds.¹²⁹ The patients with prior MI, ischemic stroke, and peripheral arterial disease derived significant benefit from dual therapy.¹³⁰ A large international study in outpatients with atherothrombosis (coronary, cerebrovascular, and peripheral arterial) revealed high annual cardiovascular event rates and increased 1-year risk of events with multiple disease locations.¹³¹ Although evidence shows that patients may experience large interpatient responses to clopidogrel, with increased risk of thrombotic events if they have less than expected inhibition of platelet aggregation,¹³²⁻¹³⁴ a standardized monitoring technique and appropriate management still need to be determined.¹²

Summary of ACC/AHA Task Force Recommendations for Thienopyridines in ST Segment Elevation Myocardial Infarction

ACC/AHA Task Force recommendations for thienopyridines in STEMI are summarized as follows.¹⁰

Early Phase

- STEMI patients should receive clopidogrel, 75 mg daily, in addition to aspirin (class I, evidence level A), and clopidogrel treatment should be continued for at least 14 days (class I, evidence level B).¹¹ Since the 2004 ACC/AHA guidelines,¹⁰ the use of clopidogrel in STEMI was supported by two additional studies (COMMIT-CCS-2 and CLARITY-TIMI 28)^{118,135} and subsequently endorsed.^{136,137} Clopidogrel is preferred to ticlopidine because of fewer side effects, and is used as an alternative to aspirin in aspirin-intolerant patients receiving fibrinolytics (class IIa, evidence level C).
- STEMI patients younger than 75 years old who received fibrinolysis or who did not receive reperfusion therapy can have an oral loading dose of clopidogrel of 300 mg (class IIa, evidence level C).¹¹ Data for patients older than 75 years are awaited.

Convalescent and Postdischarge Phases

- STEMI patients who have undergone angiography and for whom PCI is planned should have a loading dose of 300 to 600 mg of clopidogrel before PCI. For patients with bare metal stents, clopidogrel (at least 75 mg daily) should be continued for 1 month. For patients with drug-eluting stents,

clopidogrel (at least 75 mg daily) should be continued for 3 months with sirolimus and 6 months with paclitaxel drug-eluting stents and 1 year in patients who are not at high risk for bleeding (class I, evidence level B).

- Continuation of clopidogrel, 75 mg daily, for 1 month to 1 year can be considered for secondary prevention in STEMI patients regardless of whether they undergo reperfusion with fibrinolytic therapy or do not undergo revascularization (class IIa, evidence level C).¹¹
- STEMI patients who are taking clopidogrel and are going for CABG surgery should have clopidogrel withheld for at least 5 to 7 days before CABG surgery, unless the urgency for revascularization outweighs the risk of excess bleeding (class I, evidence level B).¹¹
- STEMI patients with allergy to clopidogrel can be given ticlopidine (loading dose 500 mg; maintenance dose 250 mg twice daily).

β-Adrenergic Blockers

The rationale for β-blockade in acute MI is that it decreases myocardial oxygen demand (by decreasing heart rate, blood pressure, and contractility); improves the distribution of myocardial blood flow; and exerts desirable antiplatelet and antiarrhythmic effects. β-blockade has the potential for limiting infarct size, decreasing wall stress, and decreasing mortality. It is used in very early MI and over the long-term for secondary prevention after MI, regardless of the type (STEMI, NSTEMI, and unstable angina) or concomitant fibrinolytic therapy or primary PCI.^{10,12}

Mode of Action

β-blockers compete with catecholamines for two β-adrenergic receptors; β₁ receptors are primarily located in the myocardium and affect sinus node rate and atrioventricular (AV) node conduction velocity, and β₂ receptors are primarily located in bronchial and vascular smooth muscle. β-blockers act on the cardiovascular system to slow heart rate, reduce blood pressure, and reduce cardiac contractility, resulting in decreased cardiac workload, myocardial oxygen consumption, and prolongation of diastolic filling time and coronary perfusion. Given acutely, β-blockers decrease infarct size in patients who do not receive reperfusion therapy, reduce the rate of reinfarction in patients who receive reperfusion therapy, and decrease the frequency of arrhythmias.¹⁰

Low doses of selective β-blockers block β₁ more than β₂ receptors, and may be preferable for patients with pulmonary and peripheral vascular disease. Some β-blockers have intrinsic sympathomimetic activity, resulting in activation of the β receptor, and less slowing of heart rate, less prolongation of AV node conduction time, and less depression of left ventricular function. Only nonselective β-blockers without intrinsic sympathomimetic activity were shown to reduce mortality after MI,¹³⁸ and β-blockers with intrinsic sympathomimetic activity were unfavorable for secondary prevention.¹³⁹ Two large post-MI trials of oral β-blockers in the era before reperfusion showed mortality benefit.^{140,141}

Dosing, Timing, and Benefits

A meta-analysis of trials in the prethrombolytic era revealed a 7% reduction (not statistically significant) in mortality with oral β-blockade and 9% reduction (not statistically significant) in

mortality with intravenous β-blockade.¹³⁹ The β-blocker in the early studies was started within 24 hours, and the initial intravenous dose was 5 to 10 mg for propranolol,¹⁴² 5 to 10 mg for atenolol,¹⁴³ or 10 to 15 mg for metoprolol.^{144,145} In the largest trial,¹⁴³ acute intravenous atenolol was followed by an oral dose of 100 mg for 1 week, and the mortality at 7 days was reduced by 14% (from 4.3% to 3.7%). In the MIAMI study,¹⁴⁴ acute intravenous metoprolol was followed by 25 to 50 mg taken orally four times daily for 2 days and 100 mg twice daily thereafter, and the mortality at 15 days was decreased by 12% (from 4.9% to 4.3%). A substudy of MIAMI patients showed limitation of left ventricular remodeling and improved left ventricular function.¹⁴⁵ A trial of β-blockade and concomitant thrombolytic therapy suggested a reduction in reinfarction rate.¹⁴⁶ Several secondary prevention trials^{139,145,146} have shown improved survival and decreased reinfarction rate with long-term β-blocker therapy after acute MI.

In the ACC/AHA guidelines, intravenous β-blocker followed by oral dosing is recommended for acute MI patients without contraindications.^{9,10,12} In the absence of contraindications, β-blockers should be given to patients with hypertension, reflex tachycardia, rapid atrial fibrillation, or postinfarction angina. Agents with less intrinsic sympathomimetic activity and short duration of action are preferred.⁹ If tolerated, oral therapy should be continued for 2 years. Relative contraindications to β-blocker therapy include heart rate less than 60 beats/min, systolic blood pressure less than 100 mm Hg, moderate to severe left ventricular failure, signs of peripheral hypoperfusion, shock, PR interval greater than 0.24 second, second-degree or third-degree AV node block, active asthma, reactive airways disease, and MI induced by cocaine use.^{10,12}

Intravenous β-blockers should be considered in all patients with STEMI who are not receiving fibrinolytic therapy or in patients who have ongoing resting chest pain.^{10,12} Patients who do not receive fibrinolytic therapy but receive intravenous β-blockers have been shown to have decreased infarct size and mortality.^{139,143,144} The ISIS-1¹⁴³ and MIAMI¹⁴⁴ trials showed a significant, sustained benefit in mortality after day 1 when patients were given either intravenous atenolol or intravenous metoprolol initially followed by oral dosing. Although patients who receive early fibrinolytic therapy may not be expected to benefit as much from intravenous β-blockers, the TIMI-II trial showed a benefit associated with the early use of intravenous β-blockers in terms of reduced recurrent ischemia and non-fatal reinfarction.¹⁴⁴ Early administration of β-blockers within 2 hours of symptom onset reduced the composite end point of death or reinfarction.¹⁴⁴

The routine use of intravenous β-blockers in patients receiving fibrinolytic therapy has been questioned on the basis of two randomized trials^{147,148} and a post-hoc analysis from the first GUSTO-1 trial showing no benefits.¹⁴⁹ A review of early β-blockers in STEMI found no mortality benefit.¹⁵⁰ Subsequently, the COMMIT/CCS-2 trial addressed the issue of early intravenous β-blockers in acute STEMI, randomly assigning 45,582 patients (93% STEMI or new left bundle branch block on electrocardiogram [ECG]), half of whom had fibrinolytic therapy, to three 5-mg intravenous metoprolol boluses followed by oral metoprolol extended-release, 200 mg daily for 28 days, or placebo; the trial found no difference in mortality.¹²⁰ The β-blocker group in that study showed an increase in mortality, however, among patients who were hemodynamically unstable

that was balanced by a decrease in mortality among patients who were hemodynamically stable.¹²⁰ The β -blocker group also showed a decrease in ventricular fibrillation rate.¹²⁰ For every 1000 metoprolol-treated patients, however, there were 5 fewer episodes of reinfarction and 5 fewer episodes of ventricular fibrillation (mostly on day 2 onward), but 11 more episodes of cardiogenic shock (mostly on days 0 to 1).¹²⁰

The overall lack of benefit in COMMIT/CCS-2¹²⁰ may have been due to the high dose of β -blocker given to patients who were hemodynamically unstable. Risk factors for cardiogenic shock from this study included older age, female sex, evidence of congestive heart failure (CHF), time delay in presentation, lower blood pressure, prior history of hypertension, and elevated heart rate.¹²⁰ One key point from that study is that the administration of intravenous β -blockers should be targeted for specific indications, such as patients with ongoing chest pain at rest and no contraindications such as evidence of CHF. The 2007 update of the ACC/AHA guidelines recommends caution with the use of intravenous β -blockade, especially in patients who are at risk for cardiogenic shock.¹¹ Data on the short-acting intravenous β -blocker esmolol in STEMI are awaited. The long-term use of oral β -blockers is recommended for secondary prevention in high-risk patients, after they have been stabilized, with gradual dose titration.¹⁵¹

The STEMI guidelines¹⁰ assign a class IIb recommendation for intravenous β -blockers, whereas the NSTEMI guidelines¹² do not recommend early routine administration and support targeting use of β -blockers for specific indications. Both guidelines^{10,12} assign a class I recommendation for oral β -blockers. In patients receiving thrombolytics, there may be a potential benefit of early intravenous β -blockade in reducing the rate of intracranial hemorrhage.^{147,152} Data from a national registry on 60,532 patients treated with tissue-type plasminogen activator found that patients who received immediate intravenous β -blockers had lower rates of intracranial hemorrhage by 31%.¹⁵²

Patients who undergo PCI should also receive β -blockers. Although no large randomized trials of intravenous β -blocker use before PCI have been performed, it is reasonable to extrapolate benefits in patients who received fibrinolytics to the primary PCI population.^{10,153} Preprocedural intravenous β -blockers have been shown to be beneficial in a retrospective analysis from the CADILLAC trial.¹⁵⁴ Patients who received intravenous β -blockers had a lower mortality rate than patients who did not, although this benefit was limited to patients who were not taking β -blockers before admission. There is also evidence of benefits of β -blockers after PCI in terms of reduction of 6-month mortality, especially in patients with evidence of reduced ejection fraction or multivessel coronary artery disease.¹⁵⁵

There have been no trials of head-to-head comparison of different β -blockers, so the choice of agent depends on local availability and physician preference.¹² Intravenous β -blockers that have been studied in the acute phase of MI include atenolol, metoprolol, and propranolol.¹² Studied oral β -blockers administered later (i.e., 6 hours after presentation) include propranolol, timolol, atenolol, metoprolol, and acebutolol.¹⁵⁰ Despite being given later in MI, one meta-analysis showed an association with lower mortality rates, with a relative risk reduction of 21%.¹⁵⁶ A retrospective analysis from BHAT showed that patients with persistent ST segment depression on ECG benefited from the addition of propranolol at a mean of 10 days after MI.¹⁵⁷

The oral β -blocker of choice should be one without intrinsic sympathomimetic activity.^{10,12} Evidence of an almost statistically significant lesser benefit of β -blockers with intrinsic sympathomimetic activity was reported.¹⁵⁰ A large retrospective observational study of 69,338 patients found that metoprolol, atenolol, and propranolol had very similar rates of mortality reduction after 2 years, although slightly less reduction with propranolol was attributed to unmeasured differences at baseline.¹⁵⁸ In patients with depressed left ventricular ejection fraction, carvedilol may be considered.^{12,159}

One therapeutic target is a heart rate of 50 to 60 beats/min, unless there are side effects.¹² The dose of β -blocker can be titrated up to specified targets (Table 13-2).⁶⁴ Regarding the length of therapy, a meta-analysis showed that β -blockers exert their effect over time, and potentially 1 year of therapy is necessary before mortality benefits can be appreciated.¹⁵⁰ Patients with other indications for β -blocker therapy, such as left ventricular ejection fraction less than 40%, benefit from long-term therapy in various trials.¹⁶⁰⁻¹⁶³ Although most trial data were collected in patients in eras when revascularization was uncommon, evidence from MUSTT showed that high-risk patients benefited from β -blocker therapy for many years (3 to 8 years), although the benefit was mitigated by an implantable cardiac defibrillator.¹⁶³ In patients at low risk (preserved ejection fraction), the evidence for continued long-term β -blocker therapy is controversial, but there is some evidence of a mortality

Table 13-2. Target Doses for β -Blockers

β -Blocker	β Selectivity	Agonist Activity	Target Dose
Acebutolol	β_1	Yes	200-600 mg twice daily
Atenolol	β_1	No	50-200 mg daily
Betaxolol	β_1	No	10-20 mg daily
Bisoprolol	β_1	No	10 mg daily
Carvedilol*	None	Yes	6.25 mg twice daily up to 25 mg twice daily
Esmolol (intravenous)	β_1	No	50-300 μ g/kg/min
Labetalol*	None	Yes	200-600 mg daily
Metoprolol	β_1	No	50-200 mg twice daily
Nadolol	None	No	40-80 mg daily
Pindolol	None	Yes	2.5-7.5 mg three times daily
Propranolol	None	No	20-80 mg daily
Timolol	None	No	10 mg twice daily

*Labetalol and carvedilol are combined α and β -blockers. Drugs are listed alphabetically and not in order of preference.

Adapted from Gibbons PJ, Abrams J, Chatterjee K, et al: ACC/AHA 2002 guideline update for the management of patients with chronic stable angina. *J Am Coll Cardiol* 2002;41:159-168.

benefit.¹⁶² The Cardiovascular Cooperative Project showed a reduction of mortality at 2 years even in low-risk patients.¹⁶⁴ Overall, in the absence of side effects, β -blocker therapy should be continued indefinitely.

Adverse Effects

Major side effects of β -blocker therapy include hypotension, bradycardia, AV block, worsening of CHF, and exacerbation of reactive airways disease. It can cause acute heart failure with pulmonary edema, active bronchospasm, hypotension, and severe bradycardia. β -blocker therapy is contraindicated in MI secondary to cocaine use because β -blockers may exacerbate coronary vasospasm.¹⁶⁵

Relative contraindications include chronic obstructive pulmonary disease (COPD) or asthma, reduced left ventricular ejection fraction, and peripheral artery disease. Patients with mild pulmonary disease not taking β agonists benefit from β -blockers after acute MI, but patients with severe COPD or asthma or taking β agonists do not benefit.¹⁶⁶ After 2 years, patients with COPD receiving β -blocker therapy had a higher survival rate than patients who did not receive therapy.¹⁶⁴ The concern that β -blocker therapy might worsen COPD or reactive airways disease has been addressed by one meta-analysis showing that cardioselective β -blockers do not worsen pulmonary function tests in patients with mild to moderate COPD or reactive airways disease.¹⁶⁷ Because the benefit of β -blockers is significant, it is recommended that lower initial doses of cardioselective β -blockers and careful titration upward be used,¹² and confirmation of COPD or reactive airways through pulmonary function testing be done if there is any question of the diagnosis.

In patients with decreased left ventricular function or evidence of heart failure, acute β -blocker therapy is contraindicated, although long-term therapy is beneficial.^{10,12} Older β -blocker trials were done without ACE inhibitors and did not assess patients with asymptomatic left ventricular dysfunction.^{143,144,168} Data from several ACE inhibitor trials in patients with asymptomatic left ventricular dysfunction (e.g., SAVE and SOLVD) and symptomatic left ventricular dysfunction (e.g., AIRE) show that β -blockers do have additive benefit to ACE inhibitors.¹⁶⁹⁻¹⁷¹ Regardless of the level of left ventricular dysfunction, β -blockers improve survival and produce benefits in post-MI patients with ejection fraction greater than and less than 20%.¹⁶⁴

The CAPRICORN trial also showed that there is an additive benefit of β -blockers and ACE inhibitors in patients with post-MI left ventricular dysfunction.¹⁷¹ Although there was no significant difference in the primary combined end point of mortality and rehospitalization for cardiovascular problems, there was a statistically significant difference in mortality and nonfatal MI.¹⁷² Analysis of acute β -blocker therapy in 17,809 STEMI patients receiving aspirin and ACE inhibitors was associated with an independent decrease in hospital mortality regardless of reperfusion therapy.¹⁷³ Greater benefit was found in high-risk STEMI patients, such as elderly patients and patients without reperfusion, than low-risk patients.¹⁷³ A better survival rate is found in elderly acute MI patients prescribed β -blockers at discharge.¹⁷⁴

In patients with peripheral artery disease, there has been some concern about worsening of claudication with β -blockers; however, multiple meta-analyses and a placebo-controlled trial have shown this worry to be unfounded.¹⁷⁵⁻¹⁷⁷ Long-term β -blocker therapy in STEMI survivors shows mortality benefit despite revascularization with CABG surgery or PCI.¹⁷⁸

Summary of ACC/AHA Task Force Recommendations for β -blockers in ST Segment Elevation Myocardial Infarction

ACC/AHA Task Force recommendations for β -blockers in STEMI are summarized as follows.^{10,11}

Early Phase

- STEMI patients should be promptly started within the first 24 hours on an oral β -blocker in the absence of contraindications, such as evidence of CHF, low output state, increased risk of cardiogenic shock (i.e., age >70 years, systolic blood pressure <120 mm Hg, sinus tachycardia >120 beats/min, heart rate <60 beats/min, or increased time of onset since symptoms), PR interval greater than 0.24 second, third-degree heart block, or active asthma or reactive airways diseases, regardless of concomitant fibrinolytic therapy or primary PCI (class I, evidence level A).¹¹
- STEMI patients without the same aforementioned contraindications can be reasonably given prompt intravenous β -blocker at the time of presentation if they have hypertension or tachyarrhythmia (class IIa, evidence level B).^{10,11}

Convalescence

- STEMI patients who received and tolerated a β -blocker in the first 24 hours without adverse reactions should continue to receive the drug; patients without contraindications who did not receive a β -blocker in the first 24 hours should be started on one (class I, evidence level A).¹⁰
- STEMI patients with contraindications in the first 24 hours should be re-evaluated for β -blocker therapy (class I, evidence level C).¹¹

Postdischarge

- All STEMI survivors should receive a β -blocker except patients at low risk (i.e., normal ejection fraction, successful reperfusion, no ventricular arrhythmias) or with contraindications, and treatment should be started promptly and continued indefinitely (class I, evidence level A).¹⁰
- STEMI patients with moderate to severe left ventricular failure should receive β -blocker therapy with gradual titration as a secondary prevention (class I, evidence level B).¹¹
- β -blocker therapy is considered reasonable for low-risk STEMI patients without contraindications (class IIa, evidence level A).¹⁰

Nitrates

Nitrates have been used for the management of acute ischemic syndromes for more than a century. More than 2 decades ago, nitroglycerin was given to patients with acute MI to improve hemodynamics.¹⁷⁹ Subsequently, low-dose intravenous nitroglycerin in patients with acute STEMI was shown to be safe,^{180,181} to limit infarct size,¹⁸¹⁻¹⁸⁵ to reduce infarct-related complications,^{181,183} to limit left ventricular remodeling,¹⁸¹ to improve function,¹⁸¹⁻¹⁸⁸ and to improve survival in high-risk anterior STEMI patients.¹⁸¹ A meta-analysis of randomized trials before the use of thrombolysis showed a 35% mortality reduction with intravenous nitrates and 25% reduction with oral nitrates.¹⁸⁹ Concurrent low-dose intravenous nitroglycerin and late reperfusion therapy limited remodeling and resulted in early recovery of ventricular function.^{190,191} After acute STEMI, 6 weeks of nitrate therapy

(initial low-dose intravenous nitroglycerin followed by buccal nitrate in an eccentric dosing schedule), in patients with¹⁹² and without¹⁹³⁻¹⁹⁶ thrombolytics after admission, limited left ventricular remodeling and improved function. Two large thrombolytic trials (GISSI-3 and ISIS-4) confirmed the safety of intravenous nitroglycerin in patients with acute MI¹⁹⁷ or suspected MI,¹⁹⁸ but did not show significant benefit of long-term nitrates on survival.

Mode of Action

The beneficial effects of nitrates primarily result from the endothelium-independent release of nitric oxide, direct relaxation of vascular smooth muscle, and dose-related vasodilation leading to left ventricular unloading, decreased wall stress, and improved myocardial perfusion.¹⁹⁹⁻²⁰¹ The role of nitric oxide in cardioprotection is reviewed elsewhere.²⁰²⁻²⁰⁴ Nitrates also produce vasodilation indirectly through the endothelial release of PGI₂¹⁹⁹⁻²⁰¹ and exert antiplatelet and antithrombotic effects.^{205,206} Nitroglycerin dilates coronary arteries and promotes collateral flow to ischemic regions.²⁰⁷⁻²¹⁰ Low-dose nitroglycerin produces maximal venodilation and marked reduction in left ventricular preload, chamber size, and wall stress.¹⁹⁹⁻²⁰¹ Higher doses decrease blood pressure, dilate coronary resistance vessels, can cause hypotension and decrease perfusion,^{211,212} and produce tolerance.²¹³ Reducing preload and afterload decreases myocardial oxygen demand.

After thrombolytic therapy, the combined beneficial effects of nitrates (e.g., dilation of large coronary vessels, relief of coronary spasm, antiplatelet and antithrombotic effects) can potentially prevent reocclusion, infarct extension, and postinfarction angina. Nitroglycerin-induced vasodilation of atherosclerotic arteries may benefit patients with STEMI caused by coronary spasm.¹⁰ In the conscious dog model of inferior MI, low-dose intravenous nitroglycerin increased collateral blood flow and reduced infarct size.²¹⁰ In the conscious dog model of anterior MI, administration of long-term nitrates (6 weeks) limited left ventricular remodeling and was more effective than short-term therapy (2 weeks).²¹⁴ In the same model, prolonged unloading with long-term nitrate therapy (6 weeks) after reperfused anterior MI limited left ventricular remodeling and dysfunction.²¹⁵

Low-dose intravenous nitroglycerin can be administered safely to patients with evolving anterior STEMI; dose titration avoids hypotension, tachycardia, or bradycardia.^{181,213} Patients with inferior STEMI are more sensitive to preload reduction, especially if right ventricular infarction is present.^{181,213}

Cumulative basic research evidence indicates that organic nitrates are rapidly converted to nitric oxide after entering the cell wall, and nitric oxide activates guanylate cyclase, leading to increased intracellular cyclic guanosine monophosphate (cGMP), which mediates smooth muscle relaxation and inhibition of platelet aggregation. The hypothesis that nitrates may provide an exogenous source of nitric oxide has been challenged. Nitroglycerin biotransformation occurs through reduction of mitochondrial aldehyde dehydrogenase (ALDH-2), and attenuation of ALDH-2 may explain nitrate tolerance. Chinese subjects who lack ALDH-2 show almost normal vascular and platelet responses to nitroglycerin, however. Nitrate uptake is greater in veins, but the rate of cGMP formation is greater in arteries.

Dosing, Timing, and Benefits

The 1990 ACC/AHA guidelines⁹ recommended low-dose intravenous nitroglycerin in the treatment of acute MI, provided that the initial systolic blood pressure is not less than 90 mm Hg.

The guidelines supported use of nitroglycerin for suppressing ongoing myocardial ischemic pain and for managing acute MI complicated by CHF or pulmonary edema. The guidelines also supported monitoring of blood pressure and heart rate to detect hypotension, tachycardia, or bradycardia and to avoid myocardial hypoperfusion, and recommended intravenous or topical nitroglycerin for 24 to 48 hours after thrombolysis. The 1990 ACC/AHA guidelines⁹ also cautioned against unreasonably delaying analgesia (e.g., morphine) while the anti-ischemic effect of intravenous nitroglycerin is being evaluated, the use of long-acting nitrates in the early stages of acute MI, and the use of intravenous doses of more than 200 µg/min because they are associated with the development of tolerance.

The 2004 ACC/AHA guidelines¹⁰ recognized the usefulness of low-dose intravenous nitroglycerin infusion in titrating therapy to the blood pressure response,^{199-201,216} and suggested that the infusion should begin at 5 to 10 µg/min with increases of 5 to 20 µg/min (rather than 15 µg and be titrated upward by 5 to 10 µg/min every 5 to 10 minutes as in the previous guidelines)⁹ until symptoms are relieved or mean blood pressure is reduced by 10% of the baseline level in normotensive patients and by up to 30% in hypertensive patients, but not below a systolic pressure of 90 mm Hg or a decrease greater than 30 mm Hg below baseline. In a large randomized, placebo-controlled, single-blinded trial of low-dose intravenous nitroglycerin infusion in 310 patients,^{181,213} a similar regimen was used, but began at 5 µg/min. Using this regimen, the infusion was safely continued for more than 12 hours in 89% of patients, more than 24 hours in 75% of patients, and more than 48 hours in 27% of patients. The average duration was 39 ± 25 (standard deviation) hours, and the longest infusion was 154 hours. The initial decrease in mean blood pressure was 10 ± 8% in normotensive patients (blood pressure <140/90 mm Hg) and 19 ± 9% in hypertensive patients (blood pressure >140/90 mm Hg). None of the patients in that study developed hypotension requiring alternative therapy.^{181,213} Partial tolerance developed in 24% and did not reduce the benefits.²¹³

In studies of about 200 patients, long-term nitrate therapy delivered over 6 weeks after acute MI was effective in preserving left ventricular geometry and improving function measured by echocardiography and radionuclide imaging.¹⁹²⁻¹⁹⁴ The GISSI-3¹⁹⁷ and ISIS-4¹⁹⁸ megatrials studied a different selected population (i.e., with lower mortality and with >50% receiving nitrates and other therapies) than the populations in the prethrombolytic trials.¹⁸⁹

In GISSI-3,¹⁹⁷ nitrates (intravenously for 24 hours and 10 mg transdermally for 6 weeks) did not reduce mortality significantly. The combination of nitrate and lisinopril (5 mg initially and 10 mg four times daily for 6 weeks) decreased total mortality, however, by 17% (compared with 11% with lisinopril alone), and decreased the combined end point of mortality and ventricular dysfunction in elderly patients by 21% and in women by 21%. These benefits were found despite the fact that 57% to 61% of the control patients received nitrates. Nevertheless, the nitrate group had less postinfarction angina and less cardiogenic shock.

In ISIS-4,¹⁹⁸ the 5-week mortality with mononitrate and placebo was not significantly different (7.34% versus 7.54%). The mortality rate on the first 2 days was less, however, with nitrates.

In contrast to acute STEMI, high doses of nitrates have been used in unstable angina^{200,217,218} and CHF.²⁰⁰ Nitrates are available in many forms, including intravenous, sublingual sprays,

rapid-acting and dissolving tablets, long-acting tablets, and slow-release patches.²⁰⁰ Use of nitrates does not preclude use of other antianginal drugs such as β -blockers. Patients with CHF also benefit from nitrates. Nitrates should be avoided in STEMI patients with hypotension, bradycardia, or tachycardia,²¹⁹ or with right ventricular infarction.²²⁰ They are contraindicated in patients taking phosphodiesterase inhibitors, which inhibit the breakdown of cGMP, and should not be given within 24 hours of taking sildenafil or 48 hours of taking tadalafil, and probably within 24 hours of taking vardenafil.²²¹⁻²²⁴ Tolerance to nitrate therapy typically develops after 24 hours. If intravenous nitroglycerin is still required after tolerance develops, the dosage may need to be increased. Lower doses or nitrate-free intervals prevent the development of tolerance. The steps for weaning patients off intravenous nitroglycerin and switching to oral or topical nitrates are reviewed elsewhere.¹²

In the prethrombolytic era, a meta-analysis of nitrate trials in STEMI showed a 35% reduction in mortality.¹⁸⁹ In the postthrombolytic era, the mortality benefit of nitrate therapy was small in ISIS-4 (7.4% with nitrate versus 7.7% without nitrate)¹⁹⁸ and nil in GISSI-3.¹⁹⁷ The proportion of patients with STEMI was approximately 60% in GISSI-3 and 80% in ISIS-4.

Based on lack of a proven long-term survival benefit in those large trials, the ACC/AHA guidelines¹⁰ do not recommend routine nitrate therapy in STEMI patients, although the trials were confounded by nitrate use in the control groups, and the proportion of patients with STEMI was approximately 60% in GISSI-3 and 80% in ISIS-4. A trial of long-term intermittent transdermal nitroglycerin in survivors of acute STEMI showed improvement of left ventricular function and prevention of remodeling, although the beneficial effects were limited to patients with depressed ventricular function and receiving a low dose.^{225,226} A trial with the addition of isosorbide dinitrate and hydralazine to standard CHF therapy showed improved survival in black patients.²²⁷ A trial of intravenous versus buccal nitroglycerin in unstable angina showed no mortality benefit.²²⁸ STEMI¹⁰ and unstable angina/NSTEMI guidelines¹² recommend targeted over routine nitrate therapy.

Adverse Effects

The side-effect profile includes hypotension, tachycardia, bradycardia, and headache. Rarely, methemoglobinemia can develop. Patients with inferior STEMI, especially right ventricular infarction, are more sensitive to preload reduction. Continuous long-term use results in the development of tolerance.

Summary of ACC/AHA Task Force Recommendations for Nitrates in ST Segment Elevation Myocardial Infarction

ACC/AHA Task Force recommendations for nitrates in STEMI are summarized as follows.¹⁰

Early Phase

- STEMI patients with ongoing ischemic pain first should receive 0.4 mg of sublingual nitroglycerin every 5 minutes for a total of three doses and be assessed for intravenous nitroglycerin after that (class I, evidence level C) to relieve ongoing ischemic pain, control hypertension, and manage pulmonary hypertension (class I, evidence level C).
- STEMI patients should not be given nitrates if systolic blood pressure is less than 90 mm Hg or 30 mm Hg or more below

baseline, heart rate is less than 50 beats/min or greater than 100 beats/min, or right ventricular infarction is suspected (class III, evidence level C), and if a phosphodiesterase inhibitor was used in the preceding hours (24 hours for sildenafil and vardenafil; 48 hours for tadalafil) (class III, evidence level B). Nitrates should not be used if hypotension limits the use of β -blockers.¹⁰

- Nitrates should be used for pulmonary congestion in STEMI patients, unless systolic blood pressure is less than 100 mm Hg or more than 30 mm Hg below baseline (class I, evidence level C).

Convalescence

- In the first 48 hours after STEMI, intravenous nitroglycerin therapy should be used for persistent ischemia, CHF, or hypertension, but should not preclude β -blocker and ACE inhibitor therapy, which have been proven to reduce mortality. Beyond 48 hours, intravenous, oral, or topical nitrates should be used for recurrent angina or persistent CHF if their use does not preclude β -blocker or ACE inhibitor therapy (class I, evidence level B). Beyond 24 to 48 hours, continued nitrate therapy may be helpful, but benefit is not established (class IIb, evidence level B). Nitrates should not be used in patients with hypotension, severe bradycardia, tachycardia, or right ventricular infarction (class III, evidence level C).

Postdischarge

- There is no advice in the guidelines for use of nitrates after discharge. Nitrates are not approved for secondary prevention after STEMI. They are used for anti-ischemic therapy and left ventricular failure.

Angiotensin-Converting Enzyme Inhibitors and Other Renin-Angiotensin-Aldosterone System Inhibitors

ACE inhibitors are recommended for the early management of acute STEMI in the 2004 ACC/AHA guidelines.¹⁰ Although ACE inhibitors were not recommended for acute MI by the 1990 guidelines,⁹ they have undergone extensive experimental and clinical evaluation in the course of acute MI and for the limitation of left ventricular remodeling after MI.^{18,19,197,198,229-241} They have emerged as effective adjunctive agents for preventing left ventricular remodeling and improving survival.

Mode of Action

The renin-angiotensin-aldosterone system (RAAS), reviewed elsewhere,^{47,242} regulates blood pressure and extracellular volume. The pathway for the formation of angiotensin II (the primary effector molecule of the RAAS) begins with angiotensinogen, secreted by the liver, and its conversion to angiotensin I by renin, and conversion of angiotensin I to angiotensin II by ACE, and subsequent degradation of angiotensin II (Fig. 13-5). Angiotensin II, acting mainly via angiotensin II type 1 (AT₁) receptors,²⁴³ exerts several physiologic actions, including vasoconstriction and aldosterone and catecholamine release (Fig. 13-6).

The beneficial effects of ACE inhibitors are related mainly to inhibition of ACE and kininase (Fig. 13-7).^{41,242} ACE inhibition results in decreased activity of RAAS; decreased formation of

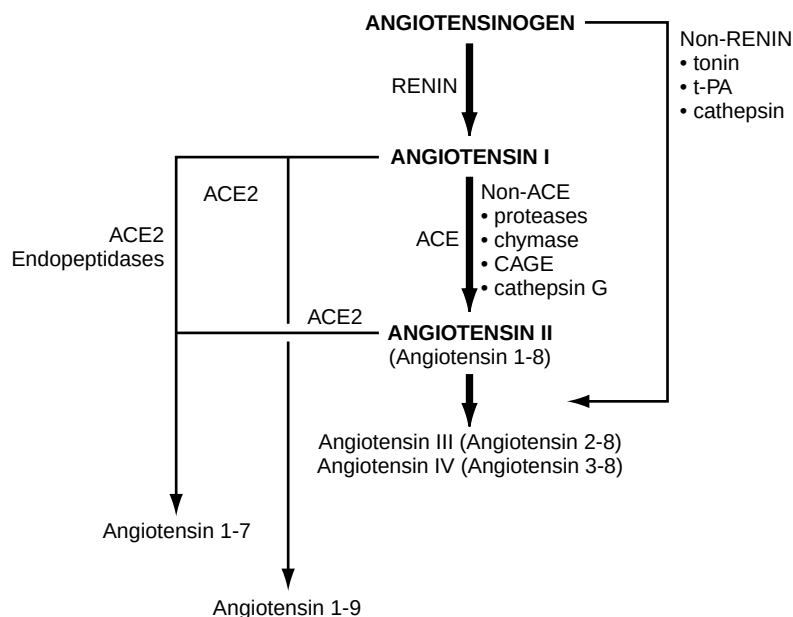


Figure 13-5. Angiotensin II formation and degradation pathways. ACE, angiotensin-converting enzyme; CAGE, chymostatin-sensitive angiotensin II generating enzyme; t-PA, tissue plasminogen activator. (From Jugdutt BI: Valsartan in the treatment of heart attack survivors. *Vasc Health Risk Management* 2006;2:125-138.)

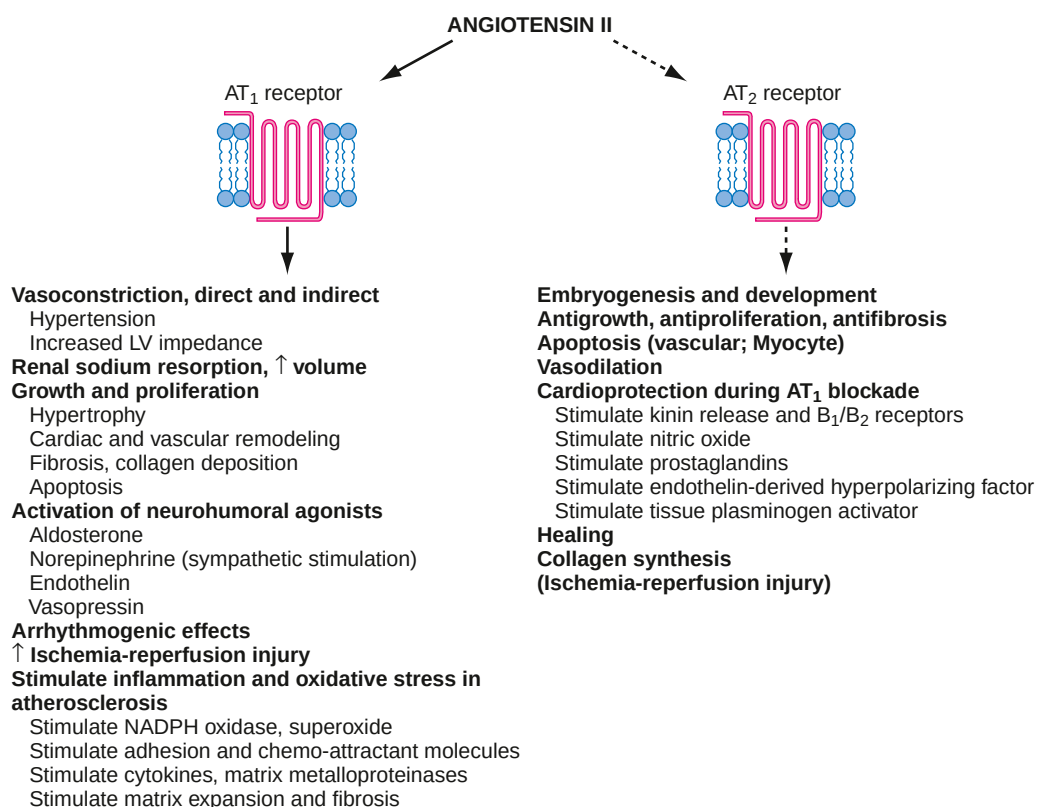


Figure 13-6. Major cardiovascular effects of angiotensin II. AT, angiotensin; LV, left ventricular; NADPH, nicotinamide adenine dinucleotide phosphate. (From Jugdutt BI: Valsartan in the treatment of heart attack survivors. *Vasc Health Risk Management* 2006;2:125-138.)

angiotensin II; decreased catecholamine secretion, inotropic stimulation, heart rate, and vasoconstrictor tone; and improved collateral flow. Kininase inhibition contributes to vasodilation. The results are increased venous capacitance and decreased preload, decreased afterload, improved perfusion, decreased

infarct size, decreased chamber size and wall stress, and decreased ventricular dilation. As with other vasodilators,²¹¹ however, treatment with high doses of the ACE inhibitor captopril fails to decrease infarct size.^{212,231} The antigrowth effects of ACE inhibitors result in inhibition of myocyte hypertrophy^{232,233}

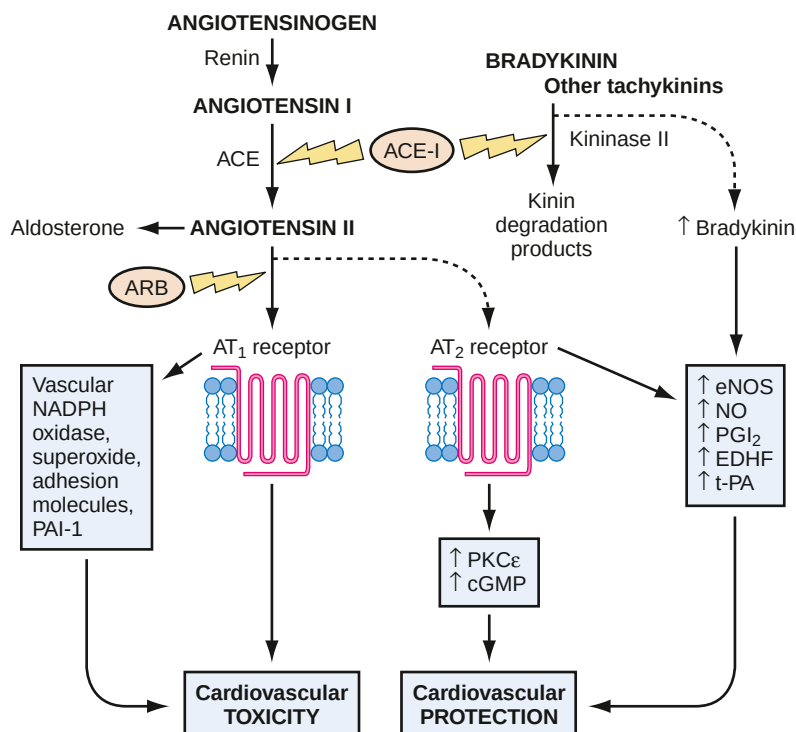


Figure 13-7. Pathways of angiotensin-converting enzyme (ACE) inhibitor–induced and angiotensin receptor blocker (ARB)–induced cardiovascular protection. cGMP, cyclic guanosine 3′ 5′ monophosphate; EDHF, endothelin-derived hyperpolarizing factor; eNOS, endothelial nitric oxide synthase; NADPH, nicotinamide adenine dinucleotide phosphate; NO, nitric oxide; PAI-1, plasminogen activator inhibitor-1; PGI₂, prostacyclin; PKCε, protein kinase Cε; t-PA, tissue plasminogen activator. (From Jugdutt BI: Valsartan in the treatment of heart attack survivors. *Vasc Health Risk Management* 2006;2:125-138.)

and collagen deposition in the noninfarct²³² and infarct zones,^{233,244-246} suggesting the need for caution when using these agents after MI.

ACE inhibitors do not block the formation of angiotensin II via alternative pathways (see Fig. 13-5) or all aldosterone formation. Angiotensin receptor blockers (ARBs) selectively block the effects of angiotensin II via AT₁ receptors,²⁴³ and aldosterone antagonists block the mineralocorticoid receptor.^{247,248} Angiotensin II degradation by ACE2 leads to formation of angiotensin-(1-7) (see Fig. 13-5), a vasodilator that is increased during ACE inhibitor and ARB therapy and may contribute to their cardioprotective effects.²⁴⁹ The rationale for using aldosterone blockade is that angiotensin II stimulates the release of aldosterone, activating the mineralocorticoid receptor. The activation of the mineralocorticoid receptor persists despite the use of ACE inhibitors, ARBs, and β-blockers.

Dosing, Timing, and Benefits

Several clinical studies tested the effect of very early and prolonged ACE inhibition after MI.²³⁴⁻²³⁶ In a study combining thrombolysis with recombinant tissue plasminogen activator and captopril (2 mg intravenously followed by incremental oral doses of 12.5 to 50 mg twice daily for 3 months), only one patient developed hypotension, and the overall effect was a greater limitation of progressive left ventricular dilation with captopril.²³⁴ It has been suggested that sulfhydryl-containing ACE inhibitors such as captopril may also act as free-radical scavengers and reduce reperfusion injury.²³⁵ In CONSENSUS II,²³⁶ the ACE inhibitor enalapril, given as 1 mg intravenously on the first day followed by oral dosing from 2.5 mg twice daily to 20 mg daily for

6 months, resulted in early hypotension in 12% and no improvement in survival. Nevertheless, 11 other ACE inhibitor studies showed improved survival (Table 13-3).^{197,198,237-240,250-254} HEART was terminated prematurely.²⁵⁵ All the trials were completed in the thrombolytic era and were conducted on selected patients. The overall results underscore the fact that final outcome represents a balance of effects and support the use of ACE inhibitors as adjunctive therapy in acute STEMI. Their overall safety in treating very early and convalescent phases of STEMI is supported by extensive trial data with the caveat that hypotension should be avoided.

SAVE showed a close correlation between limitation of left ventricular dilation and clinical benefits.²⁴¹ The collective evidence indicates that ACE inhibitor therapy after MI attenuates or delays the rate of ventricular remodeling.²⁵⁶⁻²⁵⁹ This therapeutic benefit is attributed in major part to inhibition of the effects of angiotensin II, and is supported by findings of increased ACE expression at the edge of infarct scars²⁶⁰ and markedly increased left ventricular dilation in patients with the ACE-DD genotype, which is associated with increased ACE activity.²⁶¹

The general consensus, based on trial data showing early benefit of oral ACE inhibitor therapy in STEMI, is that therapy should be given early, within 24 hours, provided that there is no evidence of hypotension or other contraindications or allergy to ACE inhibitors.¹⁰ In ISIS-4,¹⁹⁸ patients given captopril within 24 hours of their presentation showed early benefit, with separation of the survival curves within the first 5 weeks and greatest benefit in anterior MI. In patients treated early with captopril, 44 deaths were prevented on days 0 to 1, 37 deaths were prevented on days 2 to 7, and 62 deaths were prevented later on.²⁶²

Table 13-3. Major Trials of Angiotensin-Converting Enzyme Inhibitors in Heart Failure and Myocardial Infarction

Trial, Year	N	Disease	Drug	Onset	Duration	Outcome
CONSENSUS, 1987 ²⁵⁰	253	HF	Enalapril	—	20 mo	27% ↓ mortality; ↓ morbidity
SOLVD (symptomatic), 1991 ²³⁸	2569	HF	Enalapril	≥4 wk	41.4 mo	16% ↓ mortality; ↓ morbidity
SOLVD (asymptomatic), 1992 ²³⁹	4228	HF	Enalapril	≥4 wk	37.4 mo	8% ↓ mortality (NS); ↓ morbidity
CONSENSUS II, 1992 ²³⁶	6090	MI	Enalapril	<24 hr	6 mo	No decrease in mortality; hypotension
SAVE, 1992 ²³⁷	512	MI	Captopril	3-16 days	42 mo	19% ↓ mortality; ↓ morbidity
AIRE, 1993 ²⁴⁰	2006	MI	Ramipril	3-10 days	15 mo	27% ↓ mortality; ↓ morbidity
GISSI-3 (6-wk effects), 1994 ¹⁹⁷	19,394	MI	Lisinopril	≤24 hr	6 wk	11% ↓ mortality; ↓ morbidity
ISIS-4, 1995 ¹⁹⁸	58,050	MI	Captopril	≤24 hr	35 days	7% ↓ mortality; ↓ morbidity
TRACE, 1995 ²⁵¹	6676	MI	Trandolapril	3-7 days	24 mo	34.7% ↓ mortality; ↓ morbidity
CCS-1, 1995 ²⁵²	13,634	MI	Captopril	≤36 hr	1 mo	6% ↓ mortality; ↓ morbidity
SMILE, 1995 ²⁵³	1556	MI	Zofenopril	≤24 hr	6 wk	29% ↓ mortality; ↓ morbidity
GISSI-3 (6-mo effects), 1996 ²⁵⁴	19,394	MI	Lisinopril	≤24 hr	6 wk	6.2% ↓ mortality and LV dysfunction combined
HEART, 1997 ²⁵⁵	352	MI	Ramipril	≤24 hr	1-14 days	↓ LV remodeling

HF, heart failure; LV, left ventricular; MI, myocardial infarction; NS, nonsignificant.

Adapted from Jugdutt BI: Valsartan in the treatment of heart attack survivors. *Vasc Health Risk Management* 2006;2:125-138.

In GISSI-3,¹⁹⁷ patients given lisinopril within 24 hours showed early benefit, with 21 fewer deaths on days 0 to 1, 42 fewer deaths on days 2 to 7, and 12 fewer deaths later.²⁶² In the SMILE trial,²⁵³ with anterior MI patients without fibrinolytic therapy, there was a trend toward mortality benefit in the first 6 weeks. In CCS-1,²⁵³ there was a 0.5% absolute mortality benefit.

A meta-analysis of all the trials, comprising more than 100,000 patients, showed a benefit of 4.6 fewer deaths for every 1000 patients treated with ACE inhibitor therapy.²⁶³ Patients with anterior MI, age 55 to 74 years, and a heart rate greater than 80 beats/min tended to benefit more.²⁶³ Benefit occurred early, with approximately 40% of prevented deaths in the first 7 days.

Based on the ISIS-4 and GISSI-3 data, where the maximum dose of ACE inhibitor was achieved within 48 hours, the dose of ACE inhibitor should be rapidly titrated upward to achieve the full dose by 24 to 48 hours.¹⁰ Besides reperfusion and aspirin, ACE inhibitor therapy is the only other therapy shown to reduce 30-day mortality when CHF complicates STEMI.¹⁰ The survival benefit of ACE inhibitor therapy seems to be a class effect.¹⁰

The CONSENSUS II trial²⁶⁴ was stopped early by the Safety Committee because of concerns that there was an adverse effect in elderly patients who experienced early hypotension with enalapril. At the end of 6 months, there was a trend (not statistically

significant) toward harm in patients given intravenous enalapril. For this reason, intravenous enalapril should not be used in the management of STEMI.¹⁰ Nevertheless, the potentially harmful effect at 6 months in elderly patients is noteworthy. Additional clinical studies are needed to evaluate fully the safety of ACE inhibitor therapy during healing after large STEMI in elderly patients.

The optimal length of ACE inhibitor therapy has not been determined, especially in patients who are asymptomatic, normotensive, or nondiabetic with normal left ventricular function. In STEMI patients, the general consensus is that ACE inhibitor therapy should be continued indefinitely.¹⁰ In the PEACE trial,²⁶⁵ there was no benefit after a mean follow-up of 4.8 years in patients who were medically managed with aspirin, β -blocker, and a statin, and had an ejection fraction 40% or greater and stable coronary artery disease with prior revascularization in 72%. There was a reduction in blood pressure, but no reduction in mortality, infarction, or coronary revascularization rate.²⁶⁵

In view of extensive experience with ACE inhibitors in STEMI, ACE inhibitors remain the preferred RAAS inhibitor, and ARBs are used in ACE inhibitor-intolerant patients.¹⁰ Several trials investigated the benefits of ARBs in patients with MI and CHF, using an ACE inhibitor as comparator and on top of

Table 13-4. Major Trials of Angiotensin Receptor Blockers in Heart Failure and Myocardial Infarction

Trial, Year	N	Disease	Angiotensin Receptor Blocker	Comparator	Outcome
ELITE, 1997 ²⁶⁶	722	HF	Losartan	Captopril	Unexpected 46% ↓ in mortality (secondary end point)
RESOLVD, 1999 ²⁶⁷	768	HF	Candesartan	Enalapril	Early trend in ↑ mortality and HF (secondary end point)
ELITE II, 2000 ²⁶⁸	3152	HF	Losartan	Captopril	Not superior
Val-HeFT, 2001 ²⁶⁹	5010	HF	Valsartan	ACE inhibitor	Not superior; ↓ composite end point
OPTIMAAL, 2002 ²⁷⁰	5477	MI	Losartan	Captopril	Not superior (noninferiority criteria not met)
CHARM-Overall, 2003 ²⁷¹	7601	HF	Candesartan	ACE inhibitor	Improved primary outcome (mortality and morbidity)
CHARM-Added, 2003 ²⁷²	2548	HF	Candesartan	ACE inhibitor	Improved primary outcome (clinical, morbidity)
CHARM-Alternative, 2003 ²⁷³	2028	HF	Candesartan	ACE inhibitor	Improved primary outcome (mortality and morbidity)
CHARM-Preserved, 2003 ²⁷⁴	3023	HF	Candesartan	ACE inhibitor	Similar primary outcome (improved secondary outcome)
VALIANT, 2003 ²⁷⁵	14,703	MI	Valsartan	Captopril	Not superior, noninferior

ACE, angiotensin-converting enzyme; HF, heart failure; MI, myocardial infarction.

Adapted from Jugdutt BI: Valsartan in the treatment of heart attack survivors. *Vasc Health Risk Management* 2006;2:125-138.

background therapy (Table 13-4).²⁶⁶⁻²⁷⁵ In ELITE,²⁶⁶ losartan showed an unexpected reduction in the secondary end point of all-cause mortality by 46% relative to captopril. Although the study was small and not designed to assess mortality, this effect was thought to be due primarily to a reduction in sudden cardiac death. ELITE II,²⁶⁸ which was designed to assess superiority of losartan over captopril in reducing mortality, showed similar survival rates.

In the large CHARM trials,²⁷¹⁻²⁷⁴ candesartan improved cardiovascular death or heart failure hospitalization in patients taking ACE inhibitors and patients intolerant to ACE inhibitors. Compared with placebo in patients not receiving ACE inhibitors, candesartan reduced the composite primary end point of cardiovascular death or admission for heart failure, although overall mortality did not improve. In a substudy of patients with low ejection fraction ($\leq 40\%$) in the CHARM trial, candesartan reduced all-cause mortality, cardiovascular death, and heart failure hospitalizations.²⁷⁶ In RESOLVD,²⁶⁷ candesartan was compared with enalapril and the combination of candesartan and enalapril; this study was prematurely terminated because of an early trend in increased mortality and heart failure hospitalization (secondary end point) in the candesartan and combined therapy groups, although combined therapy more effectively prevented left ventricular remodeling than monotherapy. In OPTIMAAL,²⁷⁰ which was designed to test for superiority of an ARB on survival and other major cardiovascular outcomes in high-risk post-MI heart failure patients with captopril as comparator, losartan did not show superiority over captopril, but noninferiority criteria were also not met.

In VALIANT,²⁷⁵ which was designed to assess superiority of valsartan over captopril, and the efficacy and safety of long-term treatment with valsartan, captopril, and the combination

of valsartan and captopril in 14,703 high-risk patients with MI and left ventricular systolic dysfunction (ejection fraction $<40\%$) or heart failure or both, patients were randomly assigned 0.5 to 10 days after acute MI and followed for a median period of 24.7 months. There was no difference in the primary end point of all-cause mortality. Although valsartan was noninferior to captopril, adverse events were greater with the combination of valsartan and captopril; valsartan monotherapy was associated with more hypotension and renal dysfunction, and captopril monotherapy was associated with cough, rash, and taste disturbance.

This study established conclusively that valsartan was as effective as captopril in reducing mortality in high-risk patients after MI. The authors also performed a statistical comparison of the VALIANT results with the results of SAVE, AIRE, and TRACE using an imputed placebo, and showed that the 25% risk reduction in all-cause mortality in VALIANT was comparable to reductions in the ACE inhibitor trials. The finding that the valsartan plus captopril combination increased adverse events including hypotension underscores the need for careful monitoring of blood pressure when combining RAAS inhibitors after MI, and supports the caveat regarding vasodilator-induced hypotension in acute MI.

In a substudy of VALIANT,²⁷⁷ 21.5% of the 14,703 patients were elderly (≥ 75 years old), and their outcomes remained poor. With increasing age, mortality, composite end points, and heart failure admissions all increased. Adverse events from captopril and valsartan or both were also more common in elderly patients.

In Val-HeFT,²⁶⁹ which randomly assigned 5010 patients with heart failure to treatment with valsartan or placebo in addition to standard therapy, valsartan did not reduce the primary end point of all-cause mortality, but treatment reduced the composite end

point of mortality and morbidity, improved clinical signs and symptoms of heart failure, and decreased heart failure hospitalizations. A post-hoc analysis of the combined end point revealed that valsartan had a favorable effect in patients who did not receive ACE inhibitors or β -blockers, but an adverse effect in the 30% of patients who received the combination of valsartan, ACE inhibitor, and β -blocker.²⁷⁸ In a substudy of Val-HeFT,²⁷⁹ valsartan improved left ventricular size and ejection fraction in all groups except those taking valsartan together with an ACE inhibitor and a β -blocker. The finding that valsartan decreased mortality by 33% ($P = .017$) and the combined end point by 44% ($P < .001$) in patients not taking ACE inhibitors²⁷⁹ supports the use of valsartan as an alternative in ACE inhibitor-intolerant patients.

Valsartan is recommended in STEMI as an alternative to an ACE inhibitor and in ACE inhibitor-intolerant patients, with a target dose of 160 mg twice daily.¹⁰ Candesartan is also recommended for the same indication, with a target dose of 32 mg daily.¹⁰

Two large trials showed that aldosterone blockade reduces total mortality and hospitalization for heart failure in post-MI patients with left ventricular systolic dysfunction.²⁸⁰⁻²⁸³ In RALES,²⁸⁰ 1663 patients with severe CHF (left ventricular ejection fraction $\leq 35\%$) of ischemic origin in 55% received the aldosterone blocker spironolactone (target dose 50 mg daily if the patient did not develop hyperkalemia) or placebo in addition to background therapy with an ACE inhibitor, diuretic, digoxin, and β -blocker. The trial was prematurely terminated because of the finding of a 30% reduction in all-cause mortality over the 24 months of follow-up. Potassium-sparing diuretics were excluded. Although there were no significant differences in rates of hyperkalemia in the spironolactone group, the rates of breast pain and gynecomastia were higher. In a substudy of RALES,²⁸¹ spironolactone was associated with increased levels of markers of cardiac fibrosis or collagen synthesis, suggesting that limitation of excessive extracellular matrix turnover may have contributed to the benefits.

In the EPHEsus study,²⁸² 6642 patients with acute MI, left ventricular ejection fraction 40% or less, and heart failure were randomly assigned to receive the selective aldosterone blocker eplerenone (target dose of 50 mg daily) or placebo in addition to optimal background therapy. Eplerenone reduced all-cause mortality by 15% and cardiovascular mortality by 17%. Although serious hyperkalemia increased by 1% and 1.6% in these studies, this did not result in deaths. Potassium-sparing diuretics were excluded from this trial. In a substudy of EPHEsus,²⁸³ eplerenone begun at a mean of 7.3 days after acute MI was shown to reduce the 30-day all-cause mortality, supporting the initiation of eplerenone in the hospital. RALES and EPHEsus support long-term aldosterone blocker therapy in patients with heart failure and ejection fraction less than 40%, preserved renal function, and normokalemia.

Several post-MI trials showed that RAAS inhibition limited left ventricular remodeling with progressive left ventricular dilation after MI and improved outcome. These include SAVE with captopril^{237,241}; HEART with ramipril^{255,284}; VALIANT with valsartan, captopril, or both.²⁸⁵ Several heart failure trials also showed beneficial effects of RAAS inhibition on left ventricular remodeling, including V-HeFT I and II^{286,287} and RESOLVD.²⁶⁷

ACE inhibitor therapy also has proven benefits in unstable angina/NSTEMI patients with left ventricular dysfunction or

ejection fraction less than 40%,^{12,263,288,289} diabetics with post-MI left ventricular dysfunction,²⁹⁰ and high-risk patients for coronary events without left ventricular dysfunction.²⁸⁹ Long-term benefit of ACE inhibitor therapy was also shown in the TRACE trial, which followed patients with post-MI left ventricular dysfunction for 10 to 12 years.²⁹⁰

The ACC/AHA heart failure guidelines provide recommendations for initial and target doses of ACE inhibitors, ARBs, and aldosterone blockers (Table 13-5).²⁹¹

Adverse Effects

The side effects of ACE inhibitors include hypotension, acute renal failure, hyperkalemia, increased cough, angioedema, and anaphylactic reactions. ACE inhibitors are contraindicated during pregnancy because of the risk of renal toxicity in the fetus. ARBs have a similar side-effect profile except for minimal cough and lower rates of angioedema. The side effects of aldosterone receptor blockers include hyperkalemia and hypotension. Spironolactone can result in painful gynecomastia in men or menstrual irregularities in women. Eplerenone, being a selective mineralocorticoid blocker, does not have those side effects.

Before starting ACE inhibitor or ARB therapy, one should ensure that the patient is volume replete and begin with a low dose because hypovolemic patients have elevated renin levels, and ACE inhibitors and ARBs may cause a precipitous decrease in blood pressure. In patients with bilateral renal artery stenosis, chronic renal failure, hypertensive nephrosclerosis, CHF, and polycystic kidney disease, in whom the glomerular filtration rate (GFR) is maintained by an increased resistance at the efferent arteriole, ACE inhibitors lower this resistance and decrease GFR and renal function. Typically, creatinine begins to increase a few days after initiating therapy so that a patient's renal function should be checked after initiating ACE inhibitor therapy and followed for the first 3 months.²⁹² Some decrease in GFR may occur, especially in patients with pre-existing renal disease. With a GFR decline greater than 30%, ACE inhibitor or ARB therapy should be stopped and the GFR allowed to return to normal.²⁹²

Hyperkalemia (potassium concentration >5.1 mEq/L) is a common side effect that can be ruled out by measuring potassium levels. It is more common in diabetic patients taking NSAIDs, patients taking potassium-sparing diuretics, and elderly patients.²⁹²⁻²⁹⁴ The risk of hyperkalemia is much higher in patients taking multiple drugs that act on the RAAS, such as ACE inhibitors, ARBs, and aldosterone receptor blockers.²⁹⁵

Cough as a side effect ranges from 10% to 20% with ACE inhibitors, but is much less common with ARBs.^{292,296} It typically begins within the first 1 to 2 weeks, but may take 6 months to manifest. The cough is thought to be due to increased levels of kinins, substance P, and potentially other mediators such as prostaglandins and thromboxane.^{296,297} ACE metabolizes kinins and substance P, and ACE inhibitor therapy increases levels of these substances in the bloodstream. Kinins increase production of prostaglandin that stimulates the C-fibers in the airway and triggers coughing.²⁹⁶

ARB therapy does not have the same effect because it mainly targets AT_1 receptors that are not involved in the cough pathway; the rate of cough as a side effect is the same as with placebo (3%).²⁹⁸ Women are more commonly affected than men.²⁹⁶ Chinese patients have a nearly 50% risk of developing cough with ACE inhibitor therapy.²⁹⁹ Typically, the cough resolves when ACE inhibitor therapy is stopped, within 1 to 4 days, but may

Table 13-5. Initial and Target Doses for Renin-Angiotensin-Aldosterone System Inhibitors

Drug	Initial Dose	Target Dose
ACE Inhibitors		
Captopril	6.25 mg three times daily	50 mg three times daily
Enalapril	2.5 mg twice daily	10-20 mg twice daily
Fosinopril	5-10 mg daily	40 mg daily
Lisinopril	2.5-5 mg daily	20-40 mg daily
Perindopril	2 mg daily	8-16 mg daily
Quinapril	5 mg twice daily	20 mg twice daily
Ramipril	1.25-2.5 mg daily	10 mg daily
Trandolapril	1 mg daily	4 mg daily
Angiotensin Receptor Blockers		
Aldosterone		
Antagonists		
Candesartan	4-8 mg daily	32 mg daily
Eplerenone	25 mg daily	50 mg daily
Losartan	25-50 mg daily	50-100 mg daily
Spironolactone	12.5-25 mg daily	25 mg daily or twice daily
Valsartan	20-40 mg daily	160 mg daily

Note: Drugs are listed alphabetically and not in order of preference.

Adapted from Hunt SA: ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2005;46:e1-e82.

take 4 weeks.^{296,300} Asthmatic patients are not more susceptible to the cough side effect, but bronchospasm has been reported.³⁰¹ Patients who develop cough as a side effect on ACE inhibitor therapy should be switched to ARB therapy because of the high rate of recurrence with the same or another ACE inhibitor.²⁹²

Angioedema is a life-threatening complication of ACE inhibitor and ARB therapy. Angioedema is caused by two different mechanisms. One involves mast-cell degranulation that increases vascular permeability, and the other involves kinin-related causes, which are triggered by increased bradykinin levels and complement-related mediators that also increase vascular permeability. The angioedema caused by ACE inhibitor and ARB therapy is thought to be related to the kinin pathway rather than mast-cell degranulation. Urticaria and pruritus are usually not present in angioedema caused by the kinin pathway.

Angioedema typically occurs in 0.1% to 0.7% of patients treated with ACE inhibitors.^{296,302,303} Risk factors for angioedema include African-American race, a history of prior drug rash, age older than 65, and history of seasonal allergies.³⁰³ It starts within the first week of therapy, but delayed reactions several years later have been reported.^{302,304,305} When angioedema develops, there is a high risk of recurrence if ACE inhibitor therapy is continued.³⁰⁵ Angioedema has also been associated

with ARB therapy despite the belief that ARBs do not affect kinin metabolism,³⁰⁶⁻³⁰⁸ but its rate is lower than with ACE inhibitors. Patients started on ARB therapy after ACE inhibitor–induced angioedema have a higher risk of angioedema than the general population,^{304,309,310} but no large trials have been done to quantify this risk. A small retrospective review showed that 2 of 26 patients who were thought to have angioedema from ACE inhibitor therapy and switched to ARB therapy developed recurrent angioedema.³¹⁰ A careful risk-benefit assessment should be done before starting a patient who had angioedema from ACE inhibitor therapy on ARB therapy.^{304,309} Hereditary or acquired defects in complement 1-esterase inactivator, a component of the kinin pathway that regulates bradykinin, can be unmasked by ACE inhibitor or ARB therapy.^{296,309,311,312}

There have been concerns in various trials regarding ACE inhibitor and aspirin interactions. The CONSENSUS II, GUSTO-1, and EPILOG trials showed an association, with significantly lesser benefits in patients who were treated with aspirin and an ACE inhibitor.^{313,314} Other reviews did not find the same association, however.^{198,315-318} One review using non-randomized data of nearly 100,000 patients showed that 89% of patients taking an ACE inhibitor and aspirin had a similar benefit as patients taking an ACE inhibitor and no aspirin.³¹⁶ The consensus is that although there may be an interaction between ACE inhibitors and aspirin, it is of small magnitude, and the benefits of ACE inhibitor and aspirin outweigh this potential adverse drug reaction.¹⁰ Using smaller doses of aspirin seems to mitigate this interaction.³¹⁸

Summary of ACC/AHA Task Force Recommendations for Angiotensin-Converting Enzyme Inhibitors and Other Renin-Angiotensin-Aldosterone System Inhibitors in ST Segment Elevation Myocardial Infarction

ACC/AHA Task Force recommendations for ACE and other RAAS inhibitors in STEMI are summarized as follows.^{10,11}

Early Phase

- Patients with anterior STEMI, pulmonary congestion, and left ventricular ejection fraction less than 40%, without hypotension (systolic blood pressure <100 mm Hg or 30 mm Hg below baseline) or contraindications (i.e., ACE inhibitor intolerance), should be started on an oral ACE inhibitor within the first 24 hours (class I, evidence level A).
- An ARB, such as valsartan and candesartan, should be used in patients who are intolerant to ACE inhibitor therapy (class I, evidence level C).
- An oral ACE inhibitor in the first 24 hours of STEMI can also be used for patients with normal left ventricular ejection fraction in the absence of hypotension or contraindications and without anterior STEMI, pulmonary congestion, or ejection fraction less than 40% (class IIa, evidence level B).
- STEMI patients should not be given an intravenous ACE inhibitor in the first 24 hours because of the risk of hypotension (class III, evidence level B), with the possible exception of refractory hypertension.
- STEMI patients with pulmonary congestion should be given a short-acting ACE inhibitor, starting with a low dose (e.g., 1 to 6.25 mg of captopril), provided that there is no hypotension (systolic blood pressure <100 mm Hg or >30 mm Hg below baseline) (class I, evidence level A).

Convalescent Phase

- STEMI patients who tolerate an ACE inhibitor should be continued on it over the long-term (class I, evidence level A).
- An ARB, such as valsartan or candesartan, should be used in ACE inhibitor–intolerant STEMI patients with evidence of CHF or left ventricular dysfunction (ejection fraction <40%) (class I, evidence level B).¹¹
- An aldosterone antagonist should be added in patients without significant renal dysfunction (creatinine should be ≤ 2.5 mg/dL in men and ≤ 2 mg/dL in women) or hyperkalemia (potassium should be ≤ 5 mEq/L) who are already receiving an ACE inhibitor in therapeutic doses but have a left ventricular ejection fraction less than 40% and symptomatic heart failure or diabetes (class I, evidence level B).
- An ARB, such as valsartan or candesartan, can be useful as an alternative in STEMI patients who tolerate an ACE inhibitor, provided that there is evidence of heart failure or a left ventricular ejection fraction less than 40% (class IIa, evidence level B).

Postdischarge

- STEMI patients without contraindications at discharge should be prescribed a long-term ACE inhibitor (class I, evidence level A). A long-term aldosterone blocker should be prescribed for patients without renal dysfunction or hyperkalemia, who are receiving an ACE inhibitor and have an ejection fraction less than 40% and heart failure or diabetes (class I, evidence level A). A long-term ARB should be prescribed in ACE inhibitor–intolerant patients who have evidence of heart failure and ejection fraction less than 40% (class I, evidence level B). An ARB can be used as an alternative to an ACE inhibitor for the same indications (class IIa, evidence level B). An ACE inhibitor may be combined in the long-term if there is persistent heart failure and left ventricular dysfunction (class IIb, evidence level B).
- STEMI patients who are not at lower risk (i.e., normal left ventricular ejection fraction, well-controlled cardiovascular risk factors, and revascularization performed) should be started and continued indefinitely on ACE inhibitors unless contraindicated (class I, evidence level B).¹¹
- STEMI patients who are at lower risk can be given ACE inhibitors (class I, evidence level B).¹¹
- STEMI patients who are ACE inhibitor intolerant and have hypertension can be given an ARB (class I, evidence level B).¹¹
- STEMI patients who have heart failure secondary to systolic dysfunction can be given an ARB in combination with an ACE inhibitor (class IIb, evidence level B).¹¹

Calcium Channel Blockers

Calcium channel blockers (CCBs) are not helpful as adjunctive therapy in acute STEMI. Despite experimental and clinical evidence of anti-ischemic, cardioprotective, and antiremodeling effects, systematic overviews raise concern about an increased mortality risk with routine use of CCBs. Routine use of CCBs in patients with acute MI is not recommended.

Mode of Action

CCBs block the entry of calcium into cells or transmembrane calcium flux through voltage-dependent L-type and T-type calcium channels. The major sites of action are the vascular smooth

muscle cells, cardiomyocytes, and sinoatrial and AV node cells. The voltage-gated L-type calcium channel is long-acting, slow-activating, and blocked by all CCBs. The channel normally allows calcium entry for initiating contraction by calcium-induced calcium release from the sarcoplasmic reticulum. The T-type (transient) channel plays a role in depolarization of the sinoatrial and AV nodes. CCBs inhibit the slow inward calcium current, exert a negative inotropic effect on myocardium, and dilate vascular smooth muscle. As vasodilators, CCBs reduce myocardial oxygen demand and increase supply and are effective anti-ischemic and spasmolytic agents. They also reduce myocardial oxygen demand by decreasing heart rate and contractility.

CCBs were used in acute MI for limiting infarct size and limiting coronary vasospasm.³¹⁹⁻³²² They prevent calcium overload in ischemic cells. They are effective in postinfarction angina. CCBs have been classified into the dihydropyridines, such as nifedipine, and the nondihydropyridines, such as verapamil and diltiazem. Dihydropyridines cause more inhibition of vascular smooth muscle, and nondihydropyridines cause more inhibition of myocardial contractility.

Dose, Timing, and Benefits

Several studies evaluated the effect of CCBs in acute MI. A meta-analysis of the trials indicated that their routine use for treating acute MI did not reduce mortality or morbidity.³²³ The lack of benefit was probably attributable to reflex tachycardia, coronary steal from ischemic myocardium, negative inotropism, and decreased conduction.

Although nifedipine was thought to reduce infarct expansion in one study,³²⁴ its use is contraindicated in acute MI because of the lack of effect on infarct size and the potentially deleterious effects on survival. Nifedipine, a first-generation dihydropyridine CCB, has been studied in acute MI acutely and long-term.^{323,325-333} Data from trials such as TRENT and SPRINT I found no evidence of harm.^{325,326} Other trials such as SPRINT II,³²⁷ a trial by Muller and colleagues,³²⁸ and results from the Augsburg Myocardial Infarction Follow-up Study 1985-1993,³²⁹ found evidence of harm, however, with increased mortality rates when patients with MI were treated with nifedipine.³²⁷⁻³²⁹ There are other data showing harm with nifedipine.^{333,334} HINT was stopped early because of concern that nifedipine caused harm, but subset analysis showed that with the addition of metoprolol, nifedipine did have some benefit.^{334,335} Short-acting, immediate-release nifedipine may cause harm in STEMI by reducing coronary artery perfusion pressure, inducing coronary steal, and increasing reflex sympathetic activity, leading to increased myocardial oxygen demand, and does not reduce reinfarction or mortality. The unstable angina/NSTEMI and STEMI guidelines caution against using nifedipine.^{10,12}

DAVIT II showed that STEMI patients with normal ejection fraction started on immediate-release verapamil in the second week after admission had reduced mortality.³³⁶ Patients with depressed ejection fraction did not have the same mortality benefit, however, if they had evidence of CHF or depressed ejection fraction.³³⁶ CRIS, with verapamil in post-MI patients with normal ejection fraction and no CHF, showed no difference in mortality, but a nonsignificant reduction in reinfarction and a significant reduction in angina.³³⁷ The collective evidence indicates that verapamil is not beneficial in post-MI patients with CHF or depressed ejection fraction and may be harmful.^{323,338-340} Verapamil was detrimental in patients with

heart failure or bradycardia during the first 24 to 48 hours after STEMI.^{323,336,338,339} All trials used oral verapamil, and none showed a mortality benefit after STEMI.

Diltiazem was shown to reduce early reinfarction and recurrent angina in patients with non-Q wave MI (NSTEMI).³⁴¹ There is some evidence that early diltiazem is beneficial in MI.³⁴² A small pilot study of 69 patients presenting with STEMI and given thrombolytic therapy and intravenous diltiazem followed by oral diltiazem or placebo showed a benefit in early postinfarction ischemia and reinfarction at 35 days.³⁴³ Older trial data from MDPIT and DRS suggested a benefit of oral diltiazem in STEMI (Q wave MI) and NSTEMI (non-Q wave MI) patients with preserved ejection fraction and no signs of heart failure.^{323,338,341,344-346} The MDPIT patients with impaired ventricular function (ejection fraction <40%) did worse, however, in terms of mortality than patients with normal ventricular function. There were some potentially confounding factors with MDPIT because about 50% of the patients in the diltiazem and placebo groups were also treated with β -blockers. Also, diltiazem therapy was started 3 to 15 days after MI in MDPIT and 24 to 72 hours after MI in DRS.

Data from MDPIT and DRS showed, however, that there may be more benefit with diltiazem in NSTEMI and a harmful mortality effect in patients with left ventricular dysfunction. The INTERCEPT trial evaluated patients with STEMI and normal ejection fraction treated with thrombolytic therapy and placebo or oral diltiazem³⁴⁷ and showed no significant difference in the primary end point of death, reinfarction, or ischemia at 6-month follow-up. There have been no trials with diltiazem and primary PCI.

The 2004 ACC/AHA guidelines for STEMI¹⁰ and the 2007 guidelines for unstable angina/NSTEMI¹² support the use of nondihydropyridine CCBs such as verapamil and diltiazem (but not the dihydropyridine CCB nifedipine) for heart rate control when β -blocker therapy is contraindicated. Verapamil and diltiazem can also be used for refractory angina in addition to β -blocker therapy and nitrates.¹² Diltiazem, verapamil, and nifedipine all are contraindicated in patients with heart failure, poor ejection fraction, and AV block. None of the CCBs studied has been shown to reduce mortality in acute MI, and they may be harmful in patients with heart failure.

Adverse Effects

The main side effects of CCBs include hypotension, bradycardia, AV block, and worsening of CHF. Potential risk to the fetus during pregnancy indicates the need for caution.

Summary of ACC/AHA Recommendations for Calcium Channel Blockers in ST Segment Elevation Myocardial Infarction

ACC/AHA recommendations for CCBs in STEMI are summarized as follows.¹⁰

Early Phase

- For STEMI patients in whom β -blockers are ineffective or contraindicated (as for bronchospasm allergy to β -blockers), it is reasonable to give verapamil or diltiazem for the relief of ongoing ischemia, controlling rapid ventricular response in atrial fibrillation or flutter as long as there is no CHF, left ventricular dysfunction, or AV block (class IIa, evidence level C). Intravenous or oral short-acting or long-acting forms may be used.

- STEMI patients with left ventricular systolic dysfunction and CHF should *not* be given verapamil or diltiazem (class III, evidence level A). Immediate-release nifedipine should *not* be given because it causes reflex sympathetic activation, tachycardia, and hypotension (class III, evidence level B).

Convalescent Phase and Postdischarge

- No advice is provided in the 2004 guidelines.¹⁰ CCBs are effective in angina (equal in efficacy to β -blockers), coronary vasospasm, cold-induced angina, and supraventricular tachycardias. Verapamil is used in Scandinavian countries for post-MI protection on the basis of a modest benefit in the Danish DAVIT-1 and DAVIT-2 trials.³³⁶ Short-term diltiazem also reduced recurrent ischemia and infarction.³⁴¹ New-generation CCBs continue to be evaluated for their potential value for stunned myocardium, cardioprotection during CABG surgery, and antiremodeling therapy. Second-generation dihydropyridine CCBs (e.g., amlodipine and felodipine) relax smooth muscle, reduce blood pressure, and have little effect on inotropism or heart rate. They have not been studied in acute MI. Evidence from multiple CHF and stable angina trials shows that these agents cause no harm even in patients with low ejection fraction and do not worsen ejection fraction.³⁴⁸⁻³⁵⁴

Magnesium

Experimental and clinical studies suggested that early magnesium in MI might limit infarct size, prevent serious arrhythmias, and reduce mortality. Meta-analyses of seven trials from 1984-1991 suggested the efficacy of magnesium therapy for reducing mortality in acute MI (4.4% absolute risk reduction).^{355,356} The ISIS-4 trial, mounted in part to test the hypothesis that 24 hours of intravenous magnesium sulfate (8 mmol initial bolus, followed by 72 mmol) might improve survival, indicated no significant reduction in 5-week mortality and perhaps a slight increase (7.64% versus 7.24%).¹⁹⁸ There was an excess of heart failure and cardiogenic shock during or after the infusion, an increase in hypotension requiring termination of treatment, and cutaneous flushing, but no net effect on early 0- to 1-day mortality.¹⁹⁸ The subsequent LIMIT-2 showed a mortality benefit (2.5% absolute risk reduction).³⁵⁷ The MAGIC trial using early intravenous magnesium in high-risk STEMI patients showed no mortality benefit at 30 days (15.3% versus 15.2%).³⁵⁸

Evidence from 68,684 patients in 14 trials from 1980-2002 does not support routine use of magnesium for treating STEMI patients.^{10,358-372} Magnesium should be used, however, for treating hypomagnesemia and ventricular arrhythmias such as torsades de pointes.¹⁰ Serum magnesium (and potassium) levels should be checked on admission because electrolyte deficits increase the risk of arrhythmias after MI. A magnesium deficit may develop in STEMI patients because of diet, aging, and prior diuretic use. It is often difficult to correct a potassium deficit when a concurrent magnesium deficit is present.

Summary of ACC/AHA Task Force Recommendations for Magnesium in ST Segment Elevation Myocardial Infarction

ACC/AHA Task Force recommendations for magnesium in STEMI are summarized as follows.¹⁰

Early Phase

- It is reasonable to correct magnesium deficits, especially in patients receiving diuretics before STEMI (class IIa, evidence level C), and to treat torsades de pointes with magnesium (1- to 2-g intravenous bolus over 5 minutes) (class IIa, evidence level C). Otherwise, routine intravenous magnesium should *not* be used in STEMI (class III, evidence level A). There is no definite advice on subsequent use of magnesium.

Lidocaine

Cardiac arrhythmias are common after STEMI and after reperfusion. Most episodes of ventricular fibrillation and ventricular tachycardia occur in the first 48 hours. The pharmacologic management of ventricular fibrillation and ventricular tachycardia after STEMI has been reviewed.¹⁰ The prophylactic use of lidocaine in early MI was controversial before.⁹ Its use in patients at high risk for developing ventricular fibrillation is declining in the era of reperfusion, β -blockers, and antiarrhythmic agents such as amiodarone and procainamide.¹⁰

A meta-analysis of 14 trials with lidocaine indicated a 33% reduction in the risk for developing primary ventricular fibrillation, but no mortality benefit and an increased risk of bradycardia and fatal asystole.³⁷³ Lidocaine was recommended for the control of ventricular premature beats that are more frequent than six per minute, are closely coupled (R-on-T), are multiform, or occur in bursts of three or more, and for ventricular tachycardia or ventricular fibrillation resistant to defibrillation.⁹ In GUSTO-I and GUSTO-IIb, the prophylactic use of lidocaine in STEMI patients showed no mortality benefit, however.³⁷⁴ Evidence that intravenous β -blockers decrease early ventricular fibrillation in patients without contraindications³⁷⁵ supports the use of metoprolol (5 mg intravenously every 2 minutes for three doses, followed by 50 mg orally twice daily for 24 hours, and 100 mg twice daily subsequently) or atenolol (5 to 10 mg intravenously followed by 100 mg daily) for early ventricular fibrillation.¹⁰ In CAST, patients receiving class I antiarrhythmic drugs for suppression of ventricular premature beats fared poorly compared with patients given placebo,³⁷⁶ so this goal is no longer pursued after STEMI.¹⁰ No prophylactic antiarrhythmic therapy should be used when fibrinolytics are used (class III, evidence level B).¹⁰

Free Radical Scavengers

Although thrombolytic therapy is highly effective for myocardial salvage and in limiting ventricular remodeling,^{377,378} reperfusion injury and damage induced by oxygen free radicals are serious problems.^{7,8,379} Superoxide dismutase therapy has been shown to reduce infarct size in late reperfusion models.³⁸⁰ Experimental and clinical studies continue to evaluate new agents aimed at reducing reperfusion injury and improving ventricular function, such as iloprost, human recombinant superoxide dismutase, Fluosol, and others. None of these agents are currently recommended as adjunctive therapy for patients with acute STEMI.

Morphine

Morphine sulfate is the analgesic of choice for managing pain in patients with STEMI. Typically, the pain control algorithm involves a combination of opiate analgesics, nitrates, β -blockers, and oxygen.

Mode of Action, Dosage, and Benefits

Morphine binds to central nervous system receptors, preventing them from transmitting pain signals to the brain. In acute MI, morphine has analgesic, anxiolytic, and hemodynamic properties. It relieves pain that contributes to the hyperadrenergic state, decreases blood pressure via arterial dilation and venodilation, decreases heart rate via increased vagal tone and withdrawal of sympathetic tone, decreases myocardial oxygen demand, and relieves pulmonary edema. There have been no randomized controlled trials describing dosing. A dose of 2 to 4 mg intravenously, with increments of 2 to 8 mg intravenously repeated at 5- to 15-minute intervals, is commonly used.¹⁰⁻¹²

The most common side effects of morphine are nausea and vomiting, with 20% of patients affected.¹² Adverse effects include hypotension, especially prominent in patients who are volume depleted or have been given vasodilator therapy. Treatment of morphine-induced hypotension includes placing the patient in a supine or Trendelenburg position and administering intravenous saline boluses, with the addition of atropine (0.5 to 1.5 mg intravenously) for concomitant bradycardia.^{10,12} Rarely, the narcotic antidote naloxone (0.1 to 0.2 mg intravenously) or an inotropic agent is required. Respiratory compromise from morphine overdose can be treated with naloxone (0.4 to 2 mg intravenous boluses) and very rarely may require intubation for respiratory support. Other narcotics should be considered in patients with severe side effects or allergic reactions to morphine.

Evidence from an observational study reporting increased mortality (odds ratio of 1.41; 95% confidence interval 1.26 to 1.71) in unstable angina/NSTEMI patients treated with morphine³⁸¹ led the ACC/AHA guideline panel to downgrade its recommendation for patients from class I to class IIb.¹² Its use remains as a class I recommendation, however, for the relief of continuing pain in STEMI patients.¹¹

Summary of ACC/AHA Task Force Recommendations for Morphine in ST Segment Elevation Myocardial Infarction

ACC/AHA Task Force recommendations for morphine in STEMI are summarized as follows.¹⁰

- Morphine should be used to manage pain associated with STEMI (class I, evidence level C) along with other anti-ischemic therapy.

Glycemic Control and Insulin

Acute STEMI is associated with low insulin and increased catecholamines, cortisol, glucagon, and free fatty acids, which lead to increased blood glucose. Elevated glucose levels in the post-MI period correlate with increased mortality.³⁸² The first DIGAMI study showed that controlling elevated glucose reduces mortality in the acute post-MI period and up to 1 year.^{383,384} Intensive and standard therapies in DIGAMI 2 showed similar glycemic control and no difference in mortality, however.³⁸⁵ The American Diabetes Association emphasizes glucose control in the post-MI period.³⁸⁶ The target should be less than 180 mg/dL (<10 mmol/L)³⁸³ or less than 140 mg/dL (<7.8 mmol/L).^{387,388} The data are especially strong for critically ill patients.^{387,389,390} There is evidence, however, for a U-shaped curve for the relationship between mortality and blood glucose in patients with acute MI.^{391,392}

Glucose-insulin-potassium infusions in STEMI were evaluated, mostly in the era preceding reperfusion, and suggested benefit. A subsequent trial in 20,201 STEMI patients did not show a mortality benefit, however.³⁹³

Besides the need for tight glycemic control in diabetics and nondiabetics in the early phase of acute STEMI, diabetic patients need glycemic control during the convalescent and postdischarge phases. Long-term management may require insulin or oral hypoglycemic agents or both.^{394,395}

Summary of ACC/AHA Task Force Recommendations for Glycemic Control in ST Segment Elevation Myocardial Infarction

ACC/AHA Task Force recommendations for glycemic control in STEMI are summarized as follows.¹⁰

Acute Phase

- Insulin infusion should be given to normalize blood glucose in STEMI patients with complicated courses (class I, evidence level B). Insulin infusion during the first 24 to 48 hours is reasonable for managing STEMI patients with hyperglycemia even in patients with an uncomplicated course (class IIa, evidence level B).
- Glucose control should be targeted at less than 180 mg/dL (<10 mmol/L) for all post-MI patients. Critically ill cardiac patients (cardiogenic shock) may benefit from even further aggressive control of glucose to less than 140 mg/dL (<7.8 mmol/L).

Convalescence

- It is reasonable to individualize treatment of diabetics after the acute phase of STEMI with insulin, insulin analogues, and oral hypoglycemic agents for the best glycemic control (class IIa, evidence level C).

3-Hydroxy-3-methylglutaryl Coenzyme A Reductase Inhibitors or Statins

Statins are competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which is a rate-limiting step in cholesterol synthesis. All statins reduce low-density lipoprotein (LDL) cholesterol, and some also increase high-density lipoprotein (HDL) (e.g., simvastatin, rosuvastatin) and reduce triglycerides (e.g., atorvastatin, rosuvastatin). Evidence shows secondary prevention and mortality benefits with lowering of cholesterol in patients with hypercholesterolemia after MI³⁹⁶ and even patients with mild cholesterol elevation.^{397,398} Lowering cholesterol in patients with normal LDL level is also beneficial.³⁹⁹⁻⁴⁰¹ The REVERSAL trial showed that aggressive lipid lowering prevented progression of atheroma in patients with known coronary artery disease.⁴⁰² ASTEROID showed that very high intensity statin therapy was effective for regression of coronary atherosclerosis.⁴⁰³ Aggressive lipid lowering has been shown to decrease atheroma burden⁴⁰³ and is beneficial in all patients with coronary artery disease.

Early studies on the use of statin therapy for STEMI patients excluded the acute phase and began statin therapy months later.¹⁰ Studies such as PROVE-IT⁴⁰¹ and MIRACL⁴⁰⁴ showed, however, that aggressive lipid lowering in patients with acute coronary syndromes including STEMI is beneficial in the acute setting.

Patients after STEMI should be started on statins for secondary prevention. Starting therapy while the patient is in the hospital improves adherence, with no noted adverse effects,^{405,406} and adherence improves survival.⁴⁰⁷ The National Cholesterol Education Program (NCEP) guidelines recommend the in-hospital initiation of statin therapy.⁴⁰⁸ The target LDL level in the NCEP guidelines is 100 mg/dL or less,⁴⁰⁹ although reducing LDL to less than 70 mg/dL should be considered in very-high-risk patients.⁴⁰⁸ It is recommended that post-STEMI cholesterol be aggressively lowered with high-dose statins (e.g., atorvastatin, 80 mg daily); the dose should be titrated down if the patient develops side effects.

Side effects include elevated aminotransferases, myopathies, and drug interactions. Aminotransferase elevations can occur in 3% of patients taking statins; however, a meta-analysis of 35 trials found that the risk difference between patients taking statins and patients receiving placebo was 4.2 patients per 1000.⁴¹⁰ The FDA guidelines ask that liver enzyme testing be done before the initiation of statin therapy and repeated 12 weeks after that, at any dose elevation, and periodically. Statin therapy should be changed if aminotransferases remain elevated to three times normal. Statin-induced myopathies range from benign myalgias to rhabdomyolysis. Creatine kinase levels should be measured before the initiation of therapy. Clinically significant myopathy is defined as muscle symptoms with creatine kinase elevation 10 times normal. It occurs in less than 1% of patients treated with statins.⁴¹¹⁻⁴¹⁴ If the creatine kinase elevation is thought to be due to statin therapy, the statin should be discontinued.

Drug interactions are common because statins are metabolized by the cytochrome P450 enzyme system, specifically CYP3A4. The metabolism of clopidogrel is inhibited by atorvastatin.⁴¹⁵ The only exceptions are pravastatin or rosuvastatin. Although a listing of all interactions is impossible here, the clinician should be aware of them. A common interaction is between gemfibrozil and a statin other than pravastatin, which can lead to increased risk of rhabdomyolysis. Fenofibrate is safer than gemfibrozil in this respect. Other interactions include interactions with cyclosporine, macrolide antibiotics, and human immunodeficiency virus protease inhibitors.

Summary of ACC/AHA Task Force Recommendations for Lipid Management in ST Segment Elevation Myocardial Infarction

ACC/AHA Task Force recommendations for lipid management in STEMI are summarized as follows.¹⁰

- On discharge, all STEMI patients should be started on dietary therapy low in saturated fat and cholesterol, with increased consumption of omega-3 fatty acids, fruits, vegetables, soluble fiber and grains, and a balanced calorie intake.
- In the hospital, a fasting lipid profile should be done or obtained within 24 hours of symptom onset (class I, evidence level C), and the target LDL cholesterol should be maintained at less than 100 mg/dL (class I, evidence level A), prescribing drug therapy on discharge, preferably a statin, in patients with LDL cholesterol 100 mg/dL or greater (class I, evidence level A). Patients with LDL cholesterol less than 100 mg/dL or unknown should also be prescribed statin therapy (class I, evidence level B). In addition, patients with non-HDL cholesterol less than 130 mg/dL and HDL cholesterol less than 40 mg/dL should be placed on nonpharmacologic therapy (lifestyle management) to increase HDL (class I, evidence level B).

- It is reasonable to prescribe drug therapy (preferably statins) on discharge in patients with non-HDL cholesterol of 130 mg/dL or greater and LDL cholesterol less than 100 mg/dL or patients with unknown LDL cholesterol levels, with the goal of reducing non-HDL cholesterol to much less than 130 mg/dL (class IIa, evidence level B). It is also reasonable to prescribe drugs such as niacin or fibrate on discharge to increase HDL cholesterol to 130 mg/dL or greater in patients with LDL cholesterol less than 100 mg/dL or non-HDL cholesterol less than 130 mg/dL but HDL cholesterol less than 40 mg/dL (class IIa, evidence level B). It is also reasonable to add drug therapy (niacin or fibrate) to the diet regardless of LDL and HDL levels when triglyceride levels are greater than 500 mg/dL (class IIa, evidence level B).

Anticoagulants

Anticoagulants are useful as adjunctive therapy during convalescence and for secondary prevention after discharge following STEMI (Table 13-6). They can be used to prevent formation or progression of coronary thrombi, limit the formation of mural left ventricular thrombi and systemic embolization, and limit venous thrombosis and pulmonary embolism. Anticoagulants include heparin, unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), synthetic heparins such as fondaparinux and bivalirudin, and warfarin (Coumadin) (see Table 13-6; see also Chapters 9 and 13). A useful algorithm for adjunctive antithrombotic therapy after discharge includes warfarin and antiplatelet agents such as aspirin and clopidogrel (Fig. 13-8).¹⁰

Modes of Action

Thrombin is a key protease of the coagulation system. Thrombin inhibitors (e.g., heparin, UFH, and LMWH) prevent the formation of thrombin and inhibit the activity of already formed thrombin. Heparin is a mixture that consists of 66% high-molecular-weight (average mass 20 kD) and 33% low-molecular-weight (average mass 7 kD) fractions. The low-molecular-weight fraction has 85% of the total anticoagulant activity and causes little platelet activation, whereas the high-molecular-weight fraction has weak anticoagulant activity and can activate platelets. The two fractions consist of subspecies with varying antithrombin III affinity, and the low-molecular-weight fraction has high affinity for antithrombin III.

UFH is a mixture of glycosaminoglycan chains (molecular weights 5 to 3 kD) that produces its anticoagulant effect by binding to antithrombin III, which inactivates factor IIa (thrombin), factor IXa, factor Ia, and factor Xa (see Fig. 13-4). UFH prevents growth of existing thrombus, but does not lyse it.⁴¹⁶ LMWH (molecular weights 2 to 9 kD) produces more potent inactivation of factor Xa than thrombin, whereas UFH produces equal inhibition of factor Xa and thrombin. Fondaparinux is a synthetic heparin polysaccharide that binds to antithrombin with higher affinity than either UFH or LMWH and causes a conformational change that results in preferential increase in the ability of the antithrombin-fondaparinux complex to inactivate factor Xa. Direct thrombin inhibitors such as hirudin bind and inactivate thrombin⁴¹⁷ without need for a cofactor, but have little effect on generation of thrombin. Bivalirudin is a synthetic analogue of hirudin that binds reversibly to thrombin and inhibits clot-bound thrombin.

Table 13-6. Duration of Antiplatelet and Anticoagulant Therapy

Duration of Therapy	
Oral Antiplatelet Therapy	
Aspirin	Lifelong
Clopidogrel/ticlopidine	If patient had bare metal stent, minimum 1 mo
	If patient had drug-eluting stent, minimum 1 yr
	If patient has not been revascularized, can continue clopidogrel or ticlopidine for up to 1 yr
Anticoagulant Therapy	
Unfractionated heparin (intravenous)	Up to 48 hours, provided no other contraindications to discontinuation
	Can discontinue when patient has been revascularized by stenting
Low-molecular-weight heparin	Up to 8 days or duration of hospitalization, provided no other contraindications to discontinuation
	Can discontinue when patient has been revascularized by stenting
Fondaparinux	Up to 8 days or duration of hospitalization, provided no other contraindications to discontinuation
	Can discontinue when patient has been revascularized by stenting
Bivalirudin	Up to 3 days, provided no other contraindications to discontinuation
	Can discontinue when patient has been revascularized by stenting
Warfarin	If patient has left ventricular thrombus or aneurysm, 3 mo to lifelong therapy

Thrombin amplifies the generation of factor VIIIa and factor Va, enhancing thrombus formation. Thrombin also promotes platelet activation by binding to platelet thrombin receptors. Cross-linked fibrin polymer formation, via fibrinogen (factor I) and platelet GP IIb/IIIa receptors, leads to platelet aggregation (see Fig. 13-4). Thrombin also activates factor XIII (fibrin stabilizing factor) to factor XIIIa, which cross-links covalently with fibrin polymer and stabilizes clot.

The endogenous fibrinolytic system is activated to dispose of fibrin. Plasmin, the key protease of this system, is formed from plasminogen via cleavage by plasminogen activators such as tissue-type plasminogen activator and urokinase-type plasminogen activator. This conversion is modulated by plasminogen activator inhibitors PAI-1 and PAI-2. Plasmin cleaves fibrin to fibrin degradation products that have potent anticoagulant and antiplatelet actions (see Fig. 13-4). This conversion is modulated by α_2 -antiplasmin. The regulation of physiologic fibrinolysis involves plasminogen activator inhibitors and α_2 -antiplasmin and thrombin-activatable fibrinolysis inhibitor (TAFI), which is

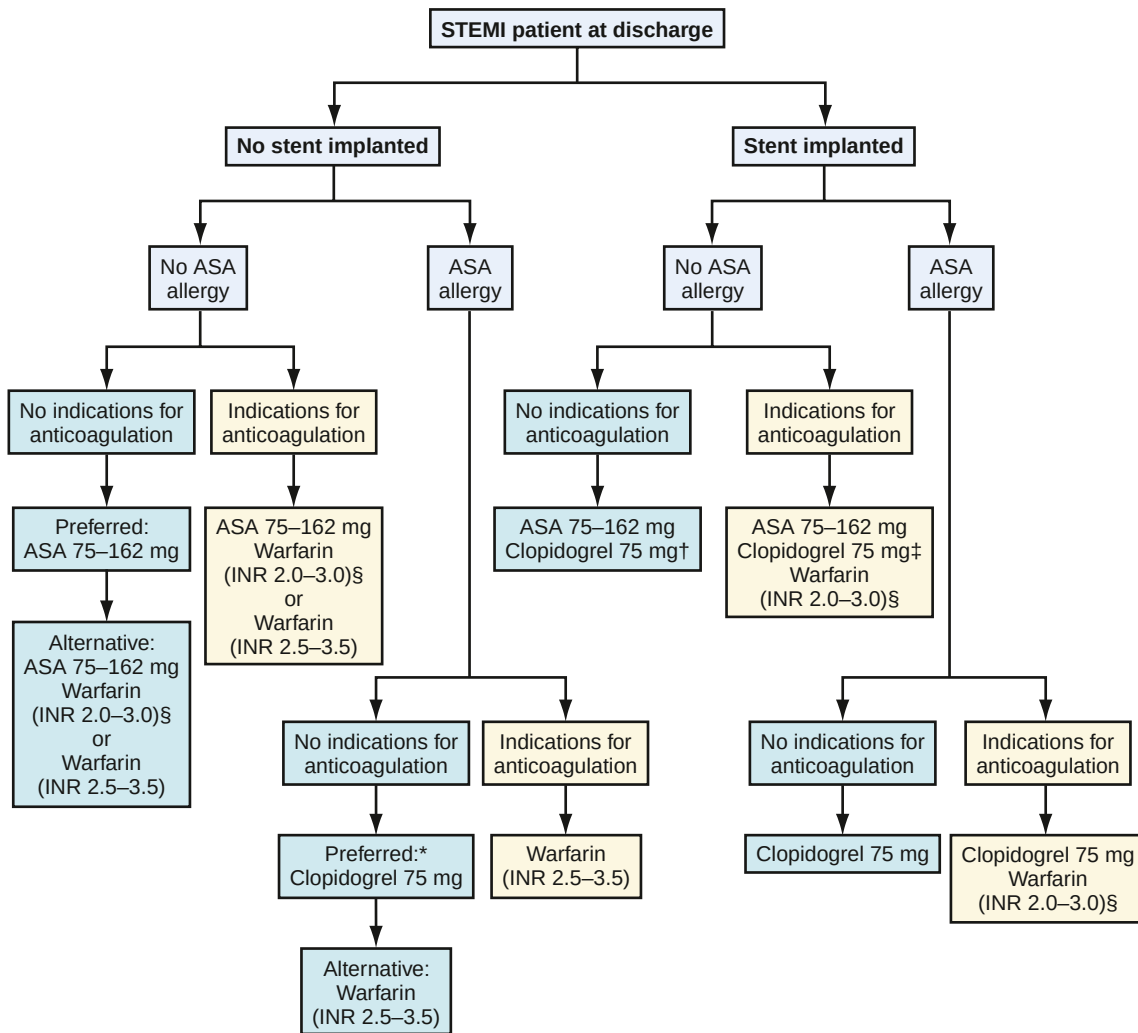


Figure 13-8. Algorithm for antithrombotic therapy at hospital discharge after ST segment elevation myocardial infarction (STEMI).

*Clopidogrel is preferred over warfarin because of increased risk of bleeding and low patient compliance in warfarin trials. †For 12 months.

‡Discontinue clopidogrel 1 month after implantation of a bare metal stent or several months after implantation of a drug-eluting stent

(3 months after sirolimus, 6 months after paclitaxel) because of potential increased risk of bleeding with warfarin and two antiplatelet agents. Continue aspirin (ASA) and warfarin long-term if warfarin is indicated for other reasons, such as atrial fibrillation, left ventricular thrombus, cerebral emboli, or extensive regional wall-motion abnormality. §An international normalized ratio (INR) of 2.0 to 3.0 is acceptable with tight control, but the lower end of this range is preferable. The combination of antiplatelet therapy and warfarin may be considered in patients younger than 75 years with low bleeding risk who can be monitored reliably. (Modified from Antman EM, Anbe DT, Armstrong PW, et al: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction—executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [Writing Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction]. *Circulation* 2004;110:588-636.)

activated by thrombin. Elevated TAF1 and TAF1 polymorphism may increase the risk of venous thrombosis and thromboembolism in patients with high factor VIII, factor IX, or factor XI levels. GP IIb/IIIa inhibitors (e.g., abciximab, eptifibatide, tirofiban) exert their effect at the final step of platelet aggregation (see Fig. 13-4).

Warfarin and coumarin derivatives inhibit the synthesis of vitamin K-dependent coagulation factors (e.g., II, VII, IX, and X) and other anticoagulant factors such as proteins C, S and Z. Because of a narrow therapeutic index; the need for stringent dose management; and interactions with drugs, foods, and comorbid conditions, warfarin may be replaced by orally active direct thrombin inhibitors.

Dosing, Timing, Benefits, and Adverse Effects

Evidence from the prethrombolytic era suggested that heparin produced a small (about 17%) decrease in mortality, so heparin was recommended as a prophylactic anticoagulant for preventing rethrombosis in all patients with acute MI.⁶⁰ Heparin is highly effective in preventing recurrent or new thrombus formation.^{49,60} It is started early, with or after thrombolytic therapy and continued over several days. In the United States, it is given intravenously, as a bolus followed by an infusion to maintain the activated partial thromboplastin time between 1.5 and 2 times control values (i.e., between 60 and 85 seconds). It is safely given together with low-dose aspirin.⁶⁰ Heparin is an adequate adjunctive agent in patients receiving the fibrin-specific recombinant

tissue plasminogen activator.⁴¹⁸ The risk of intracerebral bleed is considered minor (<3 per 1000).

In GUSTO-1,⁴¹⁹ in which intravenous and subcutaneous heparin and systemic activator streptokinase were used, an optimal activated partial thromboplastin time of between 60 and 70 seconds was associated with the lowest mortality, least bleeding complications, least reinfarction rate, and lowest frequency of hemorrhagic shock. Intravenous heparin should be given cautiously or not at all, however, when streptokinase is used, unless it is specifically indicated, as for intracavitary thrombus. Prolonged heparin is effective in preventing left ventricular thrombus after acute MI, and the response is proportional to the dose.⁴²⁰

An advantage of LMWH over UFH is that it does not require blood monitoring for titrating dose to a therapeutic activated partial thromboplastin time. Use of LMWH in patients with renal failure requires frequent monitoring of anti-factor Xa,⁴²¹ however, because it increases when creatinine clearance is less than 30 mL/min.⁴²² Side effects with both types of heparin include bleeding, thrombocytopenia, and osteoporosis. Patients at high risk for bleeding include women; elderly patients (>65 years old); and patients with comorbid states such as peptic ulcer, liver disease, and malignancy.⁴²³⁻⁴²⁵ Intravenous protamine can be used to reverse UFH.

Heparin-induced thrombocytopenia (HIT) is a well-known complication of UFH and LMWH therapy. Two types of HIT are recognized.⁴²⁶ HIT type I occurs in the first 4 days with a platelet nadir of 100,000/mm³, resolves even with continued therapy, and is thought to be non-immune related.⁴²⁷ HIT type II occurs within 5 to 10 days in 1% to 3% of patients and is immune-mediated.⁴²⁸ It should be suspected when the platelet count decreases more than 50%, or if there is evidence of venous or arterial thrombosis or evidence of necrosis at heparin injection sites.⁴²⁹ LMWH is associated with lower rates of HIT than UFH.⁴³⁰

Monitoring of platelet counts is recommended for patients on heparin therapy. Patients exposed to heparin during the previous 3 months can develop early HIT type II owing to circulating antibodies.^{428,431} Management of HIT type II includes immediate discontinuation of LMWH or UFH, with careful attention to routine heparin flushes and heparin-bonded catheters.⁴³² Patients who have a history of HIT type II should not be re-exposed to either type of heparin because a recurrence can be expected 2 to 3 days after re-exposure. A HIT assay can be done to ensure that antibodies are no longer detectable before restarting heparin. STEMI patients who still require anticoagulation with heparin can be given bivalirudin.¹⁰ Because of its long half-life, LMWH should not be used.

Heparin therapy in conjunction with thrombolytic therapy or primary PCI is addressed elsewhere. There have been no randomized controlled studies or new data to guide the management of STEMI patients who do not undergo reperfusion therapy. As part of the trial design, ISIS-2 patients were treated with aspirin and subcutaneous or intravenous UFH and did not show a survival advantage in the intravenous heparin group.³ Other trials showed that heparins induce less overall systemic anticoagulant effect and less breakdown of fibrinogen or depletion of coagulation factors.⁴³³ Although postlytic intravenous UFH increased bleeding in other trials, a statistically nonsignificant 18% decrease in mortality was also found.⁴³⁴ The LATE trial, designed to test alteplase versus placebo, showed lower

mortality in the group that received off-protocol intravenous heparin.⁴³⁵

It is recommended that STEMI patients who require heparin be given UFH as an intravenous infusion, with a bolus of 60 U/kg (maximum 4000 U) followed by infusion of 12 U/kg/hr (maximum 1000 U/hr). Weight-based initial dosing for intravenous heparin is preferred⁴³⁶ because of evidence that the effects of heparin are primarily mediated by weight.⁴³⁷ A useful target is an activated partial thromboplastin time range of 50 to 70 seconds, or 1.5 to 2 times control values, based on data showing that ranges above this have increased risks of bleeding, stroke, and mortality, whereas ranges below this have increased mortality.^{437,438} Anticoagulation can be continued beyond 48 hours after thrombolytic therapy in patients at high risk for thromboembolism, such as anterior STEMI, severe left ventricular dysfunction, CHF, history of systemic or pulmonary embolization, atrial fibrillation, or echocardiographic evidence of thrombus.^{10,439,440}

LMWH for the management of STEMI has also been studied. CREATE⁴⁴¹ randomly assigned 15,570 patients in India and China presenting with STEMI or new left bundle branch block, who had reperfusion therapy with either primary PCI or thrombolytic therapy, to LMWH (reviparin) or placebo. Subgroup analysis showed benefits in the patients who did not receive reperfusion therapy. Overall, LMWH prolonged survival regardless of whether the patient had primary PCI, lytic therapy, or no reperfusion therapy.⁴⁴¹ TETAMI compared UFH and LMWH in patients who did not receive reperfusion therapy.⁴⁴² The patients who were ineligible for acute reperfusion therapy were randomly assigned to UFH or enoxaparin and to placebo or tirofiban. The groups treated with UFH and placebo versus enoxaparin and placebo showed no difference in overall mortality.

The effect of the factor Xa inhibitor fondaparinux (2.5 mg/day) was studied in the OASIS-6 trial of 12,092 STEMI patients.⁴⁴³ The patients were divided into two strata. The first stratum, consisting of 5658 patients with no indication for heparin, was assigned to fondaparinux, 2.5 mg daily, early and for up to 8 days, or placebo; the second stratum, consisting of 6434 patients with an indication for heparin (e.g., fibrin-specific thrombolytic, primary PCI, or no reperfusion), was assigned to fondaparinux for up to 8 days or UFH for 48 hours. The results showed a reduction in 30-day mortality or reinfarction with fondaparinux compared with control (from 11.2% to 9.7%), with benefits apparent at 9 days and driven primarily by reductions in stratum 1. In stratum 2 patients who were not managed with primary PCI, fondaparinux was superior to UFH in preventing death or reinfarction at 30 days. The overall findings indicated that in STEMI patients who are not managed with primary PCI, fondaparinux reduces mortality and reinfarction without increasing bleeding and strokes.⁴⁴³

There are some theoretical advantages in using a direct thrombin inhibitor over heparin. After thrombolytic therapy, a procoagulant state is induced by thrombin bound to soluble fibrin derivatives.⁴⁴⁴ In contrast to direct thrombin inhibitors, a heparin-antithrombin III complex is unable to inactivate a thrombin-bound clot because it cannot penetrate the clot.⁴⁴⁵ Activated platelets have been documented to release heparin inhibitory factors that neutralize heparin but have no effect on the thrombin inhibitor hirudin.⁴⁴⁶ The direct thrombin inhibitor bivalirudin has also been studied in patients undergoing

thrombolytic therapy.^{447,448} Bivalirudin can be used as an alternative to heparin in patients with HIT.¹⁰ A useful dose regimen is to give an initial bolus of 0.25 mg/kg intravenously followed by an infusion at 0.5 mg/kg/hr for 12 hours, and 0.25 mg/kg/hr for the next 36 hours for a total of 48 hours.⁴⁴⁸

Several pathways are involved in platelet activation besides TXA₂ stimulation (blocked by aspirin) and ADP-mediated platelet activation (blocked by clopidogrel). Vascular injury exposes subendothelial von Willebrand factor or collagen to blood. Platelets adhere, and the GP IIb/IIIa receptors on activated platelets (see Fig. 13-4) help to bind platelets to fibrinogen or von Willebrand factor. Cross-linking occurs between other platelets as the final step in platelet activation, with the help of fibrinogen and the GP IIb/IIIa receptors.⁴⁴⁹ Side effects of GP IIb/IIIa inhibitors include increased risk of bleeding and thrombocytopenia. The risk of bleeding is increased by the concurrent use of other anticoagulants (e.g., aspirin, clopidogrel, heparin) in typical STEMI patients.

A careful risk-benefit analysis is needed before starting GP IIb/IIIa inhibitors. Two types of thrombocytopenia may develop with their use⁴⁵⁰ and must be distinguished. Pseudothrombocytopenia is benign and is due to platelet clumping induced by anticoagulant in the tube used for taking blood. True thrombocytopenia can also occur, and is more likely with abciximab than with tirofiban or eptifibatide. Thrombocytopenia with abciximab occurs within the first 24 hours, and even in the first 30 minutes of the infusion,⁴⁵¹ but occurs much later with other drugs.⁴⁵² A meta-analysis of patients treated with GP IIb/IIIa inhibitors showed higher rates of thrombocytopenia.⁴⁵³ Significant clinical events have been reported, including higher death rates and MI, and need for revascularization and blood transfusions.⁴⁵⁴ Platelet counts and hemoglobin should be monitored during GP IIb/IIIa inhibitor therapy. Re-exposure to the drug should be avoided because the risk of developing thrombocytopenia again is increased.⁴⁵⁵ The use of GP IIb/IIIa inhibitors in STEMI depends on whether the patient proceeds to have primary PCI, primary thrombolysis, or no reperfusion. Patients who do not receive reperfusion therapy do not show any benefit from adjuvant GP IIb/IIIa therapy and should not receive it.⁴⁴²

The ACC/AHA guidelines do not recommend GP IIb/IIIa inhibitors for achieving reperfusion in STEMI.^{10,11,456} The evidence for the combination of GP IIb/IIIa inhibitors and thrombolytics is weak; this treatment is associated with little mortality benefit and increased bleeding risk.¹⁰ There are recommendations for use of GP IIb/IIIa inhibitors, such as abciximab (class IIa, evidence level B) and tirofiban and eptifibatide (class IIb, evidence level C), in conjunction with primary PCI for STEMI.⁵⁷

Warfarin dosing is highly dependent on the individual and dietary vitamin K intake, and should be titrated by measuring the patient's response through the INR. The antithrombotic properties of warfarin do not occur until 72 to 96 hours. Its major side effect is related to its anticoagulant effect, which may be reversed with vitamin K or fresh frozen plasma. After MI, thrombotic risk is augmented because of culprit lesion progression and elevation of thrombin,^{457,458} so long-term warfarin therapy may reduce cardiac events. An uncommon but serious side effect of warfarin therapy, typically following large loading doses, is skin necrosis, which occurs in the first few days of therapy,⁴⁵⁹ and may be related to protein C deficiency.⁴⁶⁰ Treatment

of warfarin-induced skin necrosis includes stopping warfarin, administering protein C,⁴⁶¹ giving vitamin K to reverse warfarin, and switching to intravenous heparin for anticoagulation. In patients who still require oral anticoagulation, warfarin has been started at low doses together with protein C to ensure there is no deficiency.^{462,463}

Several trials and meta-analyses have assessed the effectiveness of long-term anticoagulation with varying levels of target INRs from low level to high intensity (<1.5, 1.5 to 2.5, >2.5).⁴⁶⁴⁻⁴⁷⁶ A large meta-analysis showed that warfarin therapy reduced stroke and MI rates, but did not reduce mortality and almost doubled bleeding rates.⁴⁶⁵ The trials included in that meta-analysis looked at patients on warfarin and aspirin, but not clopidogrel. Current management practices with early revascularization imply that patients will be receiving clopidogrel for some time. There have been no trials on the safety or efficacy of the combination of aspirin, clopidogrel, and warfarin. STEMI patients should be considered for long-term warfarin therapy for secondary prevention, provided that they have no risk factors for bleeding, and their INRs can be reliably monitored.¹⁰ This recommendation has been challenged,⁴⁷⁷ however, and warfarin is recommended only if there are established indications for patients with unstable angina/NSTEMI.¹²

Indications for long-term warfarin use after STEMI include atrial fibrillation and evidence of left ventricular thrombus or aneurysm or both. There have been no randomized controlled studies of warfarin for left ventricular thrombus, but such patients have been studied in multiple observational trials.⁴⁷⁸⁻⁴⁸³ A meta-analysis showed that anticoagulated patients had an 86% reduction in embolization rate.⁴⁴⁰ Most embolic events occur within 4 months.^{478,484,485} Anticoagulation with warfarin for at least 3 to 6 months is recommended for STEMI patients with a left ventricular thrombus, and indefinitely in patients with low risk of bleeding.¹⁰ The AHA/American Stroke Association guidelines recommend that warfarin therapy be continued for at least 3 months to a maximum of 1 year in patients with prior embolic events.⁴⁸⁶ Warfarin is thought to delay the resolution of a left ventricular thrombus,⁴⁸⁵ and serial echocardiograms to follow the resolution of left ventricular thrombus is a reasonable approach.^{484,485}

Left ventricular aneurysm is a common complication of STEMI, especially if reperfusion has not been performed. Approximately 50% of left ventricular aneurysms have a thrombus.⁴⁸⁰ Patients with a left ventricular aneurysm and thrombus after recent MI are at high risk of emboli—13% over a 6- to 15-month follow-up period⁴⁸²—and should be anticoagulated. Chronic left ventricular aneurysms have a lower risk of embolization—0.35% over a 5-year follow-up period—and the thrombus may be organized or endothelialized.^{487,488} Warfarin is not warranted in these patients unless other indications are present.

The benefits of warfarin therapy are less clear in STEMI patients with severe left ventricular dysfunction. The SAVE⁴⁸⁹ and SOLVD⁴⁹⁰ trials showed that patients with poor left ventricular ejection fraction tended to have increased rates of stroke that increased as ejection fraction decreased. Potentially, warfarin could reduce this risk. Cochrane analyses have shown that anticoagulation may not be helpful, however.^{491,492} Anticoagulation may be considered in individual STEMI patients with severe left ventricular dysfunction, but is not recommended routinely.¹⁰

Summary of ACC/AHA Task Force Recommendations for Anticoagulation in ST Segment Elevation

Myocardial Infarction

ACC/AHA Task Force recommendations for anticoagulation in STEMI are summarized as follows.¹⁰

Unfractionated Heparin and Low-Molecular-Weight Heparin

- The 2004 ACC/AHA guidelines,¹⁰ which did not consider the more recent studies,^{441,443} recommend UFH or LMWH for 48 hours in STEMI patients who did not receive reperfusion therapy and substitution as the clinical scenario demands.
- The 2007 ACC/AHA guideline update¹¹ recommends that STEMI patients who do not undergo reperfusion therapy be given anticoagulant therapy, ideally a non-UFH heparin regimen, for the duration of hospitalization up to 8 days (class IIa, evidence level B), or LMWH (class IIa, evidence level C), or fondaparinux (class IIa, evidence level B).
- LMWH should not be used in STEMI patients older than 75 years or with renal dysfunction (creatinine >2.5 mg/dL [$>221 \mu\text{mol/L}$] in men or >2 mg/dL [$>177 \mu\text{mol/L}$] in women).

Fondaparinux

- The 2004 ACC/AHA guidelines¹⁰ do not address fondaparinux. On the basis of OASIS-6,⁴⁴³ STEMI patients who do not undergo primary PCI should receive fondaparinux. The 2007 ACC/AHA guideline update¹¹ does not recommend fondaparinux as the sole anticoagulant in primary PCI patients (class III, evidence level C). In patients who do not undergo reperfusion therapy, fondaparinux is superior to control therapy (placebo/UFH).

Bivalirudin

- Bivalirudin can be used in STEMI patients with HIT. Evidence does not support its use for conservative management of STEMI. It can be used for bridging anticoagulation for left ventricular thrombus or poor left ventricular function (also see warfarin for long-term anticoagulation).

Warfarin

- STEMI patients with aspirin allergy should be given warfarin (class I, evidence level B), with INRs dependent on whether or not they have stents and clopidogrel is used.¹⁰
- STEMI patients with left ventricular anterior akinesis, aneurysm, or thrombus should be started on warfarin therapy for target INR 2.0 to 3.0 for 3 months (class I, evidence level B) and indefinitely in patients without risk of bleeding (class I, evidence level C) or reassessed thereafter.
- For secondary prevention, STEMI patients younger than 75 years without specific indications and who can be monitored can be given warfarin alone or together with aspirin (class IIa, evidence level B).
- Warfarin is reasonable for post-STEMI patients with left ventricular dysfunction and extensive regional wall motion abnormalities (class IIb, evidence level A), and may be considered in patients with severe left ventricular dysfunction with or without CHF (class IIb, evidence level C).

- Patients receiving warfarin along with aspirin or clopidogrel or both after STEMI are at increased risk of bleeding and should be monitored closely (class I, evidence level B).¹¹
- STEMI patients requiring aspirin, clopidogrel, and warfarin for clinical indications (i.e., atrial fibrillation, left ventricular thrombus) should have low-dose aspirin (81 mg daily) and clopidogrel (75 mg daily) with a target INR of 2.0 to 3.0 (class I, evidence level A).¹¹

Antioxidants, Vitamins, and Natural Supplements

Vitamin supplementation to reduce homocysteine levels, a marker of inflammation, has no proven benefit.⁴⁹³ The HOPE and NORVIT trials failed to show that using folate to reduce homocysteine reduced cardiac events.^{494,495} Antioxidant vitamins (i.e., vitamins A, C, and E; selenium; and beta-carotene) were found to have no benefit in reducing cardiovascular risk.^{496,497} Populations with large intake of omega-3 polyunsaturated fats were found to have lower rates of heart disease,⁴⁹⁸ and dietary supplementation with fish oil and other omega-3 polyunsaturated fatty acids was associated with a reduction in cardiovascular risk and nonfatal reinfarction within 3 months of an MI.⁴⁹⁹

A large study that examined whether or not omega-3 supplementation can reduce cardiovascular risk is the GISSI Prevenzione study, which randomly assigned 11,324 patients with recent MI in a 2 × 2 design to vitamin E (300 mg) or omega-3 supplementation with fish oil (1 g).⁵⁰⁰ This study found a reduction in the primary end point of death, nonfatal MI, and nonfatal stroke at 42 months with fish oil supplementation.⁵⁰⁰ Vitamin E (300 mg/day) had no benefit.⁵⁰⁰ The benefit of fish oil supplementation was driven by a 30% reduction in cardiovascular death and 45% reduction in sudden cardiac death. The benefits occurred quickly after randomization, with the reduction in sudden cardiac death becoming statistically significant after 4 months, and the reduction in cardiovascular, cardiac, and coronary death becoming statistically significant at 6 to 8 months.⁵⁰¹ The reduction in sudden cardiac death supports an antiarrhythmic effect of fish oil supplementation.

The unstable angina/NSTEMI guidelines recommend encouraging patients to increase their consumption of omega-3 fats through either increasing fish consumption or capsule supplementation.¹² At least two servings of fish a week are thought to be the minimum for a benefit in reducing cardiovascular risk.⁵⁰²

Summary of ACC/AHA Task Force Recommendations for Secondary Prevention Using Vitamin and Dietary Supplements after ST Segment Elevation Myocardial Infarction

ACC/AHA Task Force recommendations for secondary prevention using vitamin and dietary supplements after STEMI are summarized as follows.¹⁰

- For secondary prevention after STEMI, patients can increase fish consumption or add fish oil supplementation to reduce cardiovascular risk. Available evidence does not support the use of antioxidant vitamin supplementation (i.e., vitamins A, C, and E; selenium; and beta carotene) or folate (with or without vitamin B₆ or B₁₂ supplementation) for secondary prevention.

Conclusion

Adjunctive pharmacologic therapy should be considered for all STEMI patients whether or not they are treated with reperfusion therapy. This therapy is necessary to minimize infarct size, ventricular remodeling, reinfarction, recurrent angina, and mortality, and to maximize ventricular function. The agents can be used to widen the time frame for reperfusion therapy and to minimize reperfusion injury and ventricular dysfunction. Agents of proven benefit that are underused include low-dose aspirin, β -blockers, and ACE inhibitors; they should be prescribed more readily. The continued use of low-dose intravenous nitroglycerin in early acute STEMI is justified for control of ischemic pain and remodeling benefits. Long-term administration of nitrates should be used for recurrent angina, but eccentric dosing should be used to limit development of tolerance. Lidocaine, magnesium, and current calcium blockers have no proven benefit as routine therapy.

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Medical Management of Unstable Angina and Non-ST Segment Elevation Myocardial Infarction

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CHAPTER 14

Anti-ischemic Therapies
Antiplatelet Therapy
Antithrombotic Therapies

Statin Therapy
Postdischarge Therapy
Conclusion

IN THE SPECTRUM of acute coronary syndromes (ACS), unstable angina (UA) and non-ST segment elevation myocardial infarction (NSTEMI) are caused by atherosclerotic plaque rupture and thrombosis, resulting in nonocclusive or transiently occlusive blockage. This chapter describes the initial medical management of UA/NSTEMI, which focuses on relief of ischemic pain and antithrombotic therapy to prevent further thrombosis and embolism of an ulcerated plaque, and early, intensive statin therapy.

Anti-ischemic Therapies

Anti-ischemic therapy is routine for all patients with ACS and has not changed significantly in the last several decades. It generally consists of nitrates (either sublingual or intravenous) and intravenous followed by oral administration of β blockade. In patients who cannot tolerate β blockade because of severe bronchospastic lung disease, the addition of a nondihydropyridine calcium antagonist can be considered (Table 14-1).

Nitrates

Despite their routine use in patients with ACS, data showing that nitroglycerin reduces mortality or reinfarction are sparse.^{1,2} Nitroglycerin mainly provides symptom relief. Relief of symptoms is achieved by several mechanisms, including arterial vasodilation, reduction in coronary vasospasm, reduced myocardial oxygen demand (by decreasing preload and afterload), augmentation of collateral blood flow, and inhibition of platelet aggregation. There is no optimal intensity of nitroglycerin therapy, but a loading dose should be administered using sublingual nitroglycerin followed by either a topical or an intravenous agent. The dose is generally titrated until symptoms abate or side effects occur, most notably headache and hypotension. Caution should be exercised in patients who are volume depleted or relatively hypotensive or both because these patients may be sensitive to the preload reduction, and the beneficial effects of the nitrates may be outweighed by severe reduction in the mean arterial pressure.

β Blockers

In the absence of contraindications, all patients with ACS should be treated with intravenous β blockade as soon as possible to minimize the risk of arrhythmia or reinfarction.³⁻⁵ The cardioprotective effects of β blockers occur by reducing sympathetic activation and myocardial ischemia, attenuating the toxicity associated with high circulating catecholamines. β blockers decrease myocardial oxygen demand by reducing heart rate, contractility, and systolic blood pressure, and by prolonging diastolic filling, which may allow for increased coronary perfusion time. The antiarrhythmic effects of β blockers result from direct cardiac electrophysiologic activity with decreased spontaneous firing of ectopic pacemakers, slowed conduction, and increased refractory period of the atrioventricular node. Contraindications include β blocker allergy, bradycardia (heart rate <60 beats/min), heart failure, shock, and second-degree or third-degree atrioventricular block.

A meta-regression analysis of randomized controlled trials after myocardial infarction (MI) showed that β blockers reduce the odds of death in long-term trials by 23% and in short-term trials by 4%.⁶ In addition to the immediate administration of intravenous β blockade, patients who survive MI should be continued on oral agents indefinitely. A study in nearly 70,000 patients prescribed a β blocker (atenolol, metoprolol, or propranolol) after acute MI showed that these agents were associated with a 40% improvement in survival at 2 years, and suggested that the specific β blocker chosen has little influence on mortality.⁷

COMMIT has called into question the practice of routinely using intravenous β blockade in patients with ST segment elevation MI. Although benefits in reduction of reinfarction and ventricular fibrillation were noted, an excess of early shock was associated with use of intravenous β blockers.⁸ In UA/NSTEMI patients, the beneficial anti-ischemic and antiarrhythmic effects of intravenous β blockers may be counterbalanced by adverse effects in hemodynamic stability if administered rapidly and at high doses in patients with even mild heart failure or hypotension. In such patients, withholding β blockade 12 to 24 hours until hemodynamic stabilization has been confirmed may be prudent.

Table 14-1. Recommendations for Anti-Ischemic Therapy: Continuing Ischemia or Other Clinical High-Risk Features Present*

Bed/chair rest with continuous ECG monitoring
Supplemental oxygen with arterial saturation <90%, respiratory distress, or other high-risk features for hypoxemia. Pulse oximetry can be useful for continuous measurement of SaO_2
NTG 0.4 mg sublingually every 5 min for a total of 3 doses; afterward, assess need for intravenous NTG
Intravenous NTG for first 48 hr after UA/NSTEMI for treatment of persistent ischemia, HF, or hypertension
Decision to administer intravenous NTG and dose should not preclude therapy with other mortality-reducing interventions such as β blockers or ACE inhibitors
β blockers (via oral route) within 24 hr without a contraindication (e.g., HF) regardless of concomitant performance of PCI
When β blockers are contraindicated, a nondihydropyridine calcium channel blocker (e.g., verapamil or diltiazem) should be given as initial therapy in the absence of severe left ventricular dysfunction or other contraindications
ACE inhibitor (via oral route) within first 24 hr with pulmonary congestion, or LVEF ≤ 0.40 , in the absence of hypotension (systolic blood pressure <100 mm Hg or <30 mm Hg below baseline) or known contraindications to that class of medications
ARB should be administered to UA/NSTEMI patients who are intolerant of ACE inhibitors and have either clinical or radiologic signs of HF or LVEF ≤ 0.40

*Recurrent angina or ischemia-related ECG changes (≥ 0.05 mV ST segment depression or bundle branch block), or both, at rest or with low-level activity; or ischemia associated with HF symptoms, S_3 gallop, or new or worsening mitral regurgitation; or hemodynamic instability or depressed left ventricular function (LVEF <0.40 on noninvasive study); or serious ventricular arrhythmia. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; HF, heart failure; LVEF, left ventricular ejection fraction; NTG, nitroglycerin; PCI, percutaneous coronary intervention; UA/NSTEMI, unstable angina/non-ST segment elevation myocardial infarction.

Adapted from Anderson JL, Adams CD, Antman EM, et al: ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction) Developed in Collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *J Am Coll Cardiol* 2007;50:e1-e157.

Calcium Antagonists

For patients in whom β blockade is contraindicated, calcium antagonists can be considered to alleviate anginal symptoms. The antianginal effects of calcium channel blockers are mediated through a reduction of myocardial oxygen demand secondary to decreased afterload and myocardial contractility. Dihydropyridines (nifedipine and amlodipine) and nondihydropyridines (verapamil and diltiazem) have antianginal properties, but dihydropyridines can result in reflex tachycardia, so these are generally avoided unless a β blocker can be administered

concurrently. Nondihydropyridines, especially verapamil, can cause bradycardia and significant depression of myocardial contractility, and should be used cautiously when added to β blocker therapy. Similar to β blockers, nondihydropyridines are generally avoided completely in patients with congestive heart failure and significant atrioventricular dysfunction.

Apart from severe bronchospastic lung disease, allergy, and possibly cocaine ingestion, the contraindications for β blockers are the same as the contraindications for calcium antagonists. No definitive data exist to suggest that there are substantial reductions in ischemic complications of MI with these agents. A meta-analysis of trials of patients with acute MI or UA who were treated with calcium antagonists found that these agents do not reduce the risk of initial or recurrent infarction or death,⁹ reinforcing the fact that β blockers are the preferred initial therapy, and calcium channel blockers should not be routinely used as first-line therapy for ACS.

Antiplatelet Therapy

Circulating platelets play a crucial role in normal hemostatic function; however, platelet aggregation and thrombosis are maladaptive processes in ACS. Atherosclerotic plaque rupture during ACS exposes thrombogenic subendothelial components, leading to platelet deposition and activation.¹⁰ Platelet activation is associated with surface expression of greater numbers of glycoprotein (GP) IIb/IIIa receptors that are available for binding fibrin strands and platelet cross-linking. In addition to cross-linking as part of the aggregation process, activated platelets also release local mediators that can induce further platelet accumulation and activation, vasoconstriction, thrombosis, and mitogenesis. Platelet activation leads not only to thrombus formation in the epicardial artery, but also distal embolization and occlusion of the microcirculation, which have been associated with poor outcomes.^{11,12} Because of the significant contribution of platelets to the pathophysiology of ACS, one of the cornerstones of medical therapy is directed at inhibiting their deleterious effects.

Aspirin

Numerous trials consistently show the benefits of aspirin in patients with ACS,¹³⁻¹⁸ and its use has become the foundation of medical management for UA/NSTEMI. Aspirin acts by inhibiting cyclooxygenase-1 within platelets, which interferes with the biosynthesis of thromboxane A_2 , prostacyclin, and other prostaglandins. These prostanoids are the main determinants of platelet aggregation in this pathway.

Acute treatment with aspirin is recommended for all patient with suspected ACS, unless contraindicated, and should be continued indefinitely. Current American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend an initial dose of aspirin of 162 to 325 mg.² In clinical practice, most physicians in the United States use initial doses of aspirin of 325 mg during the initial phase of ACS. After stent implementation, a maintenance dose of 325 mg is recommended for 1 month with bare metal stents and for 6 to 12 months with drug-eluting stents. Thereafter, or in the absence of percutaneous coronary intervention (PCI), the optimal maintenance dose of aspirin is 75 to 162 mg daily.² Ibuprofen interferes with the cardioprotective effects of aspirin¹⁹; an alternative nonsteroidal anti-inflammatory drug ideally should be prescribed to patients requiring indefinite aspirin therapy. If ibuprofen use cannot be

avoided, it should be taken at least 30 minutes after or at least 8 hours before aspirin.²

There is growing evidence that many individuals may exhibit aspirin resistance.²⁰ Whether the term *aspirin resistance* represents a clinical failure of aspirin therapy (i.e., stroke, MI) or some level of residual platelet aggregation despite therapy remains a matter of debate. Nevertheless, this syndrome has been variously described as relative failure to inhibit platelet aggregation or failure to prolong bleeding time, or the development of a clinical event while on aspirin therapy. Presently, no test of platelet function is currently preferred to assess the antiplatelet effect of aspirin in the individual patient because it is difficult to assess the clinical significance of in vitro platelet function studies. In patients with contraindications or intolerance to aspirin or patients who experience a cardiac event while taking aspirin (e.g., aspirin failures), clopidogrel, 75 mg daily, is a suitable alternative.

Thienopyridine Agents

Thienopyridine agents block the adenosine diphosphate receptor P2Y₁₂ on the platelet surface, inhibiting platelet activation. The currently approved agents, clopidogrel and ticlopidine, have been widely used. Because of the adverse potential of ticlopidine (i.e., neutropenia and rarely thrombotic thrombocytopenic purpura), clopidogrel has emerged as the preferred thienopyridine.

The widespread use of clopidogrel in the treatment of ACS is based primarily on the CURE and CREDO trials.^{21,22} The CURE trial compared the benefit of aspirin plus clopidogrel (300 mg loading dose, then 75 mg/day) treatment versus aspirin alone in 12,562 patients with UA/NSTEMI for 3 to 12 months. The use of clopidogrel reduced the risk of cardiovascular death, recurrent MI, or stroke significantly by 20%, from 11.5% in the placebo group to 9.3% in the clopidogrel group. A reduction of death, nonfatal MI, stroke, or refractory or severe ischemia was already present within 24 hours of randomization.²¹ The beneficial effects of clopidogrel were noted across all subgroups regardless of whether high-risk features were present, such as electrocardiogram (ECG) changes or elevated cardiac biomarkers, suggesting broad use for this agent as adjunctive therapy in all UA/NSTEMI patients if no contraindications exist.

In PCI-CURE, an observational substudy of the CURE trial, 2658 patients underwent PCI a median of 10 days after randomization.²³ All patients received an open-label thienopyridine after PCI for approximately 30 days, after which the original blinded study drug was restarted for an additional 8 months. Pretreatment with clopidogrel was associated with a 30% reduction in risk of cardiovascular death, recurrent MI, or target vessel revascularization at 30 days (6.4% versus 4.5%). The benefit of pretreatment and long-term therapy with clopidogrel before PCI was also observed in the CREDO trial.²² CREDO comprised 2116 patients, 55% of whom had UA/NSTEMI and were to undergo PCI, and compared pretreatment with clopidogrel, 300 mg, followed by maintenance therapy, 75 mg, versus placebo with 1-year follow-up. Patients allocated to placebo received 75 mg of clopidogrel at the time of PCI, followed by 75 mg daily for 1 month and placebo thereafter. The benefit of pretreatment with 300 mg of clopidogrel was primarily observed among patients who had received pretreatment 15 hours or more before PCI.²⁴

Taken together, the PCI-CURE and CREDO trials suggest that ACS patients should be treated early with clopidogrel before PCI, and treatment should be continued for 9 to 12 months.

A suggested algorithm for antiplatelet therapy after an episode of UA is outlined in Figure 14-1.

More recent investigation in this area has focused on the optimal timing and loading dose of clopidogrel before PCI. ARMYDA-2 randomly assigned patients to receive either a 300-mg or 600-mg loading dose of clopidogrel 4 to 8 hours before PCI, and found that the 600-mg loading dose significantly reduced periprocedural MI.²⁵ Most patients in ARMYDA-2 underwent PCI for stable angina (75%). Cuisset and colleagues²⁶ randomly assigned 292 consecutive patients with non-ST segment elevation ACS undergoing stenting to receive a 300-mg or 600-mg loading dose of clopidogrel at least 12 hours before PCI. During the 1-month follow-up, 18 (12%) cardiovascular events occurred in the 300-mg group compared with 7 (5%) events in the 600-mg group. Based on the current available evidence, all patients without contraindications who present with ACS should be given a 300-mg loading dose of clopidogrel, and in situations in which longer durations of pretreatment are impossible, 600 mg may be used when given at least 2 hours before PCI.²

Several new thienopyridine agents are currently being investigated. Prasugrel is a thienopyridine that has been shown in pre-clinical studies to be more potent and to have a more rapid onset of action than clopidogrel.²⁷ It was evaluated in the TRITON-TIMI 38 study, in which 13,608 ACS patients undergoing PCI were randomly assigned to prasugrel or clopidogrel. Although prasugrel therapy was associated with significantly reduced rates of ischemic events, this benefit came at a cost of more major bleeding events.²⁸ AZD-6140, another newer thienopyridine with greater potency than clopidogrel, is currently being evaluated. Cangrelor, an intravenous agent with an extremely short half-life and rapid onset of action,²⁹ is the subject of the ongoing CHAMPION-PLATFORM and CHAMPION-PCI trials.

Glycoprotein IIb/IIIa Receptor Inhibitors

Platelet activation is associated with surface expression of greater numbers of GP IIb/IIIa receptors available for binding fibrin strands and platelet cross-linking. Several large, randomized clinical trials have shown improved clinical outcomes with the administration of GP IIb/IIIa receptor inhibitors (GPIs) in patients presenting with ACS and after PCI to inhibit platelet aggregation.³⁰ Although intravenous agents seem to be beneficial, the oral GPI, in contrast, has been ineffective and may increase mortality.³¹ Three intravenous GPIs are currently available for clinical use: abciximab, tirofiban, and eptifibatide. Abciximab is a GPI that comprises Fab fragment of the chimeric human-murine monoclonal antibody 7E3. Tirofiban is a non-peptide inhibitor of the platelet GP IIb/IIIa receptor, interfering with aggregation by mimicking the geometric, stereotactic, and charge characteristics of the platelet integrin-binding domain sequence. Eptifibatide is a nonimmunogenic, cyclic heptapeptide with an active pharmacophore that is derived from the structure of barbourin, a platelet GPI from the venom of the Southeastern pigmy rattlesnake.³² Table 14-2 summarizes the clinical indications for GPI administration.

The TIMI risk score for UA/NSTEMI³³ (Fig. 14-2) and GRACE prediction score³⁴ (Fig. 14-3) have been validated for UA/NSTEMI patients to predict patients at increased risk of adverse clinical outcomes. The decision whether to initiate therapy with a GPI and which agent to use should be determined based on an assessment of the patient's risk, and whether an early invasive versus selective treatment strategy is anticipated.³⁵ Among high-risk, troponin-positive UA/NSTEMI patients treated with medical

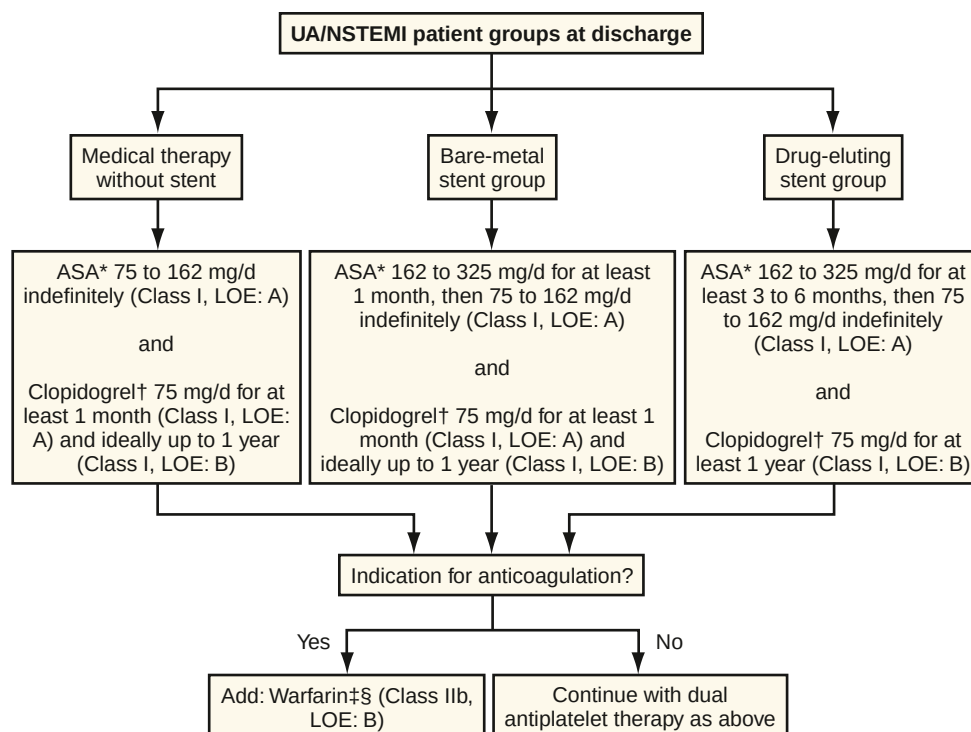


Figure 14-1. Suggested algorithm for antiplatelet therapy in follow-up after unstable angina and non-ST segment elevation myocardial infarction (UA/NSTEMI). ASA, aspirin. (Adapted from Anderson JL, Adams CD, Antman EM, et al: ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *J Am Coll Cardiol* 2007;50:e1-e157.)

*For aspirin (ASA) allergic patients, use clopidogrel alone (indefinitely), or try aspirin desensitization.

†For clopidogrel allergic patients, use ticlopidine, 250 mg by mouth twice daily.

‡Continue ASA indefinitely and warfarin longer term as indicated for specific conditions such as atrial fibrillation; LV thrombus; cerebral, venous, or pulmonary emboli.

§When warfarin is added to aspirin plus clopidogrel, an INR of 2.0 to 2.5 is recommended. INR = international normalized ratio; LOE = Level of Evidence; LV = left ventricular; UA/NSTEMI = unstable angina/non-ST-elevated myocardial infarction.

therapy alone, benefits have been shown with eptifibatide (PUR-SUIT)³⁶ and tirofiban (PRISM, PRISM-PLUS, and RESTORE).³⁷⁻³⁹ In contrast, mortality was higher among medically treated patients who received abciximab in the GUSTO 4 ACS trial.⁴⁰

Antman and colleagues⁴¹ conducted a meta-analysis of GPIs in six large trials involving 31,402 UA/NSTEMI patients who were not scheduled to undergo PCI. Significant reduction in the odds for the combined end point of death or MI was observed in the GPI group at 5 days (5.7% versus 6.9% for placebo/control; odds ratio [OR] 0.84, 95% confidence interval [CI] 0.77 to 0.93) and at 30 days (10.8% versus 11.8%; OR 0.91, 95% CI 0.85 to 0.98). Bleeding rates were significantly higher (2.4% versus 1.4%; $P < .0001$), but there was no increase in intracranial bleeding (0.09% versus 0.06%).

The observed benefit of GPI was largely confined to patients who went on to have PCI or coronary artery bypass graft surgery within 30 days (OR for death or MI 0.89, 95% CI 0.80 to 0.98). Patients with positive cardiac biomarkers were identified as a high-risk cohort, and much of the benefit seemed to be among the patients with a positive troponin T or I concentration (0.1 ng/mL) (OR 0.85, 95% CI 0.71 to 1.03). For the patients who did *not* undergo early revascularization (25,555 [81%] in this analysis), there was no significant reduction in death or MI (OR 0.95, 95% CI 0.86 to 1.05). Among low-risk, troponin-negative patients in

whom a selective invasive strategy is selected, there is less benefit of adding a GPI, and it is generally not recommended.

For patients in whom an early invasive strategy is selected, all three GPIs have been shown to reduce the incidence of death or MI in patients with UA/NSTEMI undergoing PCI.^{36,39,42-44} An analysis of data from 12,296 patients in CAPTURE, PUR-SUIT, and PRISM-PLUS using abciximab, eptifibatide, and tirofiban showed that intravenous GPI added to heparin and aspirin significantly reduced the rate of death or nonfatal MI during drug infusion (2.5% versus 3.8%) and during the first 48 hours after PCI (4.9% versus 8%).⁴⁵ The benefit from GPI was primarily observed among troponin-positive patients.^{46,47} Data from more than 60,000 patients in the National Registry of Myocardial Infarction show a 5.5% absolute reduction in mortality when a GPI is initiated within the first 24 hours. In a multivariate model and after adjustment for the propensity to be treated with such agents, there was a significant 12% relative risk reduction.⁴⁸

The challenge in delivering the optimal medical therapy to patients with UA/NSTEMI is incorporating the evidence from the above-mentioned GPI studies, which were performed in the 1990s, with the more recent studies involving clopidogrel loading before PCI and newer anticoagulants. The current ACC/AHA guidelines for UA/NSTEMI patients in whom an initial

Table 14-2. Clinical Indications for Glycoprotein IIb/IIIa Receptor Inhibitors

Indication	Tirofiban	Eptifibatide	Abciximab
UA/NQMI with PCI	X	X	Refractory UA awaiting PCI within 24 hr only
UA/NQMI medically managed	X	X	Contraindicated
Elective PCI	X	X	X
Urgent/emergency PCI	X	X	X

PCI, percutaneous coronary intervention; UA, unstable angina; UA/NQMI, unstable angina/non-Q wave myocardial infarction.

Adapted from Anderson JL, Adams CD, Antman EM, et al: ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction) Developed in Collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *J Am Coll Cardiol* 2007;50:e1-e157.

invasive strategy is selected is to add either an intravenous GPI or clopidogrel to aspirin and anticoagulant therapy before diagnostic angiography (upstream) for lower risk, troponin-negative patients.² High-risk, troponin-positive patients should receive a GPI and clopidogrel before angiography (class I recommendations). The evidence for benefit in patients in whom a selective invasive strategy is selected is less clear. In that situation, the addition of eptifibatide or tirofiban to anticoagulant and oral

antiplatelet therapy may be reasonable for high-risk patients (class IIb recommendation).² Antiplatelet therapies for UA/NSTEMI are summarized in Table 14-3.

Regarding the decision of whether an early invasive or conservative approach should be chosen, current ACC/AHA guidelines support an early invasive strategy. Many of the initial data supporting this decision were derived from TACTICS TIMI-18,³³ in which 2220 patients with UA/NSTEMI were treated with an initial medical regimen of aspirin, heparin, and tirofiban, and then randomly assigned to either an early invasive strategy (cardiac catheterization within 4 to 48 hours) or an early conservative approach. The early invasive strategy was associated with a 3.5% absolute reduction in the composite end point of death, recurrent MI, or rehospitalization for ACS at 6 months (OR 0.78, 95% CI 0.62 to 0.97, $P = .025$), but most of this benefit was driven by a reduction in recurrent MI and rehospitalization.

In a meta-analysis of clinical trials using contemporary therapies (GPI or thienopyridine or both, and coronary stents for PCI), an early invasive strategy was found to improve individual outcomes of mortality.³⁴ Seven trials with 8375 patients were analyzed with a primary end point of all-cause mortality. At a mean follow-up of 23.7 months, the mortality incidence in patients assigned to early invasive therapy was 4.9% compared with 6.5% among the patients treated conservatively (relative risk 0.75, 95% CI 0.63 to 0.90, $P = .001$). Similar to TACTICS-TIMI 18, the early invasive strategy was also associated with a reduction in recurrent MI (7.6% versus 9.1%; $R = 0.83$, 95% CI 0.72 to 0.96, $P = .012$) and rehospitalization for ACS (19.9% versus 28.7%; $R = 0.69$, 95% CI 0.65 to 0.74, $P < .0001$).

The weight of available evidence shows that for patients presenting with UA/NSTEMI, an early invasive strategy of cardiac catheterization within 48 hours results in fewer ischemic complications, which is primarily driven by reductions in recurrent MI. Although these individual trials were not powered to detect a mortality benefit, a more recent meta-analysis suggests that an early invasive strategy may also confer an improved survival advantage. The benefits of an early invasive strategy were limited

TIMI RISK SCORE FOR UA/NSTEMI			
HISTORICAL	POINTS	RISK OF CARDIAC EVENTS (%) BY 14 DAYS IN TIMI 11B*	
Age ≥ 65	1	RISK SCORE	DEATH OR MI
≥ 3 CAD risk factors (FHx, HTN, $\uparrow$ chol, DM, active)	1		
Known CAD (stenosis $\geq 50\%$)	1	DEATH, MI OR URGENT REVASC	
ASA use in past 7 days	1		
PRESENTATION			
Recent (≤ 24 H) severe angina	1		
$\uparrow$ cardiac markers	1		
ST deviation ≥ 0.5 mm	1		
RISK SCORE = total points (0–7)			

*Entry criteria: UA or NSTEMI defined as ischemic pain at rest within past 24H, with evidence of CAD (ST segment deviation or +marker)

Figure 14-2. TIMI risk score for unstable angina and non-ST segment elevation myocardial infarction (UA/NSTEMI). CAD, coronary artery disease; chol, cholesterol; DM, diabetes mellitus; FHx, family history; HTN, hypertension; MI, myocardial infarction. (Adapted from Antman EM, Cohen M, Bernink PJ, et al: *The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making*. *JAMA* 2000;284:835-842.)

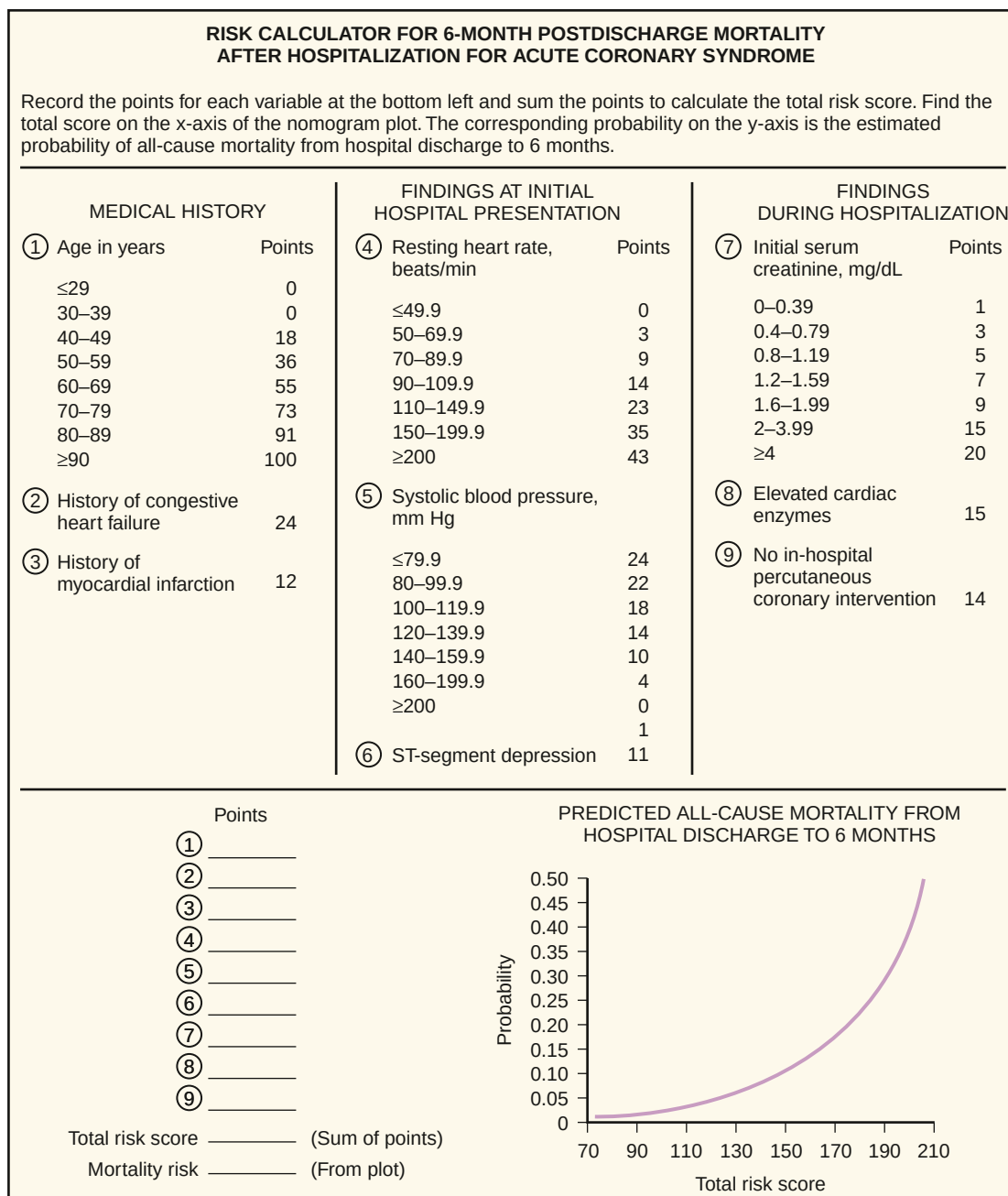


Figure 14-3. GRACE prediction score card and nomogram for all-cause mortality from discharge to 6 months. (Adapted from Eagle KA, Lim MJ, Dabbous OH, et al; GRACE investigators: A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. *JAMA* 2004;291:2727-2733.)

to moderate-risk and high-risk patients (see Figs. 14-2 and 14-3); low-risk patients are unlikely to derive benefit and may potentially experience adverse outcomes from early cardiac catheterization.

Antithrombotic Therapies

Because ACS are precipitated by the rupture of vulnerable atherosclerotic plaques with resultant formation of intracoronary thrombus, agents directed against the generation of thrombin are a hallmark of management. Unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), direct thrombin inhibitors, and factor Xa inhibitors all target this crucial step.

Heparin

UFH works to accelerate the action of circulating antithrombin, inactivating factors IIa, IXa, and Xa. Although UFH prevents thrombus propagation, it does not result in lysis of existing thrombi.^{2,35} Its benefits when combined with aspirin have been shown in numerous clinical trials, establishing UFH as a cornerstone of ACS management for more than 15 years. In the RISC trial, patients receiving heparin and aspirin had the fewest events during the first 5 days.³⁶ A meta-analysis of six UA trials showed a 33% ($P = .06$) reduction in the risk of death or MI at 2 to 12 weeks in patients treated with UFH and aspirin versus aspirin alone.³⁷

Table 14-3. Dosing for Antiplatelet and Anticoagulant Therapy in Patients with Unstable Angina/Non-ST Segment Elevation Myocardial Infarction

Drug*	Initial Medical Treatment	During PCI		After PCI	At Hospital Discharge
		<i>Patient Received Initial Medical Treatment</i>	<i>Patient Did Not Receive Initial Medical Treatment</i>		
Oral Antiplatelet Therapy					
Aspirin	162-325 mg nonenteric formulation, orally or chewed	No additional treatment	162-325 mg nonenteric formulation, orally or chewed	162-325 mg daily should be given [†] for at least 1 mo after BMS implantation, 3 mo after SES implantation, and 6 mo after PES implantation, after which daily aspirin should be continued indefinitely at a dose of 75-162 mg	162-325 mg daily should be given [†] for at least 1 mo after BMS implantation, 3 mo after SES implantation, and 6 mo after PES implantation, after which daily aspirin should be continued indefinitely at a dose of 75-162 mg
Clopidogrel	LD 300-600 mg orally; MD 75 mg orally per day	Second LD of 300 mg orally may be given to supplement a prior LD of 300 mg	LD 300-600 mg orally	For BMS, 75 mg daily for at least 1 mo and ideally for up to 1 yr; for DES, 75 mg daily for at least 1 yr (in patients who are not at high risk of bleeding) (see Fig. 14-1)	For BMS, 75 mg daily for at least 1 mo and ideally for up to 1 yr; for DES, 75 mg daily for at least 1 yr (in patients who are not at high risk of bleeding) (see Fig. 14-1)
Ticlopidine	LD 500 mg orally; MD 250 mg orally twice daily	No additional treatment	LD 500 mg orally	MD 250 mg orally twice daily (duration same as clopidogrel)	MD 250 mg orally twice daily (duration same as clopidogrel)
Anticoagulants					
Bivalirudin	0.1 mg/kg bolus; 0.25 mg/kg/hr infusion	0.5 mg/kg bolus; increase infusion to 1.75 mg/kg/hr	0.75 mg/kg bolus; 1.75 mg/kg/hr infusion	No additional treatment or continue infusion for up to 4 hr	—
Dalteparin	120 IU/kg SC every 12 hr (maximum 10,000 IU twice daily) [‡]	IV GP IIb/IIIa planned: target ACT 200 sec using UFH; no IV GP IIb/IIIa planned: target ACT 250-300 sec for HemoTec, 300-350 sec for Hemochron using UFH	IV GP IIb/IIIa planned: 60-70 U/kg [§] of UFH; no IV GP IIb/IIIa planned: 100-140 U/kg of UFH	No additional treatment	—

(Continued)

Table 14-3. Dosing for Antiplatelet and Anticoagulant Therapy in Patients with Unstable Angina/Non-ST Segment Elevation Myocardial Infarction—Cont'd

Drug*	Initial Medical Treatment	During PCI		After PCI	At Hospital Discharge
		<i>Patient Received Initial Medical Treatment</i>	<i>Patient Did Not Receive Initial Medical Treatment</i>		
Enoxaparin	LD 30 mg IV bolus may be given [¶] ; MD 1 mg/kg SC every 12 hr [¶] ; extend dosing interval to 1 mg/kg every 24 hr if estimated creatinine clearance <30 mL/min [¶]	Last SC dose <8 hr: no additional therapy Last SC dose >8 hr: 0.3 mg/kg IV bolus	0.5-0.75 mg/kg IV bolus	No additional treatment	—
Fondaparinux	2.5 mg SC once daily; avoid for creatinine clearance <30 mL/min [¶]	50-60 U/kg IV bolus of UFH is recommended by OASIS 5 investigators [¶]	50-60 U/kg IV bolus of UFH is recommended by OASIS 5 investigators [¶]	No additional treatment	—
UFH	LD 60 U/kg (maximum 4000 U) as IV bolus ^{**} ; MD IV infusion of 12 U/kg/hr (maximum 1000 U/hr) to maintain aPTT at 1.5-2 times control (approximately 50-70 sec) ^{**}	IV GP IIb/IIIa planned: target ACT 200 sec; no IV GP IIb/IIIa planned: target ACT 250-300 sec for HemoTec, 300-350 sec for HemoChron	IV GP IIb/IIIa planned: 60-70 U/kg [§] ; no IV GP IIb/IIIa planned: 100-140 U/kg	No additional treatment	—
IV Antiplatelet Therapy					
Abciximab	NA	NA	LD 0.25 mg/kg IV bolus; MD 0.125 µg/kg/min (maximum 10 µg/min)	Continue MD infusion for 12 hr	—
Eptifibatide	LD IV bolus of 180 µg/kg; MD IV infusion of 2 µg/kg/min; reduce infusion by 50% in patients with estimated creatinine clearance <50 mL/min	Continue infusion	LD IV bolus of 180 µg/kg followed 10 min later by second IV bolus of 180 µg/kg; MD of 2.0 mcg/kg/min; reduce infusion by 50% in patients with estimated creatinine clearance <50 mL/min	Continue MD infusion for 18-24 hr	—
Tirofiban	LD IV infusion of 0.4 µg/kg/min for 30 min; MD IV infusion of 0.1 µg/kg/min; reduce rate of infusion by 50% in patients with estimated creatinine clearance <30 mL/min	Continue infusion	LD IV infusion of 0.4 µg/kg/min for 30 min; MD IV infusion of 0.1 µg/kg/min; reduce rate of infusion by 50% in patients with estimated creatinine clearance <30 mL/min	Continue MD infusion for 18-24 hr	—

(Continued)

Note: Additional considerations include the possibility that a patient who has been conservatively managed may develop a need for PCI, in which case an IV bolus of 50 to 60 U/kg is recommended if fondaparinux was given for initial medical treatment; the safety of this drug combination is not well established. For conservatively managed patients in whom enoxaparin was the initial medical treatment, as noted in the table, additional IV enoxaparin is an acceptable option.

*This list is in alphabetical order and is not meant to indicate a particular therapy preference.

†In patients in whom the physician is concerned about the risk of bleeding, a lower initial American Society of Anesthesiologists dose after PCI of 75 to 162 mg/day is reasonable (class IIa, Level of Evidence: C).

‡Dalteparin was evaluated for management of patients with non-ST segment elevation myocardial infarction in an era before the widespread use of important therapies such as stents, clopidogrel, and GP IIb/IIIa inhibitors. Its relative efficacy and safety in the contemporary management era is not well established.

§Some operators use <60 U/kg of UFH with GP IIb/IIIa blockade, although no clinical trial data exist to show the efficacy of doses <60 U/kg in this setting.

¶For patients managed by an initial conservative strategy, agents such as enoxaparin and fondaparinux offer the convenience advantage of SC administration compared with an IV infusion of UFH. They are also less likely to provoke heparin-induced thrombocytopenia than UFH.

¶Available data suggest fondaparinux is associated with less bleeding than enoxaparin in conservatively managed patients using the regimens listed.

***This regimen has not been rigorously tested in prospective randomized trials.

ACT, activated clotting time; aPTT, activated partial thromboplastin time; BMS, bare metal stent; GP, glycoprotein; IU, international unit; IV, intravenous; LD, loading dose; MD, maintenance dose; NA, not applicable; PCI, percutaneous coronary intervention; PES, paclitaxel-eluting stent; SC, subcutaneous; SES, sirolimus-eluting stent; UFH, unfractionated heparin.

From Anderson JL, Adams CD, Antman EM, et al: ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction) Developed in Collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *J Am Coll Cardiol* 2007;50:e1-e157.

Much of the benefit from the administration of UFH combined with aspirin is thought to be driven by a reduction in recurrent MI. The duration of UFH in most UA/NSTEMI trials has been 2 to 5 days; the optimal duration of therapy is uncertain and likely varies by strategy. There is an important risk of rebound ischemia when the drug is stopped prematurely.^{38,39} Other disadvantages of UFH include its poor bioavailability related to its binding to many plasma proteins. Consequently, there is marked variability in the anticoagulant response and a need for frequent monitoring of the activated partial thromboplastin time, which is not standardized among laboratories. Typically, higher doses are required for diabetics, smokers, and patients weighing more than 100 kg, whereas lower doses are often required for elderly women. Rarely, autoimmune heparin-induced thrombocytopenia (heparin-induced thrombocytopenia type II) may result with serious prothrombotic complications, and should be investigated when the platelet count declines by more than 50% or to values less than 100,000/ μ L.

Low-Molecular-Weight Heparins

The limitations of UFH have led to significant attention directed to alternative antithrombotic agents, such as LMWHs. LMWHs are prepared by depolymerization of the polysaccharide chains of heparin into shorter peptides of lower weight.² LMWHs are more potent inhibitors of factor Xa than UFH. Advantages over UFH include decreased binding to plasma proteins, dose-independent clearance, and a longer half-life resulting in a more predictable anticoagulant response that does not typically require laboratory monitoring.

The ESSENCE and TIMI 11B trials, which comprised more than 7000 patients, showed a 20% reduction in major adverse cardiovascular events with enoxaparin compared with UFH.^{40,41} More recently, the efficacy and safety of enoxaparin versus UFH were evaluated when given in combination with GPIs. In INTERACT, the primary safety outcome of major bleeding not associated with coronary artery bypass graft surgery was significantly lower in the enoxaparin group (1.8% versus 4.6%). Additionally, the rate of death or nonfatal MI at 30 days was reduced by almost half (relative risk 0.55, 95% CI 0.30 to 0.96).⁴² An important caveat is that the median time to revascularization was relatively slow in this trial at 101 hours. SYNERGY, a

trial of an early invasive strategy, showed that enoxaparin was noninferior with respect to UFH for death or MI at 30 days, but was associated with an increased rate of TIMI major bleeding (9.1% versus 7.6%; $P = .008$).⁴³ Post-hoc analysis of the trial suggested that some of this excess bleeding could be attributed to crossover to UFH at the time of PCI.

Taken together, these two trials suggest that in patients receiving GPIs, enoxaparin is safest and beneficial in patients in whom a conservative or delayed invasive approach is planned, whereas UFH is preferable for patients managed with an early invasive strategy. Additionally, if patients initially treated with LMWH undergo early PCI, it is preferable to maintain a consistent anticoagulation strategy rather than crossover at the time of PCI. For patients in whom coronary artery bypass graft surgery is planned, UFH is preferable to LMWH. Finally, LMWH should be avoided in patients older than 75 years or with significant renal dysfunction (glomerular filtration rate <30 mL/min).

Direct Thrombin Inhibitors

Direct thrombin inhibitors, such as hirudin and bivalirudin, have theoretical advantages compared with UFH because they (1) bind directly and tightly with thrombin without the need for cofactors such as antithrombin III, (2) are more effective in inhibiting fluid-phase and clot-bound thrombin, (3) do not cause or aggravate heparin-induced thrombocytopenia, and (4) achieve more stable levels of anticoagulation.

In TIMI-9B and OASIS-2, hirudin showed mixed efficacy compared with UFH and excess bleeding at higher doses.^{44,45} Bivalirudin, a synthetic analogue of hirudin, was investigated in more than 13,000 patients with UA/NSTEMI in the ACUTY trial. Patients undergoing cardiac catheterization within 72 hours of presentation were assigned to one of three treatment regimens: (1) UFH or enoxaparin with or without upstream GPI, (2) bivalirudin with or without upstream GPI, or (3) bivalirudin alone. Patients assigned to the first two groups were randomly assigned further in a 2×2 factorial design, whereby if they did not receive upstream GPI it was given at the time of PCI. When used with a GPI, bivalirudin was shown to be noninferior to heparin with respect to a 30-day rate of the net clinical outcome of composite ischemia or major bleeding or both (11.8% versus 11.7%), with no significant difference in major bleeding (5.3% versus 5.7%).

When used alone, bivalirudin was superior to heparin plus GPI with respect to the rate of major bleeding (3% versus 5.7%).⁴⁶

Subgroup analysis showed that bivalirudin was comparable to heparin plus a GPI with regard to ischemic complications when clopidogrel pretreatment was administered (7% versus 7.3%), but was inferior in patients who did not receive thienopyridine pretreatment (9.1% versus 7.1). Whether this finding is due to the limitations inherent in retrospective analyses or truly represents the adverse consequences of inadequate platelet inhibition in patients not pretreated is uncertain. Nevertheless, to optimize outcomes in ACS patients receiving bivalirudin who have not had pretreatment with a thienopyridine, it is prudent to consider a concomitant GPI.

Factor Xa Inhibitors

Synthetic pentasaccharides, such as fondaparinux, act proximally in the coagulation cascade by binding to antithrombin and providing specific inhibition of factor Xa. This action results in suppression of thrombin generation without interfering with the other clotting factors. Similar to LMWHs, fondaparinux is advantageous compared with UFH because it has decreased binding to plasma proteins, has dose-independent clearance with a longer half-life, has more predictable and sustained anticoagulation, and allows once-daily administration without the need for laboratory monitoring.

OASIS-5 evaluated the safety and efficacy of fondaparinux in 20,078 patients with UA/NSTEMI.⁴⁷ After standard treatment with aspirin, clopidogrel, and a GPI (according to local practice), patients were randomly assigned to either once-daily fondaparinux or twice-daily enoxaparin. The rates of the primary composite end point of death, MI, or refractory ischemia at 9 days were similar in the two groups (5.8% versus 5.7%). A 47% reduction in major bleeding was seen in the fondaparinux group (2.2% versus 4.1%; $P < .001$). At 6 months, fondaparinux was associated with a significant reduction in mortality (5.8% versus 6.5%) and the combined end point of death, MI, and stroke (11.3% versus 12.5%).⁴⁷

These favorable results for fondaparinux were tempered by an excess of catheter-associated thrombus in patients undergoing PCI. It would be reasonable to recommend fondaparinux as the preferred anticoagulant strategy in patients managed with a non-invasive strategy, especially if they are at high risk of bleeding.

Statin Therapy

Numerous trials have shown that 3-hydroxy-3-methylglutaryl coenzyme-A reductase inhibitors, or “statins,” are safe and effective in reducing cardiovascular events in patients with or at risk for coronary artery disease.⁴⁸ Two more recent trials sought to determine whether more intensive therapy and earlier initiation after ACS would result in a greater benefit.

In the PROVE IT-TIMI 22 trial,⁴⁹ 4126 patients who had been hospitalized with UA/NSTEMI in the preceding 10 days were randomly assigned to intensive (atorvastatin, 80 mg) or standard (pravastatin, 40 mg) therapy. The primary end point was a composite of all-cause mortality, MI, readmission for UA, revascularization (>30 days after randomization), and stroke.⁴⁹ Although the study was designed to show noninferiority of the standard dose statin regimen, there was a 4% absolute decline in the rate of the primary end point in the intensive therapy group (22.4% versus 26.3%; $P = .005$). Similarly, the A to Z Trial evaluated 4497

patients hospitalized with ACS within the preceding 5 days and randomly assigned them to either 40 mg of simvastatin for 1 month followed by 80 mg thereafter (early, intensive strategy) or placebo for 4 months followed by 20 mg of simvastatin thereafter (delayed, conservative strategy).⁵⁰ The primary end point was a composite of cardiovascular death, nonfatal MI, readmission for ACS, and stroke. Although there was a trend toward a reduction in the primary end point in the intensive group, it did not reach statistical significance (14.4% versus 16.7%).

When the two trials are compared, it seems that the difference in results can be explained almost entirely by an early benefit (first 4 months) seen in PROVE IT, but not A to Z Trial. One significant factor that may have contributed to this finding is the increased rate of revascularization for the index presentation in PROVE IT compared with A to Z Trial (69% versus 44%; $P < .001$). Other factors include differences in the baseline risk factors, rates of early revascularization, intensity of early therapy, timing and magnitude of low-density lipoprotein and C-reactive protein lowering, and chance. The rates of events and event reduction during the late phase (>4 months) were very similar.⁵¹ When these two trials were pooled, a patient level analysis showed that all-cause mortality was significantly reduced in the patients with intensive statin therapy compared with the patients receiving moderate therapy (3.6% versus 4.9%; $P = .015$).⁵²

Postdischarge Therapy

Although the benefits of acute and long-term therapy with aspirin, clopidogrel, β blockers, and statins have been discussed previously, specific discussion is needed regarding UA/NSTEMI patients who sustain impairment of left ventricular systolic function. Left ventricular systolic dysfunction is the most potent predictor of sudden arrhythmic death in post-MI survivors.^{53,54} Numerous large-scale clinical trials have shown that pharmacologic therapy can dramatically reduce the risk of recurrent cardiovascular events and death in patients who survive MI with left ventricular systolic dysfunction.

Angiotensin-Converting Enzyme Inhibitors

The SAVE trial was the first study to report a benefit with angiotensin-converting enzyme (ACE) inhibitors in post-MI patients with left ventricular systolic dysfunction. At 42 months, treatment with captopril reduced cardiovascular mortality by 21% and reinfarction by 25% (mean left ventricular ejection fraction 31%).⁵⁵ Similar risk reduction was shown in the TRACE,^{56,57} SMILE,⁵⁸ and SMILE-2 trials.⁵⁹

The utility of ACE inhibition in patients without heart failure resulting from left ventricular systolic dysfunction is less clear. A systematic review⁶⁰ of three major trials (HOPE,⁶¹ EUROPA,⁶² and PEACE⁶³) showed that the absolute benefit of ACE inhibition is directly proportional to patient risk, with patients at the highest risk benefiting the most.

Angiotensin II Receptor Blockers

VALIANT evaluated the effects of captopril, valsartan, or both in patients with MI and clinical heart failure or left ventricular systolic dysfunction (mean left ventricular ejection fraction 35%).⁶⁴ This study found no significant difference between the three treatment groups with respect to cardiovascular death, recurrent MI, or rates of hospitalization for heart failure.

Table 14-4. Medications Used for Stabilized Unstable Angina/Non-ST Segment Elevation Myocardial Infarction Patients

Anti-ischemic and Antithrombotic/ Antiplatelet Agents	Drug Action	Class/Level of Evidence
Aspirin	Antiplatelet	I/A
Clopidogrel* or ticlopidine	Antiplatelet when aspirin is contraindicated	I/A
β blockers	Anti-ischemic	I/B
ACE inhibitor	EF <0.40 or CHF EF >0.40	I/A, IIa/A
Nitrates	Antianginal	I/C for ischemic symptoms
Calcium channel blockers (short-acting dihydropyridine antagonists should be avoided)	Antianginal	I for ischemic symptoms; when β blockers are unsuccessful (B) or contraindicated, or cause unacceptable side effects (C)
Dipyridamole	Antiplatelet	III/A
<i>Agents for Secondary Prevention and Other Indications</i>	<i>Risk Factor</i>	
HMG-CoA reductase inhibitors	LDL cholesterol >70 mg/dL	Ia
Fibrates	HDL cholesterol <40 mg/dL	IIa/B
Niacin	HDL cholesterol <40 mg/dL	IIa/B
Niacin or fibrate	Triglycerides 200 mg/dL	IIa/B
Antidepressant	Treatment of depression	IIb/B
Treatment of hypertension	Blood pressure >140/90 mm Hg or >130/80 mm Hg if kidney disease or diabetes present	I/A
Treatment of diabetes	Hemoglobin A _{1c} >7%	I/B
Hormone therapy (initiation) [†]	Postmenopausal state	III/A
Hormone therapy (continuation) [†]	Postmenopausal state	III/B
COX-2 inhibitor or NSAID	Chronic pain	IIa/C, IIb/C, III/C
Vitamin C, vitamin E, beta carotene, folic acid, vitamin B ₆ , vitamin B ₁₂	Antioxidant effect; homocysteine lowering	III/A

*Preferred to ticlopidine.

[†]For risk reduction of coronary artery disease.

ACE, angiotensin-converting enzyme; CHF, congestive heart failure; COX-2, cyclooxygenase 2; EF, ejection fraction; HDL, high-density lipoprotein; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; LDL, low-density lipoprotein; NSAID, nonsteroidal anti-inflammatory drug.

Adapted from Anderson JL, Adams CD, Antman EM, et al: ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction) Developed in Collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. J Am Coll Cardiol 2007;50:e1-e157.

The combination of an ACE inhibitor and angiotensin receptor blocker was associated with greater intolerance because of hypotension.

β Blockers

The CAPRICORN trial⁶⁵ is the only post-MI trial to investigate the effects of β blockade exclusively in patients with left ventricular systolic dysfunction (left ventricular ejection fraction $\leq 40\%$). The trial randomly assigned 1959 patients to receive either carvedilol or placebo within 3 weeks after admission for MI and had a mean follow-up of 1.3 years. Treatment with carvedilol was associated with a 23% reduction in all-cause mortality ($P = .031$) and a 40% reduction in fatal or nonfatal reinfarction ($P = .01$).

Conclusion

UA/NSTEMI result from atherosclerotic plaque rupture and thrombus formation and the subsequent reduction in myocardial blood flow and oxygen delivery. The initial care of these patients is directed at reducing ischemia and preventing further thrombosis and embolization (Table 14-4). When medical stabilization has been achieved, it is important to estimate the individual patient's risk for adverse events because patients at high risk are more likely to benefit from the addition of antiplatelet inhibition with GPIs and an early invasive strategy with regard to cardiac catheterization. Postdischarge care should focus on risk factor modification, such as aggressive statin therapy, tight blood pressure and glucose control, and tobacco

cessation, and the addition of an ACE inhibitor or angiotensin receptor blocker for patients who sustain impairment of left ventricular function.

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Elevated Cardiac Troponin in the Absence of Acute Coronary Syndromes: Mechanism, Significance, and Prognosis

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CHAPTER

15

Biochemistry and Assays of Troponins
Troponin and Myocardial Damage
Nonthrombotic Mechanisms of Troponin Elevation

Prognostic Significance of Troponin Elevation in
Thrombotic and Nonthrombotic Mechanisms and
Potential Treatment Strategies
Conclusion

PATIENTS PRESENTING to the emergency department with acute chest pain are often difficult to assess and triage because the etiology of their chest pain may range from benign processes to life-threatening diseases. Even patients with acute myocardial infarction (MI) may have symptoms atypical for coronary artery disease, and electrocardiogram (ECG) abnormalities diagnostic for acute coronary syndromes (ACS) may be absent. Because of these limitations, the measurement of serum biomarkers, particularly cardiac troponin, has been used to identify high-risk patients for admission to coronary care units for rapid therapeutic interventions.

Diagnostic criteria used for defining MI have changed significantly in recent years. The previously used World Health Organization definition required the presence of at least two criteria (typical clinical presentation, ischemic changes on ECG, and elevated total creatine kinase (CK) or its MB isoenzyme [CK-MB]) to diagnose an MI properly.¹ An individual with absent biomarker elevation could have been diagnosed with an MI in the appropriate clinical setting and if ECG changes existed. With the advent of more sensitive myocardial biomarkers—the cardiac troponins—new definitions have since been proposed. In 2000, a joint committee of the European Society of Cardiology/American College of Cardiology (ESC/ACC) emphasized the presence of troponin elevation and proposed a new definition for acute MI, stating that “any amount of myocardial damage” (as evidenced by the troponin level) regardless of the magnitude, “implies an impaired clinical outcome,” and should be characterized as an MI.² The 2002 American College of Cardiology/American Heart Association practice guidelines for the management of patients with unstable angina and non–ST segment elevation MI also reflected this view.³

Execution of these new guidelines into clinical practice has significantly increased the frequency of MI diagnoses. Kontos and colleagues⁴ reported that among 2181 patients presenting to the emergency department with chest pain, MI diagnoses based on cardiac troponin level increased 195% compared with diagnoses made according to CK-MB criteria. Troponin testing is now also being used as a screening tool in patients with

a low pretest probability of thrombotic coronary artery disease. Because of its high sensitivity for detecting even minimal myocardial cell necrosis, troponin may become “positive” even in the absence of thrombotic obstruction of a coronary artery. In many instances, these troponin elevations may occur due to demand ischemia, with minor epicardial coronary obstruction (or even without significant coronary artery disease), rather than an acute thrombotic coronary occlusion.⁵ One retrospective study comprising 166 patients presenting to the emergency department with elevated troponin showed that only 61% of the patients had significant coronary stenosis as per coronary angiography.⁶ Ng and colleagues⁷ showed that of 112 patients presenting to the emergency department with increased troponin I levels, 45% had a final diagnosis other than ACS.

Because of the high sensitivity but low specificity in patients with a low pretest probability of thrombotic coronary disease, the detection of even minimal troponin elevation is often immediately associated with ACS, and may divert attention from the true underlying clinical problem, leading to inappropriate admissions to coronary care units and unnecessary diagnostic and therapeutic measures, including coronary angiography. This chapter reviews potential causes of troponin elevations that are unrelated to coronary thrombosis and provides guidance on the evaluation and management of patients with nonthrombotic troponin elevations.

Biochemistry and Assays of Troponins

Cardiac troponins are regulatory proteins found on the contractile apparatus of striated muscle that control the calcium-mediated interaction of actin and myosin.^{8,9} They form complexes with actin and tropomyosin on the thin filament of the contractile apparatus and regulate contraction by initiating or inhibiting the sliding of thin filaments over thick filaments. The troponin complex consists of three subunits (Fig. 15-1): troponin C, which binds to calcium ions and regulates activation of the thin filaments during contraction; troponin T, which binds to tropomyosin and facilitates contraction; and troponin I,

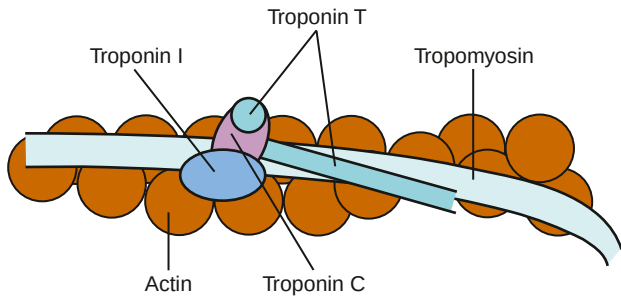


Figure 15-1. Structure of troponin.

which binds to actin and inhibits actin-myosin interactions in the absence of calcium.^{8,10,11}

The amino acid sequences of the skeletal and cardiac isoforms of cardiac troponin T and troponin I are dissimilar. Monoclonal antibodies to both of these cardiac troponins have been developed with no cross-reactivity with troponins from skeletal muscle.³ In contrast, cardiac and skeletal muscle share troponin C isoforms; no clinical assay has been developed to test for this protein because of its lack of cardiac specificity.

Current troponin assays are very sensitive, detecting even small amounts of myocardial necrosis. The ESC/ACC Committee defined MI as a troponin level greater than the upper reference limit of the healthy population—that is, greater than the 99th percentile of the reference control group with a coefficient of variation of 10% or less. Because very few assays being used meet this standard, it has been proposed that a troponin elevation greater than the 10% coefficient of variation be indicative of myocardial injury.¹² Although this reference limit may slightly reduce the sensitivity for MI according to the biochemical diagnostic criterion, it allows providers to avoid being faced with minor troponin elevations that may simply be secondary to analytic noise. With a wide variety of commercial assays being used, each institution's laboratory must first confirm the reference range in their particular population before defining their cutoff for a "significant" troponin elevation.

Troponin and Myocardial Damage

Approximately 7% of troponin T and 3% to 5% of troponin I is normally found free in the myocyte cytoplasm, whereas most is structurally bound in the contractile apparatus of the muscle fiber.¹³ The release of troponin from the myocyte to the blood can be due to reversible or irreversible cell damage.⁸ A biphasic increase in serum troponin occurs during myocardial ischemia, corresponding to the early release of free cytoplasmic proteins, followed by a gradual release of myofibril-bound cytosolic complexes as the myocytes are irreversibly damaged, and the cell membrane degrades.⁸

Speculations have been made regarding the mechanism of this early troponin release. Observations of patients with unstable angina have shown only transient troponin elevations, with values returning to baseline within a few hours.¹⁴ This pattern of early troponin increase may not necessarily be associated with irreversible myocardial necrosis. It is conceivable that myocardial troponin can also be released in the setting of increased membrane permeability. It is thought that myocardial depressive factors (released in the setting of sepsis and other inflammatory states) cause degradation of free troponin in situ to

lower molecular weight fragments.¹⁵ With increased membrane permeability, the smaller troponin fragments could be released into the systemic circulation. In this setting, myocyte damage may not be permanent, and cell necrosis does not occur. This notion is also supported by the clinical observation that myocardial depression during sepsis is a fully reversible process in most surviving patients.¹⁶

Nonthrombotic Mechanisms of Troponin Elevation

Troponin elevation can occur in the absence of ACS. Frequent conditions causing troponin elevation include hypovolemia, sepsis, heart failure, atrial fibrillation, myocarditis, myocardial contusion, pulmonary embolus, and renal failure (Table 15-1).

Demand Ischemia

The term *demand ischemia* refers to inadequate myocardial oxygen supply in the setting of increased demand and in the absence of a thrombotic coronary artery occlusion. Myocardial oxygen demand increases in several clinical conditions, including sepsis or the systemic inflammatory response syndrome,¹⁷⁻¹⁹ hypotension or hypovolemia,²⁰ and atrial fibrillation or other tachyarrhythmias.^{21,22} These disease states can predispose to tachycardia and various loading conditions on the heart. Tachycardia can augment myocardial oxygen demand while decreasing myocardial oxygen supply predominantly by reducing the time of diastole, the time period in which much of myocardial perfusion occurs. Also, systemic inflammatory processes, including sepsis, can result in higher oxygen consumption, decreased perfusion pressure, myocardial depression, and reduced delivery of oxygen to the heart, resulting in release of troponin into the systemic circulation.¹⁸

Elevated troponin is a common finding in critically ill patients and is associated with a significant increase in mortality.¹⁷ Ammann and colleagues¹⁸ reported that in 20 intensive care unit (ICU) patients with sepsis, 85% had elevated troponin levels, 59% of which had no evidence of significant coronary artery disease. A more recent study evaluating 58 ICU patients without ACS found that of the 55% that had elevated troponins, significant coronary artery disease was excluded in 72% of these patients. Levels of C-reactive protein, tumor necrosis factor- α , and interleukin-6 were markedly higher among troponin-positive patients.¹⁹ Mortality was also fourfold higher in this group. Troponin elevation is common in ICU patients without thrombotic ACS. No definitive causal relationship has yet been shown; however, it has been proposed that the inflammatory mediators involved in systemic inflammatory states may contribute to the myocardial oxygen demand-supply mismatch. In addition, whether any cardiovascular work-up or intervention could improve the mortality risk of these patients remains unclear.

Tachycardia and several tachyarrhythmias are other potential causes of demand ischemia in the absence of thrombotic coronary artery disease. Bakshi and colleagues²¹ showed that among 21 patients with elevated troponin levels but a normal coronary angiogram, tachycardia was the cause in 28%, strenuous exercise was the cause in 10%, pericarditis was the cause in 10%, and congestive heart failure was the cause in 5%; 47% of patients had no identifiable trigger.²¹ Similarly, Zellweger and associates²²

Table 15-1. Nonthrombotic Causes and Presumed Mechanism for Elevated Cardiac Troponin Level

Diagnosis	Mechanism
Demand Ischemia	
Sepsis/systemic inflammatory response syndrome	Myocardial depression/supply-demand mismatch
Hypotension	Decreased perfusion pressure
Hypovolemia	Decreased filling pressure/output
Supraventricular tachycardia/atrial fibrillation	Supply-demand mismatch
Left ventricular hypertrophy	Subendocardial ischemia
Myocardial Ischemia	
Coronary vasospasm	Prolonged ischemia with myonecrosis
Intracranial hemorrhage or stroke	Imbalance of autonomic nervous system
Ingestion of sympathomimetic agents	Direct adrenergic effects
Direct Myocardial Damage	
Cardiac contusion	Traumatic
Direct current cardioversion	Traumatic
Cardiac infiltrative disorders	Myocyte compression
Chemotherapy	Cardiotoxicity
Myocarditis	Inflammatory
Pericarditis	Inflammatory
Cardiac transplantation	Inflammatory/immune-mediated
Myocardial Strain	
Congestive heart failure	Myocardial wall stretch
Pulmonary embolism	Right ventricular stretch
Pulmonary hypertension or emphysema	Right ventricular stretch
Strenuous exercise	Ventricular stretch
Chronic renal insufficiency	Unknown

From Jeremias A, Gibson CM: Narrative review: alternative causes for elevated cardiac troponin levels when acute coronary syndromes are excluded. *Ann Intern Med* 2005;142:787.

described four patients with supraventricular tachycardia with increased levels of troponin but no evidence of epicardial coronary stenoses. It is evident from these reports that troponin release can be a result of tachycardia alone, and can be released in the absence of coronary artery disease, inflammatory mediators, and myocardial depressive factors.

Elevated cardiac troponin has also been noted in the setting of left ventricular hypertrophy. Hamwi and colleagues²³ reported that in 74 patients without any clinical evidence of active myocardial ischemia, patients in the upper tertile of left ventricular mass had increased troponin levels compared with patients in

the lowest tertile. The increased left ventricular mass necessitates a greater myocardial oxygen demand and may induce occult subendocardial ischemia. Also, flow reserve is decreased secondary to the remodeling of coronary microcirculation. Similarly, elevated troponins in the setting of aortic valve disease are thought to be associated with greater left ventricular mass and higher pulmonary artery systolic pressures.²⁴

Myocardial Ischemia with Dynamic Coronary Artery Obstruction

Myocardial ischemia, in the absence of obstructive ACS, can also be caused by vasospasm, also termed *Prinzmetal angina*. Wang and coworkers²⁵ evaluated 93 patients with suspected myocardial ischemia and a final diagnosis of nonobstructive coronary artery disease, and found that 25% of these patients had increased troponins. Ergonovine provocation testing subsequently revealed vasoconstriction in 74% of these patients, suggesting that prolonged ischemia can be induced by coronary vasospasm.

Patients with intracranial hemorrhage or acute stroke are frequently found to have elevated troponins alongside ischemic changes on the ECG. Studies have reported approximately 20% of patients with subarachnoid hemorrhages,²⁶ and 27% with acute stroke symptoms²⁷ have increased levels of troponin. It has been proposed that the subsequent imbalance of the autonomic nervous system results in excessive sympathetic activity, and ultimately an increased catecholamine effect on the myocardium.²⁸ This is comparable to the effects seen after consumption of sympathomimetic agents, which have also been associated with myocardial damage and troponin elevation. Substantial elevation of troponin I in the setting of subarachnoid hemorrhage carries an ominous prognosis.²⁹ Ramappa and colleagues²⁹ showed that mortality in patients with subarachnoid hemorrhage was significantly higher in patients with elevated troponin I levels (55% versus 27%; $p=0.01$).

Direct Myocardial Damage

Myocardial injury can also predispose to increased troponin levels secondary to cell injury via inflammation or trauma. One study of 333 patients with significant blunt thoracic trauma showed that the positive and negative predictive values of elevated troponin level predicting cardiac contusion were 21% and 94% respectively,³⁰ emphasizing the utility of troponin in ruling out any traumatic myocardial injury. Blunt cardiac trauma may also include cardiopulmonary resuscitation measures and implantable cardioverter-defibrillator shocks.³¹ Troponin elevation may also be present in infiltrative disorders, such as amyloidosis, and has been shown to have prognostic value within this population.^{32,33} Extracellular amyloid deposition may produce myocyte compression injury, inducing myocardial damage and subsequent troponin release. Troponin testing may also be used in evaluating the cardiotoxicity of anthracycline-based chemotherapeutic agents to help predict future development of a drug-induced cardiomyopathy.³⁴

Inflammatory diseases, including myocarditis, acute pericarditis, and an immune response after heart transplantation, have also been associated with an increase in troponin. Myocarditis may involve inflammatory-mediated myocyte damage, causing the release of cardiac troponins and sometimes, the production of regional wall motion abnormalities on echocardiogram.³⁵ The level of troponin I elevation has been shown to correlate directly

with the size of myocardial inflammation.³⁵ Acute pericarditis can be associated with epicardial myocyte damage. Troponin I has been reportedly elevated in an estimated one third of patients with acute pericarditis, but, as opposed to many other conditions, has not been shown to be a poor prognostic indicator in this patient population.^{36,37} Chronically elevated troponin levels after cardiac transplantation may be a poor prognostic indicator. Labarrere and associates³⁸ performed a prospective cohort study involving 110 patients who had undergone cardiac transplantation and showed that troponin levels, which remained elevated in 51% of these transplant patients, were associated with more fibrin deposition in the microvasculature and myocardium, and a higher risk for graft failure and coronary artery disease.

Heart Failure

Heart failure can lead to troponin release via myocardial strain and myocyte death. Myocardial strain is produced by volume and pressure overload of the right and the left ventricle, causing excessive wall tension with resulting myofibrillary damage. Myocardial strain may be defined as the percentage change of a structure compared with its initial length with the application of stress.²⁴ Support for the "strain" theory comes from multiple studies that show a close positive correlation between troponin and B-type natriuretic peptide (BNP),³⁹ a marker of right and left ventricular wall strain. Troponin degradation has also been shown to be a result of increased preload independent of myocardial ischemia in isolated rat hearts.⁴⁰ It has also been hypothesized that increased myocardial wall stress may lead to decreased subendocardial perfusion, with resulting troponin elevation and decline in left ventricular systolic function.⁴¹

Many reports have described troponin elevation in normal individuals after ultraendurance exercise.^{42,43} This troponin elevation may be related to an increase in myocardial strain during exercise, although catecholamine-induced vasospasm has also been suggested as an explanation.⁸

Progressive myocyte loss is now thought to play a prominent role in the progression of cardiac dysfunction; it may explain the ominous prognosis of patients with congestive heart failure and elevated troponin levels. In vitro experiments with myocytes established a link between myocardial wall stretch and programmed cell death,⁴⁴ which may also represent a cause of increased troponin in this setting. In the setting of acute or chronic congestive heart failure, additional factors, including the activation of the renin-angiotensin system, sympathetic stimulation, and inflammatory mediators, may be partially responsible for myocyte injury and cell death.

Several small studies documented troponin elevation in the presence of congestive heart failure without evidence of ACS. These studies have also established a relationship between troponin elevation and increased mortality during follow-up. Of 238 patients with advanced heart failure who were referred for cardiac transplantation evaluation, 49% were found to have elevated cardiac troponin levels.⁴¹ Patients with detectable troponin had significantly higher BNP levels, type natriuretic peptide levels, higher pulmonary wedge pressures, lower cardiac indices, and a twofold increase in mortality.

Pulmonary Disease

Troponin elevations have also been observed in pulmonary embolism, pulmonary hypertension, and chronic obstructive pulmonary disease (COPD), usually secondary to right heart

strain. Acute pulmonary embolism is characterized by increased right ventricular oxygen demand and intramural pressures and decreased cardiac output, possible features contributing to the right ventricular ischemia or injury that may result.⁴⁵ The reported incidence of troponin elevation in patients with acute pulmonary embolism ranges from 16% to 50%, and elevated levels are associated with a significant increase in mortality.⁴⁶⁻⁴⁸ In contrast to acute myocardial injury, troponin elevation in pulmonary embolus usually resolves within 40 hours. Hsu and colleagues⁴⁹ found that the combination of right ventricular enlargement and elevated troponin I significantly increased 100-day mortality (31.4%) compared with patients with right ventricular dilation alone (17%), elevated troponin I alone (3.7%), or neither (16%). As a result, several authors have advocated the utility of measuring troponin in patients with acute pulmonary embolism to help identify high-risk patients and help determine whether embolectomy or thrombolysis is clinically indicated.^{45,50-52}

Of patients with chronic pulmonary hypertension, troponin was detectable in 14% and was associated with higher heart rates, lower mixed venous oxygen saturation, higher levels of BNP-type natriuretic peptide, and significantly worse cumulative survival at 2 years (81% versus 29%).⁵³ Exacerbations of COPD can also increase troponin levels.⁵⁴ During a COPD exacerbation, the increase in the work of breathing, worsening of pulmonary hypertension, and more negative intrathoracic pressure along with the increase in left ventricular afterload all are possible factors contributing to myocardial injury. Elevated troponin I levels in critically ill COPD patients have been reported to be an important predictor of in-hospital mortality.^{54,55}

Chronic Renal Insufficiency and End-Stage Renal Disease

Persistently elevated cardiac troponin is frequently observed in patients with end-stage renal disease (ESRD).⁵⁶⁻⁵⁸ The prevalence of increased troponin in asymptomatic ESRD patients may be as high as 53%.⁵⁸ This increased troponin may be the result of small areas of clinically silent myocardial necrosis,^{59,60} but other causes, such as increased left ventricular mass and impaired renal troponin excretion, have also been proposed.⁶¹⁻⁶³ There is often a reluctance to use troponin in hemodialysis patients as a diagnostic tool because of the assumption that renal failure per se leads to increased troponin levels and to a false diagnosis of ACS.

Brunet and colleagues⁶² measured the mean basal troponin levels in hemodialysis patients without evidence of ACS (e.g., asymptomatic, no ECG changes) and showed that 2% to 3% of these patients had abnormal troponin I, and 27% had abnormal troponin T. These results suggest that elevated troponin T levels can lead to false-positive diagnoses of ACS, whereas increased troponin I levels should not be neglected in these patients because they are more diagnostic for acute MI. Sharma and coworkers⁶³ showed that in 121 ESRD patients selected for renal transplantation, although elevated troponin T levels did not predict the presence of coronary artery disease, they were often associated with global left ventricular dysfunction as seen on dobutamine stress echocardiogram.

Although the exact mechanism of troponin elimination is unknown, troponin is believed to be cleared by the reticulo-endothelial system because of the relatively large molecular size of troponin.⁵⁸ More recent evidence shows, however, that

troponin T is fragmented into molecules small enough to be renally excreted; this may explain the high prevalence of troponin elevation in patients with severe renal failure.⁶¹ In addition, although it is well known that uremia increases the free serum concentration and clearance of protein-bound drugs, the effect of uremia on the clearance of different troponin subunits is unclear.

Regardless of the cause, detectable troponin in stable patients with ESRD seems to be a powerful predictor of increased long-term, all-cause, and cardiovascular mortality,^{56-59,64-71} and may be an even stronger risk factor in conjunction with elevated C-reactive protein levels.^{56,72} In the GUSTO IV trial, troponin was found to be an independent predictor of death or MI across the entire spectrum of renal function in 7033 patients with ACS.⁷³

Prognostic Significance of Troponin Elevation in Thrombotic and Nonthrombotic Mechanisms and Potential Treatment Strategies

In patients with a high clinical suspicion for thrombotic coronary artery disease, troponin elevation has been associated with a worse prognosis.⁷⁴ The mortality risk seems to correlate with the level of troponin increase. With increasing levels of troponin, a statistically significant increase in mortality exists, with a relative risk for death of 7.8 among the group with the highest level of troponin.⁷⁵ Although impaired epicardial blood flow and the presence of thrombus are associated with increases in troponin,^{76,77} poor myocardial perfusion is an independent predictor of troponin elevation in patients with ACS.⁷⁸

Similarly, troponin elevation in the setting of nonthrombotic disease states, including congestive heart failure, sepsis, pulmonary disease, and renal insufficiency, have also been associated with higher short-term and long-term mortality risks. The reasons for this impaired survival are unclear, but possibly may be secondary to underlying quiescent coronary artery disease or myocardial necrosis with loss of myocytes. Because of the worse prognosis associated with this biomarker, patients with nonthrombotic conditions and an increase in troponins generally should receive a proper diagnostic evaluation, and management should be geared toward treating the underlying disorder.

Discerning the etiology of an elevated troponin (i.e., whether it is secondary to a thrombotic or nonthrombotic mechanism) can be difficult. The presence of chest pain, atherosclerotic risk factors, ischemic changes on the ECG, and regional wall motion abnormalities on echocardiography can help to identify a thrombotic origin for the elevated troponin, and further cardiovascular evaluation, including early cardiac risk stratification, may be implemented.³ In patients with a low pretest probability of coronary artery disease, the underlying cause of the troponin elevation can usually be discerned from a thorough history and physical examination, especially in conditions such as congestive heart failure, sepsis, pulmonary embolism, cardiac contusion, myocarditis, and pericarditis. Data examining the efficacy and outcomes of various therapies in patients with troponin elevation in the absence of ACS are sparse. Patients with a nonthrombotic condition are unlikely to derive benefit from anti-thrombotic, antiplatelet, or invasive revascularization therapies

that are commonly used in thrombotic ACS. Rather, management should be targeted toward treating the underlying cause.

Although an elevated troponin level may be associated with increased risk of morbidity and mortality, a normal troponin level does *not* mean that the patient is not at risk. Heesch and colleagues⁷⁹ reported that patients presenting with ACS in the absence of troponin elevation still had an estimated 4% incidence of MI and death at 30 days.

Conclusion

Troponin is an exceptionally sensitive biomarker that is used to detect myocardial damage.⁸⁰ Its measurement in clinical practice, however, has been referred to by some authors as a double-edged sword,⁸¹ because the detection of even minor troponin increases may be associated with ACS and divert focus from other possible clinical problems. When patients with suspected ACS “make troponins,” guidelines for management exist, and treatments, including antithrombotic, antiplatelet, and interventional therapies, may be implemented. No data support the role of these therapies, however, in the management of patients with a nonthrombotic syndrome causing a troponin increase. Instead, treatment should be aimed at the underlying disorder.

Finally, although the high sensitivity of troponin may be used to help “rule out” a non-ST segment elevation MI, its low specificity for ACS makes it difficult to “rule in” an event. Consequently, when tested indiscriminantly in populations with low cardiac risk profiles, the positive predictive value of troponin becomes significantly reduced. In the absence of thrombotic ACS, an elevated troponin can aid with determining prognosis, and screening may still be justified on this basis.

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Complications of Acute Myocardial Infarction

Recurrent Ischemia after Reperfusion Therapy for Acute Myocardial Infarction

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CHAPTER 16

Predictors
Incidence
Consequences

Prevention
Recognition
Treatment

RECURRENT ISCHEMIA after acute myocardial infarction (MI) is a heterogeneous process. It is most often caused by reocclusion of the infarct-affected artery by thrombosis, but also may occur as a result of spasm, extension of subintimal hemorrhage (usually after angioplasty at that site), inadequate collaterals to the same territory in the face of increased myocardial oxygen demand, or “ischemia at a distance”¹ unrelated to the initial culprit site. Recurrent ischemia also may result in processes as disparate as recurrent MI or occult reocclusion without any symptoms.

Predictors

Symptomatic recurrent ischemia after presentation with MI is more likely in patients treated with thrombolysis rather than primary percutaneous coronary intervention (PCI) (see later), patients with recurrent electrocardiogram (ECG) changes, patients with substantial myocardial salvage, patients with high-grade residual stenoses, and patients with augmented platelet and thrombin activation. Demographic and clinical variables have not proved to be helpful in predicting which patients will develop reocclusion.^{2,3} One large series found, however, that clinical predictors of reinfarction included advanced age, shorter time to thrombolysis, nonsmoking status, prior MI or angina, female sex, anterior infarction, and lower systolic blood pressure.⁴ Other authors have reported that right coronary artery infarcts and infarcts associated with bradycardia on admission are more prone to reocclusion.⁵

The TIMI-4 trial attempted to identify angiographic predictors of reocclusion after thrombolysis.⁶ TIMI grade 2 flow, lesion ulceration, presence of collaterals, and eccentric lesions were associated with a significantly higher rate of infarct-related artery reocclusion (Fig. 16-1). In contrast to these findings, other studies, such as GUSTO and TAMI, did not find angiographic

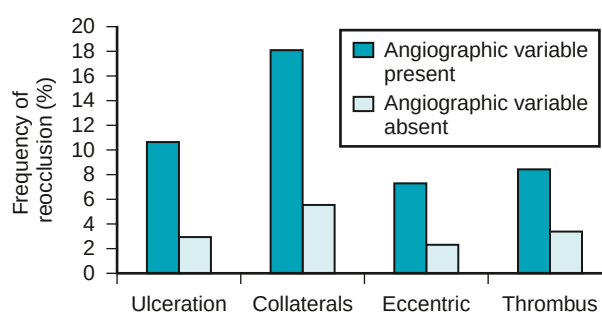


Figure 16-1. Infarct-related artery reocclusion.

features at a 90-minute baseline study to be helpful for predicting reocclusion.^{7,8} There were, however, important differences among these trials that could explain the different findings.⁶ Other authors have associated the following characteristics with persistent symptoms, adverse in-hospital outcomes, or reocclusion: lesion ulceration,⁹⁻¹² high-grade residual stenosis and reduced lumen area,¹³⁻¹⁷ and lack of restoration of normal coronary flow (TIMI flow <3).¹⁸⁻²²

Incidence

In the era before reperfusion, recurrent angina with or without ECG changes occurred in 19% to 37% of patients, but reinfarction was far less common. Recurrent ischemia was more frequently seen in patients who had not initially developed a Q wave MI,²³⁻²⁶ although this classic teaching has not been a uniform finding.²⁶ After coronary reperfusion, within the first few hours of infarction, the risk of recurrent ischemia is higher than without reperfusion, presumably because the risk is higher with an open

infarcted artery and salvaged myocardium. In a meta-analysis of nearly 50,000 patients from six large, placebo-controlled thrombolytic trials of patients usually treated less than 6 hours from the onset of symptoms, reinfarction occurred in 3.6% of patients treated with thrombolytic agents compared with 3% of patients who did not undergo thrombolysis ($P < .001$).²⁷⁻³² In the two placebo-controlled thrombolytic trials in which all patients had symptoms for at least 6 hours before treatment (i.e., EMERAS³³ and LATE³⁴), there was no difference in the incidence of reinfarction between patients treated with or without thrombolysis (2.4% versus 2.9%; $P = .10$), presumably because MIs treated later had less salvaged myocardium.

After apparently successful fibrinolysis by clinical criteria, and despite adjunctive pharmacologic therapy, early recurrence of ischemia or ST segment shifts (threatened reocclusion) have been observed in 20% to 30% of patients,^{35,36} thrombotic coronary reocclusion has been observed in 5% to 15% before hospital discharge and in 25% by 3 months,^{2,3,37-39} and early reinfarction has been observed in 3% to 5%.^{4,39-43} When symptomatic reocclusion occurs after thrombolytic therapy, it generally occurs (80% of the time) within the first 2 days after treatment. Only a few reocclusions occur during the initial hospitalization, however. Reocclusion is clinically silent in more than 50% of cases and tends to occur later.³ In the APRICOT study,³⁸ 300 patients treated with recombinant tissue plasminogen activator (rt-PA) with patent infarct-affected arteries, documented by angiography 24 to 48 hours after treatment, underwent protocol-required repeat cardiac catheterization 3 months later. The patients were further randomly assigned to treatment with aspirin, warfarin, or neither drug. At follow-up, 25%, 30%, and 32% in the three groups had reocclusions, only 25% of which were associated with a recurrent MI. Because reocclusion can be clinically silent, late angiography remains the gold standard in assessing the frequency of reocclusion.

In an overview by Granger and colleagues⁴⁴ of 1183 patients with paired angiograms, 14% of patients receiving rt-PA versus 8% of patients treated with non-fibrin-specific agents had reocclusion ($P = .002$). This finding was not confirmed, however, in the similarly sized angiographic arm of the GUSTO-I study, possibly because of the more vigorous treatment of patients receiving rt-PA with heparin in the latter study. Also, patients treated with accelerated or weight-adjusted rt-PA regimens consistently had lower rates of reocclusion than patients treated with the original U.S. Food and Drug Administration–approved 3-hour dosing regimen.^{5,45} In two reviews of almost 76,000 patients from GUSTO-I, GUSTO-III, TIMI, and InTIME II trials, reinfarction occurred in 4.3% of patients at a median of 2 to 4 days after fibrinolytic therapy, and was independent of the fibrinolytic agent used.^{4,39}

Reinfarction might occur in a new territory, rather than reflecting failed fibrinolysis in the index territory. This issue was addressed in a report from the HERO-2 trial of bivalirudin versus unfractionated heparin before streptokinase administration. Confirmed reinfarction occurred in 552 patients (3.2%). Among these patients, 4% (0.15% of all patients) had ST segment elevation in a new territory at a mean of 46 hours.⁴⁶

Multiple randomized trials have been done to compare PCI with thrombolytic therapy. PCI enhances survival with a lower rate of intracranial hemorrhage and recurrent MI. In a review of 23 trials, primary PCI was better than thrombolytic therapy at reducing death (7% versus 9%; $P = .0002$) and nonfatal

reinfarction (3% versus 7%; $P < .0001$). The review included 7739 patients; streptokinase was used in 8 trials ($n = 1837$), and fibrin-specific agents were used in 15 trials ($n = 5902$). Stents were used in 12 trials, and platelet glycoprotein (GP) IIb/IIIa inhibitors were used in 8 trials. The results seen with primary PCI remained better than the results seen with thrombolytic therapy during long-term follow-up, and were independent of the type of thrombolytic agent used, and whether or not the patient was transferred for primary PCI.⁴⁷

Several randomized trials (DANAMI-2, STAT, STOPAMI-1, and STOPAMI-2) have shown a better outcome with primary stenting compared with thrombolysis.⁴⁸⁻⁵¹ The largest is the DANAMI-2 trial, which was discontinued prematurely because of a significant reduction in the primary end point of mortality, reinfarction, or stroke at 30 days with PCI (8% versus 13.7%). The benefit was primarily due to less reinfarction.⁴⁸

The clinical efficacy of primary balloon angioplasty in acute ST segment elevation myocardial infarction (STEMI) and other settings is limited by the risks of early reocclusion and late restenosis, providing the rationale for the use of intracoronary stents. Initial nonrandomized studies suggesting that primary stenting was more effective than primary balloon angioplasty⁵²⁻⁵⁴ were followed by randomized trials.⁵⁵⁻⁵⁸ A 2005 meta-analysis evaluated nine randomized trials comprising 4433 patients.⁵⁹ Stenting was associated with significant reductions in reinfarction (odds ratio [OR] 0.52 at 30 days, OR 0.67 at 1 year) and target vessel revascularization (OR 0.45 at 30 days, OR 0.47 at 1 year). There was no significant difference in mortality (OR 1.06 at 1 year). Finally, in a 2007 meta-analysis of eight randomized trials of drug-eluting stents versus bare metal stents involving 2786 patients, reinfarction was less common with drug-eluting stents (OR 0.72), whereas there was no difference in stent thrombosis (OR 0.86) or mortality (OR 0.76).⁶⁰

Consequences

The consequences of reocclusion depend partly on the amount of newly ischemic myocardium, the capacity of the remaining myocardium to compensate, and whether adequate coronary flow is promptly re-established. Whether symptomatic or silent, reocclusion is associated with significant morbidity and mortality in the short-term and the long-term. In the report by Ohman and coworkers³ from the TAMI study, reocclusion was associated with about a threefold risk of worsened ventricular function, heart failure, and conduction abnormalities, and a higher in-hospital mortality ($P = .01$) than maintained coronary patency (Table 16-1).

In the University of Michigan 1984-1990 experience,⁶¹ of 405 patients with paired baseline and prehospital discharge angiography, the mortality rate for patients with sustained reperfusion was 2%, but it was 15% after reperfusion and reocclusion. Risk factors for death after recurrent ischemia were advanced age, hemodynamic instability at the time of initial presentation, multivessel disease, and failure to obtain successful reperfusion within 90 minutes of recurrent ischemia (all $P < .05$).⁶¹

In two reviews of almost 76,000 patients from GUSTO-I, GUSTO-III, TIMI, and InTIME II,^{4,39} patients with reinfarction had a higher overall mortality rate at 30 days (11.3% to 16.4% versus 3.5% to 6.2% without reinfarction), which could be markedly reduced with PCI during index hospitalization.^{4,39} The data were conflicting as to whether 30-day survivors of reinfarction

Table 16-1. Consequences of Coronary Reocclusion after Thrombolytic Therapy for Acute Myocardial Infarction*

Clinical Event	Infarct Artery Patent (% of Patients)	Infarct Artery Reoccluded (% of Patients)
Improvement in LVEF, baseline to day 7	+3	-1
Pulmonary edema	4	19
Sustained hypotension	17	25
Second-degree or third-degree AV block	13	25
In-hospital death	5	11

*TAMI trial (N = 810 patients).

AV, atrioventricular; LVEF, left ventricular ejection fraction.

do^{4,39} or do not^{4,39} have a modest increase in risk from 30 days to 1 year. In the TIMI and InTIME II trials, most deaths occurred early, and the risk of additional deaths between the index hospital period and 2 years was not significantly increased in patients with recurrent MI.³⁹

Prevention

The thrombus associated with reocclusion after thrombolytic therapy or stenting is typically platelet-rich⁶² and resistant to further thrombolysis. The effect of thrombolytic agents on platelet function is complex, involving thrombin activation and perturbation of the GP IIb/IIIa and the GP Ib receptors, but in aggregate, platelet activation is often demonstrable.^{63,64}

The effect of aspirin, a weak platelet antagonist, has been studied in several trials, most notably ISIS-2.^{29,65} Reinfarction was essentially halved with aspirin usage in ISIS-2 (1.8% versus 3.3%; $P < .0001$), and an overview suggested that reocclusion was similarly reduced (11% versus 25%; $P < .001$).

Thienopyridines were initially considered as an alternative to aspirin in patients with STEMI. The benefit of this approach was suggested by results from the CAPRIE trial, which was not limited to STEMI, and the STAMI trial, which showed that clopidogrel and ticlopidine are at least as effective as aspirin.⁶⁶⁻⁶⁸ The role of clopidogrel in addition to aspirin must be considered in the context of the form of reperfusion therapy (primary PCI, thrombolysis, or no reperfusion). In the setting of STEMI treated with thrombolytic therapy, two randomized trials (CLARITY-TIMI 28 and COMMIT/CCS-2) showed clear evidence of benefit from early administration of clopidogrel in addition to aspirin.^{69,70}

No randomized trials have specifically evaluated the efficacy of clopidogrel in addition to aspirin in patients with STEMI who are not reperfused. Half of patients in COMMIT/CCS-2, which showed benefit from clopidogrel therapy, were not reperfused, however.⁶⁹ Most physicians also extrapolate from the benefit seen with clopidogrel in patients with non-ST segment elevation acute coronary syndromes who were not revascularized in the CURE trial.⁷¹ No randomized trials have evaluated the efficacy of clopidogrel in addition to aspirin in patients with STEMI who are treated with primary PCI. Most clinicians give clopidogrel based on extrapolation from randomized trials (PCI-CURE

and CREDO) in patients with non-ST segment elevation acute coronary syndromes. These trials showed that clopidogrel improves short-term and long-term cardiovascular outcomes—reduction of acute thrombotic complications—when given in addition to aspirin in patients treated with PCI.^{72,73}

Along with aspirin, heparin has also been a standard treatment after thrombolytic therapy. GUSTO-I results suggest that heparin is unnecessary when streptokinase is the thrombolytic agent used, but several studies have suggested that heparin improves short-term patency after rt-PA use.^{74,75} Hsia and colleagues⁷⁶ observed that the degree of elevation of activated partial thromboplastin time (aPTT), not the use of heparin, was crucial in determining patency after rt-PA use. In the HART study, if the aPTT in the first 12 hours after rt-PA use was less than 45 seconds, only 45% of infarct-affected arteries were patent at follow-up, but if the aPTT was longer than 60 seconds, 95% of vessels were open. Higher aPTT values are associated with a greater risk of bleeding. Data from the much larger GUSTO-I study suggest that the optimal compromise in reducing both risks is to have the aPTT between 63 and 72 seconds.⁷⁷

Two randomized studies addressed the issue of how long heparin should be continued in this setting.^{78,79} Both studies concluded that heparin could be safely discontinued in most patients after 24 hours. American College of Cardiology (ACC)/American Heart Association (AHA) 2004 STEMI guidelines recommended infusions of heparin routinely for 48 hours, and for a longer period only in patients with an ongoing indication for anticoagulation.⁸⁰⁻⁸²

Although no new trials specifically focusing on heparin in STEMI have been reported, numerous studies have compared alternative anticoagulant regimens (reviparin, fondaparinux, or enoxaparin) with heparin or placebo. In these studies, the new regimen was administered for the duration of the index hospitalization. The CREATE (reviparin versus placebo),⁸³ OASIS-6 (fondaparinux versus placebo or heparin),⁸⁴ and ExTRACT-TIMI-25 (enoxaparin versus heparin)⁸⁵ trials provided a rationale for a new recommendation of anticoagulation therapy for a minimum of 48 hours, preferably extended to the duration of the index hospitalization (up to 8 days) for patients undergoing reperfusion with fibrinolytics.⁸⁶ In the reperfused cohort of the CREATE trial, reviparin was associated with fewer deaths, reinfarctions, and strokes (11% versus 12.3% at 30 days). Reviparin was associated, however, with higher rates of life-threatening bleeding (1.1% versus 0.4% at 30 days).^{83,86} In the subset of OASIS-6 trial patients submitted to thrombolysis, fondaparinux was superior to control therapy (placebo or unfractionated heparin) with lower rates of death, reinfarction and severe hemorrhage at 30 days.^{86,89} This benefit was not observed in the cohort submitted to primary PCI, with a trend toward worse outcome.^{84,86}

In the ExTRACT-TIMI 25 trial, enoxaparin compared with unfractionated heparin was associated with lower rates of death and reinfarction (9.9% versus 12% at 30 days), but with higher rates of severe hemorrhage (2.1% versus 1.4% at 30 days). Findings were consistent among subgroups, regardless of thrombolytic agent type, age (dose was adjusted for patients >75 years old), or postlysis PCI.^{85,86} In the 2007 update ACC/AHA STEMI guidelines, unfractionated heparin, enoxaparin, and fondaparinux were considered as anticoagulation regimens with established efficacy as ancillary therapy to thrombolysis.⁸⁶ Anticoagulation regimens with unfractionated heparin or low-molecular-weight

heparins should be maintained if patients proceed to PCI, without crossover to other agents.⁸⁶ Fondaparinux is associated, however, with catheter thrombosis, and additional anticoagulation with anti-factor IIa activity, such as unfractionated heparin or bivalirudin, is recommended.⁸⁶

The search for better agents led to direct thrombin inhibitors and to antagonists of the final common pathway of platelet aggregation, the GP IIb/IIIa receptor. Direct thrombin inhibitors have the putative advantages over heparin of accessing clot-bound thrombin, having no reliance on antithrombin III (in which some patients are deficient), having no natural inhibitors, and being easier to regulate therapeutic levels.⁸⁸ The phase II TIMI-5 study suggested that these characteristics would translate into clinical benefits, with greater coronary patency after rt-PA use with hirudin than heparin (98% versus 89%; $P = .01$) and with a reduction in in-hospital death or reinfarction (7% versus 17%; $P = .02$).⁸⁹ These results were not confirmed by the larger GUSTO-IIa and TIMI-9a studies,^{87,90} however, both of which were stopped prematurely because of an excess of bleeding and strokes with hirudin.

Clinical experience with bivalirudin in the setting of acute MI has shown some benefit.^{91,92} In a pilot trial (HERO) of 412 patients receiving streptokinase and aspirin, a dose-related improvement in TIMI grade 3 flow was observed with bivalirudin in 48% of patients in the high-dose bivalirudin group, 46% of patients in the low-dose bivalirudin group, and 35% of patients in the heparin group. There were no differences in reocclusion or clinical end point event rates, and major bleeding seemed to be less frequent with bivalirudin. Based on these favorable findings, bivalirudin was compared with unfractionated heparin in the HERO-2 mortality trial in 17,073 patients receiving streptokinase.⁹¹ At 30 days, there was no difference in mortality rates (10.5% versus 10.9% with heparin); there was a small but significant reduction in reinfarction at 96 hours with bivalirudin (1.6% versus 2.3%); there was a nonsignificant trend toward more episodes of severe bleeding (0.7% versus 0.5%; $P = .07$) and intracerebral bleeding (0.6% versus 0.4%; $P = .09$) with bivalirudin; and there was a significant increase in moderate and mild bleeding with bivalirudin.

In the HORIZON AMI trial, patients treated with primary PCI (stenting) were randomly assigned to unfractionated heparin plus a GP IIb/IIIa inhibitor (abciximab or eptifibatide), or to bivalirudin monotherapy stopped at the end of the procedure plus provisional GP IIb/IIIa inhibitors for large thrombus or refractory no-flow. Only 7.2% of patients in the bivalirudin-treated group also received GP IIb/IIIa inhibitors in the catheterization laboratory. At 30 days, investigators saw a 24% reduction in net adverse clinical events and a 40% reduction in major bleeding—the primary end points of the study. Major adverse cardiac events, defined as all-cause death, reinfarction, ischemic target vessel revascularization, or stroke, were not different between the two groups. There were no significant differences between any of the individual event rates that made up the major adverse cardiac events end point, with the exception of cardiac mortality, which was significantly reduced in patients in the bivalirudin arm of the study.⁹³

Combination therapy using a half-dose of a thrombolytic agent with a GP IIb/IIIa inhibitor may be more likely to restore coronary perfusion; promote ST segment resolution at 90 minutes; and reduce the incidence of recurrent ischemia, nonfatal reinfarction, and rescue PCI. Despite these benefits, two large

trials, GUSTO V^{94,95} and ASSENT-3,^{96,97} and a meta-analysis found no improvement in survival compared with conventional thrombolytic therapy, and bleeding was increased, particularly in patients older than 75 years.⁹⁸ Presently, the use of GP IIb/IIIa inhibitors with thrombolysis is not recommended.^{80-82,99}

Adjunctive abciximab therapy during primary PCI for STEMI was evaluated after angioplasty alone in RAPPORT and CADILLAC and with stenting in ISAR-2, ADMIRAL, CADILLAC, and ACE. In a meta-analysis that included all five trials, abciximab therapy in patients undergoing primary PCI was associated with significant reductions in mortality at 30 days (2.4% versus 3.4% with placebo) and 6 to 12 months (4.4% versus 6.2%), and in reinfarction at 30 days (1% versus 1.9%); there was no increase in bleeding.⁹⁸ This analysis provides strong support for the concept that abciximab is beneficial in reducing acute ischemic events during primary PCI with stenting. Several trials tested the (upstream) abciximab hypotheses. The more recent, large FINESSE trial showed no benefit of “upstream” abciximab compared with abciximab given in the catheterization laboratory.¹⁰⁰

The pharmacologic approach may not be the only effective one for the prevention of recurrent ischemia. Improvement in coronary flow by PCI seems to reduce recurrent adverse events compared with thrombolytic use alone. Among the 20,101 patients enrolled in the TIMI trials, PCI during the index hospitalization was associated with a lower rate of in-hospital reinfarction (1.6% versus 4.5%) and a lower 2-year mortality rate (5.6% versus 11.6%). Performance of coronary artery bypass graft (CABG) surgery was also associated with a lower recurrent rate of infarction (0.7% versus 4.3%) and lower 2-year mortality rate (7.95% versus 10.6%).³⁹

Two early studies suggested less recurrent ischemia in association with intra-aortic balloon pump use than without it.¹⁰⁰⁻¹⁰² This finding was challenged by the PAMI 2 study,¹⁰³ where prophylactic intra-aortic balloon pump strategy after primary PCI in hemodynamically stable high-risk patients did not decrease the rates of infarct-related artery reocclusion or reinfarction, promote myocardial recovery, or improve overall clinical outcome. We recommend the use of intra-aortic balloon pump for hemodynamic support and in the rare instance that PCI cannot provide a satisfactory angiographic luminal (<50% stenosis) and flow (TIMI 3) result.

Lastly, considering late and very late stent thrombosis to be a form of reinfarction, the benefit and optimal duration of clopidogrel need be considered. In the only randomized trial to address early dosing, Han and colleagues¹⁰⁴ found 150 mg to be superior to 75 mg daily in reducing the risk of reinfarction after drug-eluting stenting (few of these patients were initially treated for acute MI, however).^{105,106} Consensus calls for at least 12-month dosing of clopidogrel after drug-eluting stenting. Beyond that, data are conflicting regarding the benefit of more protected dosing.^{105,106}

Recognition

Many reocclusions are silent. Because of the lack of sensitivity and specificity of single-lead ECG systems to detect changes that might be seen on a 12-lead ECG, some cardiologists have advocated routine 12-lead continuous monitoring for 48 hours. Not all studies have found re-elevation of ST segments to be associated with worsened outcome, but most have.^{107,108}

Recurrent chest pain with any ECG changes, silent ST segment elevation, a 30% to 50% increase of creatine kinase after it has reached its early peak, new heart failure, high-grade atrioventricular block, or ventricular tachycardia (the last with considerably less specificity) should alert the clinician to the possibility of coronary reocclusion. Because reocclusion can be clinically silent, late angiography remains the gold standard in assessing the frequency of reocclusion.

The 2004 ACC/AHA Task Force recommended some specific guidelines for the diagnosis of reinfarction after acute STEMI.^{81,82} Within the first 18 hours of the initial MI, a recurrent elevation in cardiac biomarkers alone should not be relied on to diagnose reinfarction, but should be accompanied by recurrent ST segment elevation on ECG and at least one other supporting criterion (e.g., recurrent chest pain or hemodynamic decompensation). For patients more than 18 hours from the initial MI, a biomarker increase of at least 50% and at least one additional criterion are sufficient for the diagnosis.^{81,82} The joint ESC/ACCF/AHA/WHF (European Society of Cardiology/American College of Cardiology/American Heart Association/World Health Federation) Task Force for the redefinition of MI established the following as criteria for diagnosing reinfarction: recurrent ischemic symptoms or ECG changes or both after the initial MI together with an increase 20% or greater of biomarkers (preferably troponin) measured after the recurrent event with at least one value above the 99th percentile of the reference range.¹⁰⁹⁻¹¹²

Treatment

PCI is the treatment of choice for patients with recurrent MI. The magnitude of the benefit was illustrated in a retrospective review of 20,100 patients from the TIMI and InTIME-II trials of fibrinolytic therapy.³⁹ Among the 4.2% of patients with a recurrent MI, the in-hospital mortality was 23.6% in patients who were treated medically and did not undergo revascularization compared with 5.2% with PCI; an equivalent benefit was seen with the smaller number of patients who underwent CABG surgery. A similar dramatic reduction in mortality with revascularization was noted in another review.⁴⁰ In GUSTO-I and ASSENT-2, 4% of patients ($n = 2301$) experienced reinfarction after thrombolytic therapy. The 30-day mortality did not differ between the repeat thrombolysis and revascularization groups ($P = .72$), but it was significantly lower in patients treated by these two strategies than in patients treated conservatively (11% and 11% versus 28%; $P < .001$). Stroke rates did not differ significantly between the three treatment strategies ($P = .49$).⁴⁰

PCI or surgery is also warranted in patients with STEMI who, after fibrinolytic therapy, develop spontaneous symptomatic angina or inducible post-MI ischemia on a predischARGE exercise test. Benefit from invasive therapy was shown in the DANAMI trial, in which 1008 patients were randomly assigned to conservative therapy or to revascularization with PCI or CABG surgery 2 to 10 weeks after MI.¹¹³ Revascularization was associated with a lower rate of reinfarction and admission for unstable angina; mortality after a median follow-up of 2.4 years was equivalent in both groups.

The efficacy of retreatment with a fibrinolytic agent primarily has been evaluated in patients with threatened reocclusion. There are two major problems with repeat fibrinolysis: excess bleeding risk, particularly with early reuse, and decreased efficacy, in view of initial treatment failure. Most retreatment studies have involved alteplase and, to a lesser degree, other

nonantigenic agents such as tenecteplase. Streptokinase should be avoided because of antigenicity and relative resistance.

Numerous reports have shown the feasibility and efficacy of repeat fibrinolytic therapy with alteplase.¹¹⁴⁻¹¹⁶ A retrospective study assessed the outcome of repeat infusions of alteplase in patients who developed early recurrent myocardial ischemia with threatened reinfarction after initial therapy with either alteplase (46 patients) or streptokinase (6 patients).¹¹⁴ Complete resolution of acute ischemia within 1 hour of the second infusion was achieved in 85%; half of these patients had a sustained response and avoided further coronary intervention. Bleeding complications occurred in 19%, but only 4% required transfusion.¹¹²

A later study evaluated the effects of retreatment with alteplase given for early signs of reocclusion after fibrinolysis, as manifested by recurrent chest pain lasting for more than 30 minutes with re-elevation of the ST segment.¹¹⁶ This complication occurred in 26 of 652 patients (4%) treated with alteplase, usually within 24 hours of the first infusion, particularly if intravenous heparin was not used. The second dose of alteplase was 50 mg when threatened reocclusion occurred within 24 hours of initial therapy and 100 mg after 24 hours. All patients had a good clinical response to retreatment; the new ST segment changes disappeared, and pain resolved within 100 minutes (median 50 minutes). Angiographic findings, determined at 1 hour, were less favorable. Coronary artery patency was observed in 73% of patients who had received intravenous heparin and only 40% of patients not receiving heparin. Bleeding rates were similar to those after a single dose of alteplase.

Randomized trials have not been performed to assess the comparative efficacy of repeat fibrinolysis and PCI in patients with recurrent ischemia or threatened reinfarction. As mentioned before, this issue was assessed in a retrospective review of GUSTO-I (alteplase) and ASSENT-2 (tenecteplase) trials.⁴⁰ Repeat fibrinolysis and revascularization with PCI or surgery were equally effective and were associated with significantly lower 30-day mortality than conservative therapy without any increase in the rate of stroke.

A few adjunctive agents have been proposed for threatened reocclusion or reinfarction, but clinical experience is limited. These agents include optimal antithrombin therapy (e.g., optimal heparin dosing) and antiplatelet therapy (e.g., with a GP IIb/IIIa antagonist). As noted earlier, the response to repeat alteplase is reduced in patients who are not treated with heparin.¹¹⁶ Suboptimal or inadequate anticoagulation with heparin is also associated with lower coronary patency rates,⁷⁸ whereas overly aggressive heparin is associated with an increased risk of hemorrhagic events.^{87,90} Several trials have evaluated the efficacy of a GP IIb/IIIa inhibitor with lower doses of fibrinolytic therapy to improve early reperfusion success and reduce subsequent reocclusion and reinfarction.¹¹⁷ No mortality benefit has been shown so far, and there is an increased risk of bleeding, particularly in elderly patients. GP IIb/IIIa inhibitors have not been formally tested for threatened reocclusion after fibrinolysis. The ability of abciximab to stabilize and reverse threatened reocclusion after coronary angioplasty has been reported.¹¹⁶

CABG surgery is performed infrequently for revascularization after fibrinolysis. In TIMI and InTIME-II trials ($N = 20,092$ patients), CABG surgery was performed in 1048 (5.2%) patients.³⁹ PCI is preferred in this setting because of increased risks of perioperative mortality and major hemorrhage with CABG surgery, especially if the interval between administration

of the fibrinolytic agent and surgery is short (<24 hours).¹¹⁸ Survivors of the perioperative period have better long-term outcome, however, than patients treated medically.^{39,118}

Based on available data, reopening an infarct vessel days after occlusion is not recommended.¹¹⁹⁻¹²¹ Previous smaller studies provided conflicting evidence,¹²²⁻¹²⁷ but the more recent OAT trial showed that performing late angioplasty plus stenting and optimal medical therapy on a persistent total occlusion 3 to 28 days after MI does not reduce rates of death (9.1% versus 9.4%), reinfarction (7% versus 5.3%), or New York Heart Association class IV heart failure (4.4% versus 4.5%) compared with optimal medical therapy alone.¹²⁸ Patients treated with PCI showed a trend toward more repeat MIs than patients treated medically.

A total of 381 patients enrolled in the OAT study were included in the TOSCA-2 ancillary study, in which coronary and left ventricular angiography was performed 1 year after randomization. Earlier studies have suggested that PCI beyond the accepted period of myocardial salvage might lead to improved left ventricular function and slow left ventricular remodeling. TOSCA-2 results indicated that 83% of PCI-treated patients had patent infarct-related arteries at 1 year compared with 25% in the medical therapy group ($P < .001$). Left ventricular ejection fraction improved in both groups by approximately 4%, but with no significant differences between the two groups. Change in left ventricular end-diastolic volume index was smaller in the PCI group, at 3.2 mL/m² versus 5.3 mL/m² in the medical therapy-only group, suggesting that PCI had a favorable effect in terms of reducing ventricular enlargement. This finding only trended toward statistical significance.¹²⁹

OAT trial results were taken into account in the 2007 update of the ACC/AHA/SCAI (American College of Cardiology/American Heart Association/Society of Coronary Angiography and Intervention) PCI guidelines. PCI is now not recommended in patients 24 hours to 28 days post-MI with one or two vessel disease and a totally occluded coronary artery if they are hemodynamically and electrically stable and have no ongoing or easily provoked chest pain. PCI might be used selectively, however, in patients who do not continue to do well on drug therapy alone.^{119,120}

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Cardiogenic Shock

Eric R. Bates

CHAPTER

17

Epidemiology
Pathogenesis
Clinical Presentation
Management

Reperfusion Strategies
New Approaches
Prognosis
Conclusion

DRAMATIC ADVANCES during the past several decades in diagnosing, monitoring, and treating patients with acute myocardial infarction (MI) have decreased hospital mortality rates by 50%. The organization of coronary care units in the 1960s to treat lethal arrhythmias¹ and the development of fibrinolytic therapy in the 1980s to reduce infarct size²⁻⁵ were the biggest breakthroughs. Cardiogenic shock, not arrhythmia, is now the most common cause of death in patients hospitalized with acute MI. However, neither the incidence nor the mortality rate associated with cardiogenic shock has been reduced by modern cardiac intensive care unit interventions, including vasopressor and inotropic drug infusions, hemodynamic monitoring, and intra-aortic balloon pump (IABP) counterpulsation (Table 17-1).⁶⁻¹² More recent reports show a survival advantage, however, for patients who undergo successful reperfusion with percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery.¹³⁻¹⁹ This chapter reviews the epidemiology, pathogenesis, clinical presentation, and current management of cardiogenic shock.

Epidemiology

Definition

Circulatory shock is characterized by the inability of tissue blood flow and oxygen delivery to meet metabolic demands. Cardiogenic shock is a type of circulatory shock resulting from severe impairment of ventricular pump function rather than from abnormalities of the vascular system or blood volume. It is important to separate the shock state, in which tissue perfusion is inadequate, from hypotension, in which tissue metabolic demands may be met by increasing cardiac output or decreasing systemic resistance.

The diagnosis of cardiogenic shock should include the following:

1. Systolic blood pressure less than 80 mm Hg without inotropic or vasopressor support, or less than 90 mm Hg with inotropic or vasopressor support, for at least 30 minutes.
2. Low cardiac output (<2 L/min/m²) not related to hypovolemia (i.e., pulmonary artery wedge pressure <12 mm Hg), arrhythmia, hypoxemia, acidosis, or atrioventricular block.
3. Tissue hypoperfusion manifested by oliguria (<30 mL/hr), peripheral vasoconstriction, or altered mental status.

Table 17-1. Historical Milestones in Cardiogenic Shock

1934	Fishberg et al ⁶ described the shock state as a peripheral complication of myocardial infarction
1942	Stead and Ebert ⁷ attributed the shock state to extreme myocardial dysfunction
1954	Griffith et al ⁸ used L-norepinephrine as pressor support
1967	Killip and Kimball ¹ showed no survival advantage with coronary care unit monitoring
1968	Kantrowitz et al ⁹ described the clinical use of the IABP
1972	Dunkman et al ¹⁰ showed successful treatment with CABG surgery
1973	Scheidt et al ¹¹ showed no survival advantage with IABP
1976	Forrester et al ¹² defined hemodynamic subsets using the pulmonary artery catheter
1980	DeWood et al ¹³ showed a survival advantage with early CABG surgery
1980	Mathey et al ¹⁴ showed successful treatment with fibrinolytic therapy
1982	Meyer et al ¹⁵ showed successful treatment with PTCA
1988	Lee et al ¹⁶ showed a survival advantage with PTCA
1999	Hochman et al ¹⁷⁻¹⁹ proved a survival advantage with revascularization in the SHOCK trial

CABG, coronary artery bypass graft; IABP, intra-aortic balloon pump; PTCA, percutaneous transluminal coronary angioplasty.

The failure to define cardiogenic shock consistently or to confirm hemodynamically the presence of an elevated pulmonary capillary wedge pressure and low cardiac index have previously confused the clinician and confounded the literature.

Etiology

The most common cause of cardiogenic shock is acute MI.²⁰ Often, anterior MI from acute thrombotic occlusion of the left anterior descending artery results in extensive infarction. Alternatively, a smaller MI in a patient with borderline left ventricular function

may be responsible for insufficient cardiac output. Large areas of ischemic nonfunctioning but viable myocardium occasionally lead to shock in patients with MI. The delayed onset of shock may result from reocclusion of a patent infarct artery, infarct extension, or metabolic decompensation of non-infarct zone regional wall motion. Occasionally, right ventricular MI from occlusion of a proximal large right coronary artery in a patient with inferior MI is the cause.²¹

Mechanical complications unrelated to infarct size account for approximately 12% of cases. The papillary muscle of the mitral valve may infarct or rupture, causing acute, severe mitral regurgitation.²² Rupture of the interventricular septum causing ventricular septal defect²³ or rupture of the left ventricular free wall producing pericardial tamponade²⁴ also needs to be considered. Other causes of cardiogenic shock that are not emphasized in this chapter include end-stage cardiomyopathy, myocardial contusion, myocarditis, hypertrophic cardiomyopathy, valvular heart disease, pericardial disease, and post-cardiopulmonary bypass.

Incidence

Before the emphasis on time-to-treatment and primary PCI, the incidence of cardiogenic shock had remained unchanged for more than 25 years with approximately 8% of patients with ST segment elevation myocardial infarction (STEMI)^{25,26} and 2.5% of patients with non-ST segment elevation MI^{27,28} developing cardiogenic shock. The latter group is more likely to have circumflex artery occlusion, comorbid disease, and severe three-vessel disease or left main disease.²⁸ Cardiogenic shock usually develops early after onset of symptoms, with approximately half of patients developing shock within 6 hours and 72% developing shock within 24 hours.²⁹ Others first develop a preshock state manifested by systemic hypoperfusion without hypotension.³⁰ These patients benefit from aggressive supportive therapy, and revascularization; early intervention may abort the onset of cardiogenic shock.

Pathogenesis

Pathology

The early development of cardiogenic shock is usually caused by acute thrombosis of a coronary artery supplying a large myocardial distribution, with no collateral flow recruitment.³¹ Frequently, this is the left anterior descending artery, although shock may result from coronary thrombosis in other sites if previous MI has occurred. Multivessel disease is present in two thirds of patients.³²

Autopsy studies have consistently shown that at least 40% of the myocardium is infarcted in patients who die of cardiogenic shock.³³ Various ages of infarction reflect previous infarction, reinfarction, or infarct extension.

The infarct border zone in patients without hypotension is clearly demarcated. In patients dying of shock, it is irregular, with marginal extension. Focal areas of necrosis remote from the infarct zone are also present. These findings result from progressive cell death owing to poor coronary perfusion, are reflected by prolonged release of cardiac enzymes, and contribute to hemodynamic deterioration.³⁴

Pathophysiology

Progressive hemodynamic deterioration leading to cardiogenic shock results from a sequence of events (Fig. 17-1). A critical amount of ischemic or necrotic myocardium decreases

contractile mass and cardiac output. When cardiac output is low enough that arterial blood pressure declines, coronary perfusion pressure decreases in the setting of an elevated left ventricular end-diastolic pressure. The resulting reduction in coronary perfusion pressure gradient from epicardium to endocardium exacerbates myocardial ischemia, further decreasing left ventricular function and cardiac output, perpetuating a vicious cycle. The speed with which this process develops is modified by the infarct zone, remote myocardial function, neurohumoral responses, and metabolic abnormalities.

The infarct zone can be enlarged by reocclusion of a patent infarct artery. Alternatively, infarct extension can result from side branch occlusion from coronary thrombus propagation or from thrombosis of a second stenosis stimulated by low coronary blood flow and hypercoagulability. Infarct expansion or aneurysm formation promotes left ventricular dilation, which increases wall stress and oxygen demand in the setting of decreased oxygen supply owing to low cardiac output.

Preclinical and clinical studies³⁵ have shown the importance of hypercontractility of remote myocardial segments in maintaining cardiac output in the setting of a large MI. This compensatory mechanism is lost when multivessel disease is present and produces ischemia in noninfarct segments.

A series of neurohumoral responses is activated in an attempt to restore cardiac output and vital organ perfusion. Decreased baroreceptor activity secondary to hypotension increases sympathetic outflow and reduces vagal tone; this increases heart rate, myocardial contractility, venous tone, and arterial vasoconstriction. Vasoconstriction is most pronounced in the skeletal, splanchnic, and cutaneous vascular beds to redistribute cardiac output to the coronary, renal, and cerebral circulations. An increase in the ratio of precapillary to postcapillary resistance decreases capillary hydrostatic pressure, facilitating movement of interstitial fluid into the vascular compartment. Increased catecholamine levels and decreased renal perfusion lead to renin release and angiotensin production. Elevated angiotensin levels stimulate peripheral vasoconstriction and aldosterone synthesis. Aldosterone increases sodium and water retention by the kidney, increasing blood volume. Release of antidiuretic hormone from the posterior pituitary by baroreceptor stimulation also increases water retention. Local autoregulatory mechanisms that decrease arteriolar resistance and increase regional blood flow are stimulated by hypoxia, acidosis, and accumulation of vasoactive metabolites (e.g., adenosine).

Enhanced anaerobic metabolism, lactic acidosis, and depleted adenosine triphosphate stores result when compensatory neurohumoral responses are overwhelmed, depressing ventricular function further. Arrhythmias may additionally reduce cardiac output and increase myocardial ischemia. Loss of vascular endothelial integrity because of ischemia culminates in multiorgan failure. Pulmonary edema impairs gas exchange. Renal and hepatic dysfunction can cause fluid, electrolyte, and metabolic disturbances. Gastrointestinal ischemia can lead to hemorrhage or entry of bacteria into the bloodstream, causing sepsis. Microvascular thrombosis owing to capillary endothelial damage with fibrin deposition and catecholamine-induced platelet aggregation impairs organ function further.

A systemic inflammatory state with high plasma levels of cytokines (e.g., tumor necrosis factor- α , interleukin-6) and inappropriate nitric oxide production additionally may depress myocardial function or impair catecholamine-induced

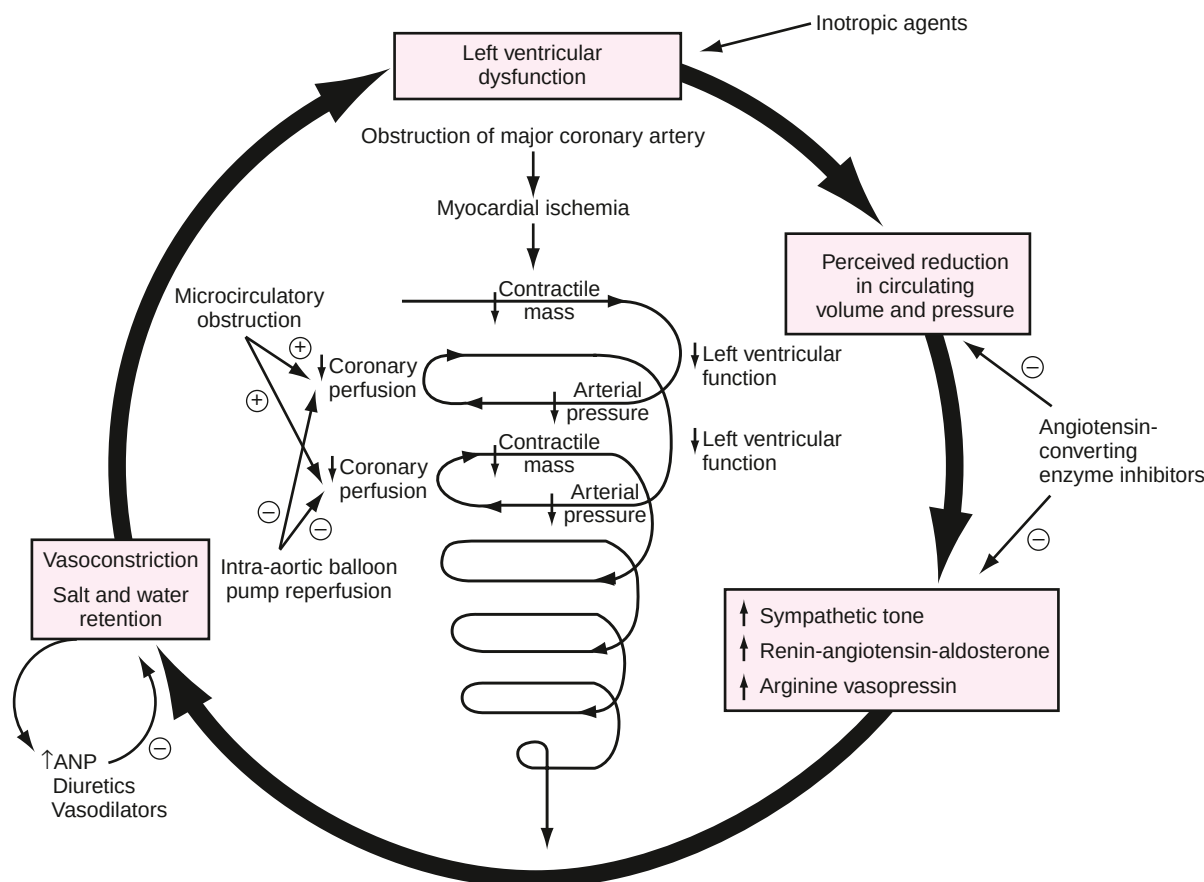


Figure 17-1. The vicious circle of mechanical and neurohormonal events that lead to progressive cardiogenic shock and death in acute myocardial infarction. ANP, atrial natriuretic peptide. (Adapted from Califf RM, Bengtson JR: *Cardiogenic shock*. *N Engl J Med* 1994;330:1724.)

vasoconstriction. All of these factors lead to diminished coronary artery perfusion and trigger a vicious cycle of further myocardial ischemia and necrosis resulting in even lower blood pressure, lactic acidosis, multiple organ failure, and ultimately death.³⁶

Clinical Presentation

History and Physical Examination

The diagnosis of acute MI must be confirmed. Noncardiac causes of shock need to be ruled out, including aortic dissection, tension pneumothorax, massive pulmonary embolism, ruptured viscus, bleeding, and sepsis. Risk factors for developing cardiogenic shock include older age, anterior MI location, hypertension, diabetes mellitus, multivessel coronary artery disease, prior MI, prior congestive heart failure, STEMI, or left bundle branch block.^{37,38}

Patients usually appear ashen or cyanotic, with cold and clammy skin. They may be agitated, disoriented, or lethargic from cerebral hypoperfusion. The pulses are rapid and faint, the pulse pressure is narrow, and arrhythmias are common. Jugular venous distention and pulmonary rales are usually present in left ventricular shock, but they may be absent. Jugular venous distention, Kussmaul sign (a paradoxical increase in jugular venous pressure during inspiration), and absent rales are found in right ventricular shock. Left ventricular dyskinesia may produce a precordial heave. A systolic thrill along the left sternal border is

consistent with mitral regurgitation or ventricular septal defect. The heart sounds are distant. Third and fourth heart sounds or a summation gallop can be auscultated. The systolic murmur of mitral regurgitation is often present; ventricular septal defect also produces a systolic murmur. The absence of a murmur does not exclude these complications, however. The extremities are usually vasoconstricted.

Electrocardiography and Laboratory Testing

A large anterior or anterolateral MI pattern is often present. Old anterior Q waves or new ST segment elevation in the right precordial leads consistent with right ventricular MI may be noted with acute inferior MI. Multiple lead ST segment depression without an injury current is another pattern that can occur with multivessel or left main disease. New left bundle branch block and third-degree atrioventricular conduction block are ominous findings. A relatively normal electrocardiogram (ECG) should alert one to other causes of shock.

Troponin and creatine kinase levels are elevated, may peak late because of prolonged washout or ongoing necrosis, and can increase secondarily with infarct extension. Lactic acidosis, hypoxemia, and mixed venous oxygen desaturation are usually present.

Echocardiography

Echocardiography can be performed rapidly and offers valuable information on the extent of left ventricular dysfunction. A dilated, hypokinetic left ventricle suggests left ventricular

shock, whereas a dilated right ventricle suggests right ventricular involvement. Normal ventricular function, low cardiac output, and mitral regurgitation are consistent with acute severe mitral regurgitation. Pericardial tamponade from hemorrhagic effusion or free wall rupture can be detected quickly. The Doppler evaluation can easily confirm the presence of significant mitral regurgitation or ventricular septal rupture. Transesophageal echocardiography is helpful in patients in whom image quality is inadequate, or when a flail mitral leaflet is suspected but not seen on transthoracic echocardiography.

Management

General Measures

Numerous supportive measures need to be instituted quickly (Fig. 17-2). If there is no clinical evidence for pulmonary edema, a fluid bolus should be given to exclude hypovolemia as a cause of hypotension. Patients with a history of inadequate fluid intake, diaphoresis, diarrhea, vomiting, or diuretic use may not have pump failure and improve dramatically with fluid administration. Because preload is critical in patients with right ventricular shock, fluid support and avoidance of nitrates and morphine are indicated (Table 17-2).

Oxygenation and airway protection are crucial. Intubation and mechanical ventilation are usually required, followed by sedation, and often muscular paralysis. These interventions also improve the safety of electrical cardioversion or cardiac catheterization, if needed, and decrease oxygen demand. Positive end-expiratory pressure decreases preload and afterload.

Hypokalemia and hypomagnesemia predispose patients to ventricular arrhythmias and should be corrected. Because metabolic acidosis decreases contractile function, hyperventilation should be considered, but sodium bicarbonate should be avoided because of a short half-life and the large sodium load.

Arrhythmias and atrioventricular heart block have a major influence on cardiac output. Atrial and ventricular tachyarrhythmias should be electrically cardioverted promptly, rather than treated with pharmacologic agents. Severe bradycardia secondary to excess vagotonia can be corrected with atropine. Temporary pacing should be initiated for high-degree heart block, preferably with a dual-chamber system. This is especially important in patients with right ventricular infarction who depend on the right atrial contribution to preload.

Aspirin and monitored unfractionated heparin should be administered to decrease the likelihood of reinfarction, ventricular mural thrombus formation, or deep venous thrombosis in the setting of low flow and hypercoagulability. Clopidogrel is best withheld until cardiac catheterization has determined the need for emergency surgery because of its prolonged action and increased risk for perioperative bleeding. Morphine sulfate decreases pain and anxiety, excessive sympathetic activity, preload, and afterload, but should be administered only in small increments. Diuretics decrease filling pressures and should be used to control volume. β blockers and calcium channel blockers should be avoided because they are negative inotropic agents. An insulin drip may be required to control hyperglycemia.

Hemodynamic Monitoring

Central hemodynamic monitoring is crucial for confirming the diagnosis and guiding pharmacologic therapy (Table 17-3). Urine output needs to be monitored hourly through catheter

drainage. An arterial catheter allows constant monitoring of the blood pressure. A pulmonary artery catheter should be inserted as soon as feasible to measure intracardiac pressures, cardiac output, systemic resistance, and mixed venous oxygen saturation. Although use of the pulmonary artery catheter has not been associated with mortality benefit in patients without MI, it is very helpful in the titration of fluids and medications in patients with cardiogenic shock.

The hemodynamic profile of left ventricular shock, as defined by Forrester and coworkers,¹² includes pulmonary artery wedge pressure greater than 18 mm Hg and a cardiac index less than 2.2 L/min/m². Others have used a pulmonary artery pressure of 15 mm Hg or 12 mm Hg and a cardiac index of 2 L/min/m² or 1.8 L/min/m². The hemodynamic profile of right ventricular shock includes right atrial pressure of 85% or more of the pulmonary artery wedge pressure, steep γ descent in the right atrial pressure tracing, and the dip and plateau (i.e., square root sign) in the right ventricular waveform. Large v waves in the pulmonary artery wedge tracing suggest the presence of severe mitral regurgitation. An oxygen saturation step-up (>5%) from the right atrium to the right ventricle confirms the diagnosis of ventricular septal rupture. Equalization of right atrial, right ventricular end-diastolic, pulmonary artery diastolic, and pulmonary capillary wedge pressures occurs with severe right ventricular infarction or pericardial tamponade owing to free wall rupture or hemorrhagic effusion. Cardiac power (mean arterial pressure $\times$ cardiac output/451) is the strongest hemodynamic predictor of hospital mortality.³⁹

Pharmacologic Support

Vasopressor and inotropic drug support are the major initial interventions for reversing hypotension and improving vital organ perfusion (Table 17-4). Failure to improve blood pressure with these agents is an ominous prognostic sign. Continued hypotension results in progressive myocardial ischemia and deterioration of ventricular function. Although many patients temporarily respond to therapy, hospital mortality rates remain unchanged without successful reperfusion therapy.

Dobutamine, a synthetic catecholamine with predominantly β_1 -adrenergic effects, is the initial inotropic agent of choice for patients with systolic pressures greater than 70 mm Hg. It has some chronotropic effect, but it has no significant vasoconstrictor, arrhythmogenic, or renal effects. Cardiac output is increased, and filling pressures are decreased.

Dopamine, a natural catecholamine, is the initial vasopressor of choice when the systolic pressure is greater than 70 mm Hg. Low dose (2 to 5 μ g/kg/min) increase stroke volume and renal perfusion by stimulating dopamine receptors. Intermediate doses have a dose-dependent β_1 -adrenergic receptor effect, increasing inotropy and chronotropy. High doses (15 to 20 μ g/kg/min) activate α -adrenergic receptors, increasing vascular resistance.

Norepinephrine is a natural catecholamine with predominantly peripheral α -adrenergic effects. It is used when the systolic pressure is less than 70 mm Hg because it is a potent venous and arterial vasoconstrictor.

Catecholamine infusions should be carefully titrated. A delicate balance must be obtained between increasing coronary perfusion pressure and increasing oxygen demand, so that

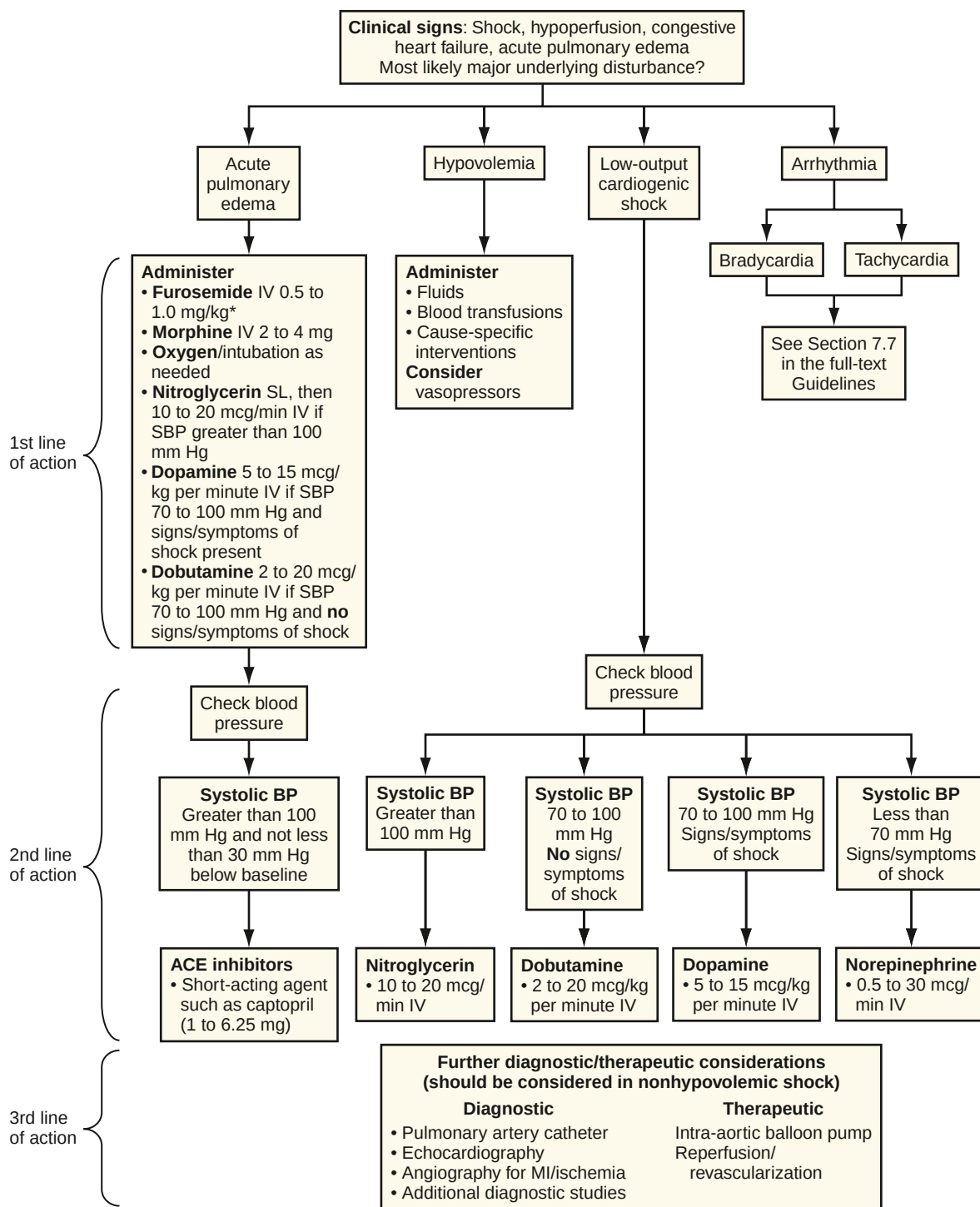


Figure 17-2. Emergency management of complicated ST segment elevation myocardial infarction. ACE, angiotensin-converting enzyme; BP, blood pressure; MI, myocardial infarction; SBP, systolic blood pressure; SL, sublingual. (From Antman EM, Anbe DT, Armstrong PW, et al: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction]. *Circulation* 2004;110:e82.)

myocardial ischemia is not exacerbated. Excessive peripheral vasoconstriction decreases tissue perfusion, increased afterload increases filling pressures, and excessive tachycardia or arrhythmias can be stimulated. Extravasation of dopamine or norepinephrine can cause tissue necrosis.

Cardiac glycosides have no significant inotropic effect in patients with severe pump failure, and they increase oxygen consumption. Ischemic myocardium is susceptible to the arrhythmogenic effects of digoxin, and intravenous administration causes coronary and peripheral vasoconstriction. Digitalis

may be employed for supraventricular tachyarrhythmias to control heart rate.

Vasodilators are useful if adequate blood pressure and coronary artery perfusion pressure can be restored. Nitroprusside is an arterial dilator and a venodilator, whereas nitroglycerin is predominantly a venodilator. Afterload reduction increases stroke volume and is especially important when mitral

regurgitation or ventricular septal rupture is present. Preload reduction decreases filling pressures and oxygen demand by reducing wall tension. The major hazard is that reduction in preload and afterload could decrease diastolic arterial pressure, compromising coronary artery perfusion pressure and resulting in extension of ischemic myocardial injury. Reflex tachycardia increases oxygen demand. Nitroglycerin and nitroprusside can be started at low-dose infusions and titrated against blood pressure and pulmonary capillary wedge pressure. There are no data on phosphodiesterase inhibitors (e.g., milrinone) for cardiogenic shock, but they can be useful in low-output states when the patient is relatively stable by augmenting myocardial contractility and producing peripheral vasodilation.

Mechanical Support

When pharmacologic therapy provides insufficient hemodynamic support, mechanical circulatory assistance can be instituted, especially when revascularization or surgical repair of mechanical complications is planned (Fig. 17-3). IABP counterpulsation reduces systolic afterload and augments diastolic perfusion pressure. The usual result is a decrease in filling pressures, systolic blood pressure, heart rate, mitral regurgitation, and left-to-right shunting across a ventricular septal rupture, along with an increase in diastolic and mean blood pressure, stroke volume, cardiac output, and urine output. Subendocardial blood flow is improved, and in contrast to vasopressor support, oxygen demand is decreased.

Kantrowitz and colleagues⁹ first reported the use of IABP counterpulsation in treating cardiogenic shock. Mueller and coworkers⁴⁰ showed improved hemodynamics and myocardial metabolism associated with IABP therapy. Weiss and associates⁴¹ showed improvement in infarct zone regional wall motion, but not adjacent non-infarct zone regional wall motion. No improvement in coronary blood flow occurs in highly stenotic coronary arteries.⁴² The IABP favorably influences systemic hemodynamics, but it does not improve ischemic zone blood flow or non-infarct zone wall motion.

The failure to improve ischemic myocardial blood flow probably explains why, despite temporary hemodynamic and clinical improvement in 75% of patients, no obvious difference in enzymatic infarct size or mortality rate with IABP counterpulsation

Table 17-2. Conventional Therapy for Cardiogenic Shock

1. Maximize volume (RAP 10-14 mm Hg, PAWP 18-20 mm Hg)
2. Maximize oxygenation (e.g., ventilator)
3. Correct electrolyte and acid-base imbalances
4. Control rhythm (e.g., pacemaker, cardioversion)
5. Sympathomimetic amines (e.g., dobutamine, dopamine, norepinephrine)
6. Phosphodiesterase inhibitors (e.g., milrinone)
7. Vasodilators (e.g., nitroglycerin, nitroprusside)
8. Intra-aortic balloon counterpulsation

PAWP, pulmonary artery wedge pressure; RAP, right atrial pressure.

Table 17-3. Hemodynamic Profiles

Left ventricular shock	High PCWP, low CO, high SVR
Right ventricular shock	High RA, RA/PCWP >0.8, exaggerated RA y descent, RV square root sign
Mitral regurgitation	Large PCWP v wave
Ventricular septal defect	Large PCWP v wave, oxygen saturation step-up (>5%) from RA to RV
Pericardial tamponade	Equalization of diastolic pressures approximately 20 mm Hg

CO, cardiac output; PCWP, pulmonary capillary wedge pressure; RA, right atrium; RV, right ventricle; SVR, systemic vascular resistance.

Table 17-4. Pharmacologic Treatment for Cardiogenic Shock

Drug	Doses	Side Effects
Dobutamine	5-15 $\mu\text{g/kg/min}$ IV	Tolerance
Dopamine	2-20 $\mu\text{g/kg/min}$ IV	Increased oxygen demand
Norepinephrine	0.5-30 $\mu\text{g/min}$ IV	Peripheral and visceral vasoconstriction
Nitroglycerin	10 $\mu\text{g/min}$, increased by 10 μg every 10 min, maximum 200 $\mu\text{g/min}$ IV	Headache, hypotension, tolerance
Nitroprusside	0.3-10 $\mu\text{g/min}$ IV	Hypotension, cyanide toxicity
Milrinone	50 $\mu\text{g/kg}$ over 10 min IV, then 0.375-0.75 $\mu\text{g/kg/min}$	Ventricular arrhythmia
Furosemide	20-160 mg IV	Hypokalemia, hypomagnesemia
Bumetanide	1-3 mg IV	Nausea, cramps

IV, intravenously.

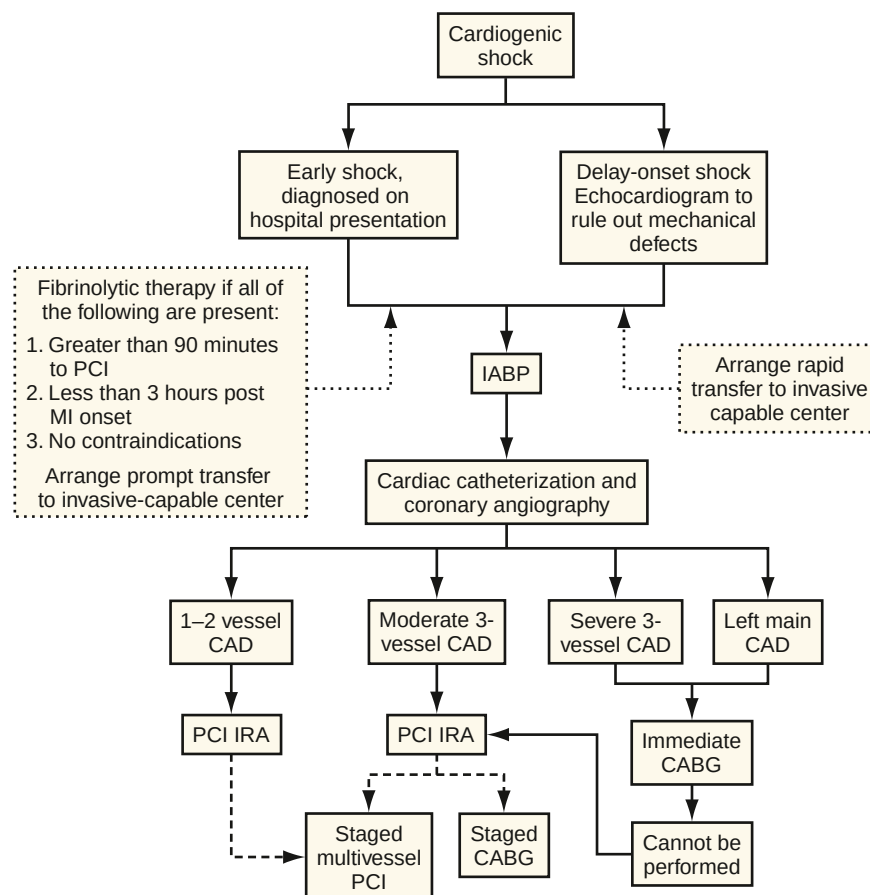


Figure 17-3. Recommendations for initial reperfusion therapy. CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; IABP, intra-aortic balloon pump; IRA, infarct-related artery; LBBB, left bundle branch block; MI, myocardial infarction; PCI, percutaneous coronary intervention. (From Antman EM, Anbe DT, Armstrong PW, et al: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction]. *Circulation* 2004;110:e82.)

has been mentioned in the literature.^{10,11} The mortality rates in a large cooperative trial were 60% during IABP support, 77% during hospitalization, and 91% at 1 year for 87 patients.¹¹ The only randomized trial was performed by O'Rourke and colleagues.⁴³ No difference in enzymatic infarct size or mortality was observed.

IABP counterpulsation offers little support to shock patients with extensively scarred ventricles or after late presentation. The best use is in patients with ischemic, viable, but nonfunctioning myocardium that can be revascularized, or with mitral regurgitation or ventricular septal rupture amenable to surgical repair. Dunkman and colleagues¹⁰ showed that the addition of CABG surgery to IABP support decreased mortality from 84% to 60%.

Several reports have examined the use of IABP counterpulsation in conjunction with fibrinolytic strategies.⁴⁴⁻⁴⁸ There were some favorable trends, but significantly more bleeding episodes. Only one randomized controlled trial has compared IABP counterpulsation plus fibrinolytic therapy with fibrinolysis alone. The TACTICS trial⁴⁸ sought to enroll 500 patients with acute STEMI complicated by shock; only 57 patients were actually enrolled. Six-month follow-up showed a trend toward mortality reduction in the IABP group, but this was not significant because of small sample size. The strategy of early fibrinolytic therapy and

IABP counterpulsation, followed by immediate transfer for PCI or CABG surgery, may be appropriate for hospitals that do not have revascularization capability.

The use of IABP therapy in patients undergoing primary or rescue PCI has been evaluated in a few studies. Early data suggested a reduction in infarct artery reocclusion rates and improvement in clinical outcome in patients without cardiogenic shock.^{49,50} A more recent trial⁵¹ failed to show any improvement in recovery of left ventricular function or survival, however, and its use is best restricted to patients with hemodynamic instability. In patients with cardiogenic shock, the IABP catheter needs to be inserted before angiography to provide optimal hemodynamic support during the procedure.

The American College of Cardiology (ACC)/American Heart Association (AHA) STEMI guidelines have given a class I (general agreement that a procedure/treatment should be performed/administered) recommendation to IABP therapy for (1) cardiogenic shock not quickly reversed with pharmacologic therapy as a stabilizing measure for angiography and prompt revascularization, (2) acute mitral regurgitation or ventricular septal defect complicating MI as a stabilizing therapy for angiography and repair/revascularization, and (3) refractory post-MI angina as a bridge to angiography and revascularization.⁵²

Contraindications for IABP counterpulsation therapy include aortic regurgitation, aortic dissection, and peripheral vascular disease. Complications occur in 10% to 30% of patients with cardiogenic shock, and include limb ischemia, femoral artery laceration, aortic dissection, infection, hemolysis, thrombocytopenia, thrombosis, and embolism.

Devices that offer greater circulatory support than IABP counterpulsation are available and have been used in cardiogenic shock as a bridge to recovery or to transplantation. These devices may be classified into devices that can be placed percutaneously and devices that require surgical placement. It is crucial to recognize which patients would require greater hemodynamic support than provided by IABP therapy.

Percutaneous cardiopulmonary bypass can be initiated at the bedside via the femoral artery and vein, and can provide 3 to 5 L/min of nonpulsatile flow and a mean aortic pressure of 50 to 70 mm Hg despite cardiac standstill.⁵³ Support is limited to several hours because of blood cell destruction. A review of 42 studies (533 patients) suggested a mean survival to discharge of 51% (median 38%) in patients with cardiogenic shock treated with percutaneous bypass.⁵⁴ Extracorporeal life support also has been used in critically ill patients, and 33% survival to discharge for adult cardiogenic shock patients has been reported.⁵⁵ These results are encouraging because extracorporeal life support in these cases has typically been placed percutaneously during arrest or near-arrest circumstances, when the expected mortality would be 100%. Left ventricular decompression is impossible with these devices.

Another strategy has been to use ventricular assist devices as a bridge to recovery or to transplant or even as destination therapy.⁵⁶ These devices can be placed percutaneously or surgically. The standard left heart support configuration of the percutaneous ventricular assist device (Tandem-Heart; Cardiac Assist, Pittsburgh, PA) uses a 21F femoral cannula placed across the interatrial septum into the left atrium, whereas a shorter 15F or 17F cannula is placed in the iliac artery, allowing left atrial to arterial assist pumping by an extracorporeal centrifugal continuous flow pump.^{56,57} This device has been successfully used in cardiogenic shock from left ventricular failure⁵⁶ and right ventricular failure (right atrial-to-pulmonary artery bypass).⁵⁸

A small trial compared IABP counterpulsation and the percutaneous ventricular assist device in patients undergoing primary PCI for acute MI complicated by cardiogenic shock. Although the percutaneous ventricular assist device provided better hemodynamic support, the risk of complications was higher, and there was no difference in 30-day mortality.⁵⁹ Surgically implanted ventricular assist devices have also been used in cardiogenic shock. These devices require placement via thoracotomy, but can be left in place long-term. In a single-center series, the Thoratec (Pleasanton, CA) biventricular assist device was used as a successful bridge to cardiac transplantation in 11 of 19 patients in cardiogenic shock.⁶⁰ Percutaneous and surgical ventricular assist devices are available only at selected centers, and early transfer of patients to these facilities should be considered for patients failing standard supportive measures.

Reperfusion Strategies

Fibrinolytic Therapy

Several multicenter randomized megatrials have shown that fibrinolytic therapy reduces mortality from acute MI.²⁻⁵ The greatest survival benefit has been confirmed for patients with

the most jeopardized myocardium (e.g., anterior infarction, new left bundle branch block). It is paradoxical and disappointing that no obvious survival benefit has been realized for the subset of patients with cardiogenic shock.⁶¹

Mathey and colleagues¹⁴ first reported that the shock state could be reversed with successful reperfusion secondary to intracoronary streptokinase administration. A multicenter registry report on 44 patients treated with intracoronary streptokinase documented a 66% in-hospital mortality rate.⁶² The importance of successful reperfusion and outcome was first suggested by this report, however. Only 43% of the patients had successful reperfusion compared with 71% for the entire study, but their mortality rate was 42% compared with 84% for unsuccessful reperfusion.

Compared with placebo, intravenous fibrinolytic therapy reduces the risk of subsequent cardiogenic shock in patients who initially present without shock.^{3,4,63} Comparative trials of fibrinolytic agents have shown variable results. Trials that show no difference in mortality between agents also do not show a reduction in the incidence of cardiogenic shock with any one agent.⁶⁴⁻⁶⁶ In contrast, comparative trials that show a mortality benefit in favor of one agent also showed a significant reduction in the incidence of cardiogenic shock in favor of that agent.⁶⁷⁻⁶⁹ Therapy with fibrinolytic agents in acute MI significantly reduces the subsequent development of cardiogenic shock, and agents that are associated with higher patency rates and improved survival in comparative studies also lead to lower rates of shock.

Fibrinolytic therapy for patients presenting in manifest cardiogenic shock is associated with low reperfusion rates and no clear-cut treatment benefit.⁶¹ Mean arterial pressure must be greater than 65 mm Hg for coronary blood flow to be maintained; flow ceases when mean arterial pressure is less than 30 mm Hg. Vasoconstriction and passive collapse of the arterial wall are additional factors that may limit the ability of the fibrinolytic agent to penetrate an intracoronary thrombus.⁷⁰ Canine studies showed that restoration of blood pressure to normal ranges with norepinephrine infusion improved reperfusion rates, suggesting that coronary perfusion pressure, not cardiac output, is the major determinant of fibrinolytic efficacy.^{71,72}

The trials that compared streptokinase with alteplase showed mortality benefit for shock patients randomly assigned to streptokinase, despite the fact that patients treated with alteplase fared better.^{64,68} Streptokinase may be beneficial in this subset of patients because it causes a prolonged lytic state in the setting of low coronary blood flow (which may reduce the risk of reocclusion), and because it is less fibrin-specific and may penetrate the thrombus better because it does not bind preferentially to the surface of the clot. Because of the limitations of fibrinolytic therapy for cardiogenic shock, it should be considered as a secondary treatment option when revascularization therapy with PCI or CABG surgery is not rapidly available. Viable patients should be transferred to a hospital with revascularization capability as soon as possible so that the potential benefits of revascularization therapy may still be obtained.

Percutaneous Coronary Intervention

Meyer and associates¹⁵ were the first to use PCI to treat cardiogenic shock. The first treatment series were reported in 1985. O'Neill and colleagues⁷³ obtained successful reperfusion in 24 (88%) of 27 patients, with an in-hospital mortality rate of 25%.

Brown and coworkers⁷⁴ had a 61% successful reperfusion rate, associated with a 42% mortality rate; the mortality rate was 82% when reperfusion was unsuccessful. Multiple small observational reports since then have consistently shown a survival benefit for patients in whom PCI was successful compared with patients in whom PCI was unsuccessful or with historical controls.

There have been a few large observational reports on reperfusion therapy for cardiogenic shock. The GUSTO-1 trial⁷⁵ included 2972 patients with cardiogenic shock treated with fibrinolytic therapy. There was a lower 30-day mortality rate for the 22% of patients who were subsequently treated with PCI compared with patients receiving only medical therapy (43% versus 61% with shock on arrival, 32% versus 61% for patients who developed shock after arrival). Another GUSTO-1 analysis included 2200 patients with cardiogenic shock.⁷⁶ Compared with a delayed strategy, angiography within 24 hours of shock onset with revascularization by PCI or CABG surgery when deemed appropriate was independently associated with reduced 30-day mortality (38% versus 62%).

A more recent large registry evaluated the outcome of 1333 patients undergoing primary PCI for cardiogenic shock.⁷⁷ The in-hospital mortality in this cohort was 46%. The independent predictors of mortality were left main disease, TIMI flow less than 3 after PCI, older age, three-vessel disease, and longer time interval between symptom onset and PCI.

None of these reports represents randomized, controlled studies of PCI. A selection bias favoring PCI over historical controls could easily have resulted from excluding elderly patients or patients in extremis or with comorbid disease. Hochman and colleagues⁷⁸ documented that patients with cardiogenic shock who are selected for cardiac catheterization are younger and less likely to die (51% versus 85%), even when not revascularized. Nevertheless, several studies and clinical experience clearly show the favorable impact a patent infarct artery can have on reversing the shock state.

Two small randomized trials have been performed. SMASH⁷⁹ randomly assigned 55 patients to undergo either emergency angiography and revascularization when indicated or initial medical management, but the trial was terminated prematurely because of poor enrollment. Mortality at 30 days was 69% in the invasive arm versus 78% in the medical arm. At 1 year, the mortality figures were 74% and 83%. Although the study failed to reach statistical significance because of sample size, the trend was clinically important.

The SHOCK trial¹⁷⁻¹⁹ randomly assigned 302 patients to emergent revascularization or immediate medical stabilization. Concurrently, the 30 participating sites collected registry data on 1190 patients presenting with cardiogenic shock who were not randomly assigned.⁸⁰ Medical stabilization included fibrinolytic therapy in more than half of the patients and inotropic and vasopressor agents. IABP counterpulsation was used in 86% of the patients. In the revascularization arm, 97% of patients underwent early angiography; 64% underwent PCI, and 36% had CABG surgery. There was no statistically significant difference in 30-day mortality between the revascularization and medical therapy groups (46.7% versus 56%; $P = .11$), but by the 6-month end point, a significant survival advantage had emerged for patients randomly assigned to revascularization (50.3% versus 63.1%; $P = .027$) that was maintained at 1 year (53.3% versus 66.4%) (Fig. 17-4).

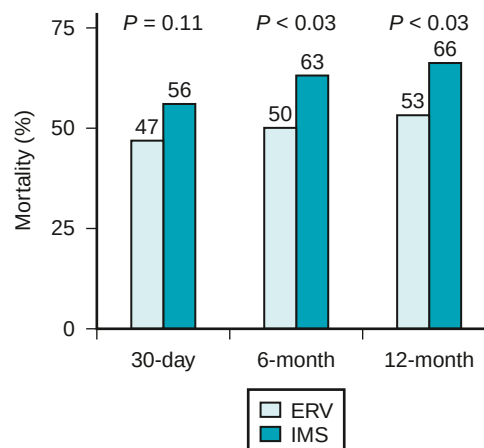


Figure 17-4. Mortality rates in the SHOCK Trial. ERV, early revascularization; IMS, immediate medical stabilization. (Data from Hochman JS, Sleeper LA, Webb JG, et al: Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock. *N Engl J Med* 1999;341:625; and Hochman JS, Sleeper LA, White HD, et al: One-year survival following early revascularization for cardiogenic shock. *JAMA* 2001;285:190.)

Emergency PCI is recommended by the ACC/AHA STEMI guidelines for patients younger than 75 years who develop shock within 36 hours of MI and who are suitable for revascularization that can be performed within 18 hours of shock, unless further support is deemed futile.⁵² The best candidates for PCI are patients without prior MI who are younger than 70 years with fewer comorbidities and symptom duration less than 12 hours. The severity, distribution, and diffuseness of coronary artery disease and the degree of left ventricular disease also influence outcome. Poor candidates because of very high mortality risk are patients with rapidly progressive hemodynamic deterioration despite therapeutic interventions and elderly patients with comorbid disease. Additionally, patients with life-shortening illnesses, no vascular access, previously defined coronary anatomy that was unsuitable for revascularization, anoxic brain damage, and prior cardiomyopathy are poor candidates. Except for elderly patients, all other subgroups had treatment benefit with revascularization in the SHOCK trial.¹⁷

Analysis of the elderly patient subgroup in the SHOCK registry⁸¹ was performed to gain further insight in patients 75 years old and older. Although the randomized trial included only 56 patients in that age group, the registry included 277 patients. Overall, in-hospital mortality in the elderly versus the younger age group was 76% versus 55% ($P < .001$). The 44 elderly patients selected for early revascularization showed a significantly lower mortality rate, however, than patients who did not undergo revascularization (48% versus 81%; $P = .0002$). Other reports⁸²⁻⁸⁴ also support the use of primary PCI in selected elderly patients with cardiogenic shock complicating MI, so age alone should not be an exclusion for selecting patients for cardiac catheterization. Prior functional status, comorbidity, and patient and family preferences are important selection criteria.

Emergency angiography determines revascularization suitability. Angiographic exclusions for PCI include unprotected left main disease, infarct artery stenosis less than 70% with TIMI-3 flow, or lesion morphology that is high risk for no-reflow or other

complications. Emergency CABG surgery may be considered for patients with left main disease, severe coronary anatomy unsuitable for PCI, multivessel disease, mechanical complications, or failed PCI if there is ongoing myocardial ischemia.

The procedure is performed most safely with the patient ventilated and sedated or paralyzed. Gas exchange is maximized, risk of aspiration is minimized, cardioversion can be performed easily, and patient movements do not interfere with the procedure. Both femoral arteries and veins are cannulated with vascular sheaths. An IABP is inserted through one femoral artery for counterpulsation support, and a pulmonary artery catheter is inserted through a femoral vein. Interventions to control volume and pressure are titrated against the systemic and pulmonary artery wedge pressures. Electrolytes and blood gases are obtained, and abnormalities are corrected. A temporary pacemaker is inserted, if necessary.

PCI should be performed only when the patient is maximally supported. Using a low osmolar ionic contrast medium, two orthogonal injections of the left coronary artery and one left anterior oblique injection of the right coronary artery are made in an attempt to identify the infarct artery. Left ventriculography should usually be avoided because of the contrast load. If PCI is to be attempted, it should be performed as quickly and efficiently as possible with limited contrast injections. Although PCI for STEMI is usually limited to the infarct artery, patients in cardiogenic shock with multivessel disease may have the best survival chance with PCI of all proximal discrete lesions. Early resolution of arrhythmias, conduction blocks, or hypotension suggests an important therapeutic benefit. Conversely, failure to improve within the first 24 hours usually predicts mortality.

Coronary stents decrease restenosis rates by 50% in elective PCI compared with balloon angioplasty, but have not reduced mortality rates in primary PCI.⁸⁵ Some observational studies in cardiogenic shock that have not completely corrected for confounding variables suggest lower mortality rates with stents than percutaneous transluminal coronary angioplasty,⁸⁶⁻⁸⁸ but others show no benefit⁸⁹ or higher mortality rates.⁹⁰ Randomized studies have not been performed. Most patients undergoing primary PCI for cardiogenic shock receive stents because they improve the immediate angiographic result and decrease subsequent target vessel revascularization in survivors.

The use of platelet glycoprotein IIb/IIIa inhibitors has been shown to improve outcome of patients with acute MI undergoing primary PCI.⁹¹ Observational studies suggest a benefit of abciximab in primary stenting for cardiogenic shock.^{87,89,90,92} Although there are no randomized controlled trials evaluating use of abciximab or other glycoprotein IIb/IIIa inhibitors in cardiogenic shock, they are commonly used as adjunctive therapy.

Surgery

Dunkman and associates¹⁰ were the first to report the use of CABG surgery for cardiogenic shock. Emergency CABG surgery is associated with mortality rates ranging from 25% to 60%. In the SHOCK trial,¹⁷ one third of the patients randomly assigned to revascularization were treated with a surgical approach. Patients were more likely to have left main disease or three-vessel disease than patients treated with PCI. Thirty-day mortality for patients undergoing surgery was equivalent to PCI mortality (42% versus 45%). The high degree of surgical expertise required, the inherent time delays, the increasing hesitancy of surgeons to operate on patients with high operative mortality

risk because of “scorecard” medicine, and the favorable results with PCI make emergency CABG surgery an increasingly rare intervention. It is more often performed electively in survivors with multivessel disease.

Surgical repair of acute mitral regurgitation,²² ventricular septal defect,²³ and free wall rupture²⁴ can be accomplished, although mortality rates are high. The use of emergency cardiac transplantation has been reported.⁹³

New Approaches

New approaches to cardiogenic shock have focused on mechanisms beyond mechanical support and revascularization. A significant proportion of patients in the SHOCK trial exhibited a systemic inflammatory response syndrome marked by fever, leukocytosis, and low systemic vascular resistance.⁹⁴ Complement activation, release of inflammatory cytokines, expression of inducible nitric oxide synthase, and inappropriate vasodilation were deemed culpable, and inhibition of nitric oxide production was explored as a therapeutic strategy. Early single-center clinical studies indicated a dramatic benefit from inhibition of nitric oxide synthase.^{95,96} The phase 2, dose-ranging trial SHOCK-2 showed modest early changes in hemodynamic parameters, but no effect on survival.⁹⁷ The large multicenter TRIUMPH trial was halted after no benefit was seen during an interim analysis.⁹⁸

There is intense clinical and basic science activity exploring delivery of stem cells to the infarcted myocardium to improve left ventricular recovery. Although the early studies remain inconclusive, it is likely that cardiogenic shock patients will be enrolled in the pivotal trials when an effective strategy to salvage or revive the infarcted myocardium is discovered.

The more recent emphasis on reperfusion therapy for all patients with STEMI, the importance of time-to-treatment, and the increasing use of primary PCI as the reperfusion modality have dramatically decreased the number of patients developing cardiogenic shock as a complication of STEMI.⁹⁹ Because cardiogenic shock is usually an in-hospital complication of MI occurring hours after infarct artery occlusion, early restoration of infarct artery patency to prevent development of the shock state is the best approach to this complication.

Prognosis

The historical early mortality rate for cardiogenic shock complicating acute MI treated with medical therapy was 65% to 80%. Current rapid reperfusion strategies and adjunctive therapies have reduced that rate to approximately 50%. Rigorous observation of high-risk patients (e.g., age >75 years, history of prior MI, ejection fraction <35%, large MI, diabetes, female gender); rapid diagnosis (e.g., careful physical examination, hemodynamic monitoring, echocardiography, cardiac catheterization); and prompt correction of arrhythmias, electrolyte and blood gas abnormalities, volume status, and hypotension may prevent the patient from spiraling into the shock state.

In the SHOCK registry,¹⁰⁰ in-hospital mortality rates increased from 34% to 51% as the number of diseased arteries increased from one to three. After PCI, the mortality rate was 86% with absent reperfusion (TIMI 0/1 flow), 50% with incomplete reperfusion (TIMI 2 flow), and 33% with complete reperfusion (TIMI 3 flow). Similarly, final TIMI flow was a major predictor of

outcome in the ALKK registry, with mortality rates of 78%, 66%, and 37% for TIMI 0/1, TIMI 2, and TIMI 3 flow.⁷⁷

In the SHOCK trial, 87% of the 1-year survivors were in New York Heart Association functional class I or II.¹⁰¹ The rate of 13 lives saved per 100 patients treated with early revascularization in the SHOCK trial at 6 months and 1 year was maintained at 3 and 6 years.¹⁹ Overall survival rates at 6 years were 32.8% in the early revascularization group and 19.6% in the initial medical stabilization group (Fig. 17-5). The 6-year survival rates for the hospital survivors were 62.4% versus 44.4%.

At 30 days in the GUSTO-1 trial,¹⁰² 20,360 (88.9%) patients without shock and 953 (50.4%) patients with shock were alive. After a median of 11 years, 69.4% without shock and 55.2% with shock remained alive. Patients receiving PCI were less likely to die (24.1% versus 34.6%). Beginning in the second year, mortality rates were 2% to 4% per year for all patients regardless of shock status (Fig. 17-6).

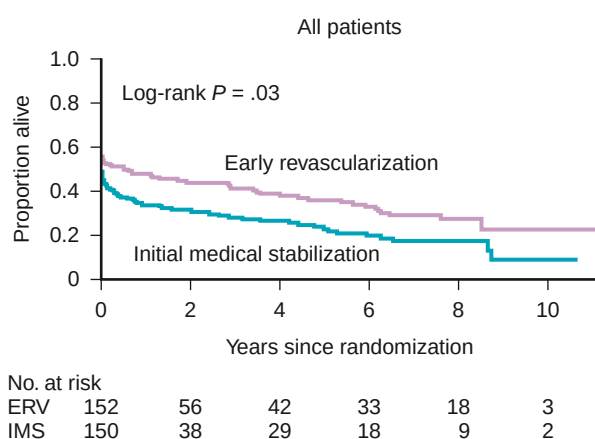


Figure 17-5. Long-term survival in the SHOCK Trial. ERV, early revascularization; IMS, immediate medical stabilization. (From Hochman JS, Sleeper LA, Webb JG, et al: Early revascularization and long-term survival in cardiogenic shock complicating acute myocardial infarction. *JAMA* 2006;295:2511.)

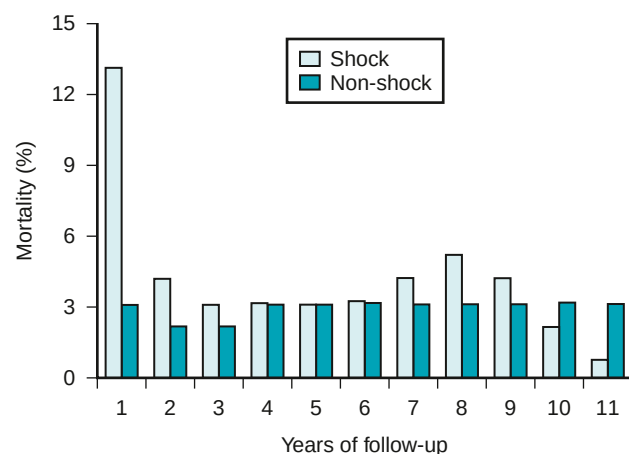


Figure 17-6. Long-term mortality rate in 30-day survivors in the GUSTO-I trial. (From Singh M, White J, Hasdai D, et al: Long-term outcome and its predictors among patients with ST-segment elevation myocardial infarction complicated by shock. *J Am Coll Cardiol* 2007;50:1752.)

Conclusion

Patients with cardiogenic shock complicating MI have a substantial survival benefit with PCI compared with no or late in-hospital revascularization. These patients need to be directly admitted or transferred to tertiary care shock centers with expertise in acute revascularization and advanced intensive care, unless further care is deemed futile. Novel therapies are needed to decrease mortality rates further in patients who develop cardiogenic shock, which remain high despite reperfusion therapy.

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Right Ventricular Infarction

Anil J. Mani, David L. Brown

CHAPTER 18

Historical Perspective
Coronary Circulation and the Right Ventricle
Ventricular Interdependence
Clinical Presentation
Diagnosis

Treatment
Complications
Prognosis
Conclusion

INFARCTION OF the right ventricle, previously considered rare and clinically unimportant,^{1,2} is now recognized as a common clinical event, occurring in one third of patients with inferior myocardial infarction (MI).³⁻⁵ Right ventricular (RV) infarction confers a worse prognosis in patients with inferior wall MI.⁴ Prompt recognition and appropriate treatment of RV infarction require a thorough understanding of the unique anatomy and pathophysiology of the right ventricle.

Historical Perspective

In 1930, Sanders⁶ reported the first clinical description of RV infarction. During the following 4 decades, RV infarction received attention mainly in autopsy series.⁷ At that time, any shock syndrome was considered the result of left ventricular (LV) infarction.^{1,2} This view was buttressed by evidence from open pericardium dog models in which destruction of the right ventricle was not associated with shock.^{8,9} The development of surgical procedures that bypassed the right ventricle, such as the Glenn and Fontan procedures, furthered the belief that the right ventricle is mainly a volume conduit contributing little to cardiac output.^{10,11}

In 1974, Cohn and coworkers¹² first called attention to RV infarction as a unique clinical and hemodynamic syndrome, characterized in its extreme form by shock, distended neck veins, and clear lung fields. During the ensuing 2 decades of intense investigation into the syndrome, the crucial role of ventricular interdependence through the pericardium and the septum was recognized.¹³⁻¹⁶ Today, a rational approach to therapy of RV infarction based on an understanding of its pathophysiology is possible.

Coronary Circulation and the Right Ventricle

In patients with right dominant coronary circulation (85% of the population), the right ventricle receives its blood supply almost exclusively from the right coronary artery (RCA), with the septum and part of the posterior wall supplied by the posterior descending artery, and the anterior and lateral RV walls

supplied by acute marginal branches of the RCA.^{17,18} The left anterior descending (LAD) artery supplies a small portion of the anterior wall of the right ventricle. In a left dominant circulation, the left circumflex coronary artery supplies the posterior descending artery, and a nondominant RCA supplies the acute marginal branches. Isolated RV infarct without LV involvement can occur with a nondominant RCA.

The angiographic hallmark of RV infarction is thrombotic occlusion of the RCA proximal to the origin of the acute marginal branches. Angiographic flow studies suggest the status of RV branch perfusion is the critical determinant of RV ischemic dysfunction.¹⁹ Proximal RCA occlusions would typically limit RV branch perfusion, in contrast to distal RCA occlusions. Mid and distal RCA occlusions less commonly cause severe RV ischemic dysfunction by flow impairment in at least one major RV branch attributable to the culprit stenosis, prior severe RV branch stenosis, or presence of RV branch thrombus.¹⁹

Not every case of proximal RCA occlusion results in RV infarction.¹⁸ This relative protection of the right ventricle from infarction is thought to be a consequence of its lower oxygen demand, its continued perfusion during systole, and the existence of collaterals from the LAD artery, which, because of the lower systolic pressure on the right side, are more capable of supplying blood in the direction of the right ventricle than in the reverse direction. The LAD collaterals to the right ventricle are mainly through the moderator band artery, a branch of the first septal perforator.²⁰ Prior severe stenosis or occlusions of the LAD artery can limit the development of collaterals to the right ventricle with the occurrence of an acute RCA occlusion increasing the extent of acute ischemic RV dysfunction.²¹

Conflicting data, particularly in autopsy series, exist concerning RV infarction in the setting of LAD obstruction producing anteroseptal infarction.^{18,22-24} With LAD occlusion, the clinician would expect the septal portion of the right ventricle and a small portion of the anterior RV wall to be affected. Andersen and colleagues,²² in an autopsy study of 107 patients, were able to detect evidence of RV infarction in more than half of the patients with anterior infarcts, but the amount of RV tissue affected was small (1% in anterior infarction versus 15% in posterior infarction). Hemodynamically significant RV infarction with LAD occlusion is probably rare.²² In the case

of a left dominant circulation, the circumflex artery supplies the posterior septum and posterior wall of the right ventricle through the posterior descending artery. Although obstruction of the circumflex artery may lead to RV involvement, hemodynamically significant RV infarctions are uncommon because the nondominant RCA continues to supply the lateral RV wall and most of the anterior RV wall through the acute marginal branches.

Ventricular Interdependence

The concept of ventricular interdependence in RV infarction is central to understanding the pathogenesis of the resultant low cardiac output state. Ventricular interdependence is mediated through the common pericardium and shared septum. In RV infarction, acute RV dilation occurs.^{15,16,24} Because the right ventricle shares a relatively fixed space with the left ventricle, the pericardial pressure abruptly increases, leading to impaired LV filling. In animal models with the pericardium removed, it is difficult to induce hypotension with RV infarction.⁸ When the pericardium is left intact,^{16,25} however, RV infarction is associated with the full syndrome, as originally described by Cohn and coworkers.¹² Incision of the pericardium leads to improvement in cardiac output, pressure equalization, and an increase in RV systolic pressure.¹⁶

The increase in right-sided diastolic pressure that occurs in RV infarction leads to a reversal of the normal left-to-right transeptal diastolic gradient.²⁶ On echocardiography, the septum can be seen to flatten and encroach on the LV diastolic dimension. During systole, the septum can be seen to move paradoxically toward the right ventricle, at times in a piston-like manner.¹⁶

Except in rare cases of isolated RV infarction,^{27,28} LV infarction accompanies RV infarction. The pericardial constraint and alterations in septal geometry lead to reduced LV filling, and cardiac output is diminished further by the decrease in LV systolic function. Development of the shock syndrome with isolated RV infarction²⁷ proves, however, that LV systolic dysfunction is not a necessary component. Echocardiographic assessment in cases of hemodynamically severe RV infarction has confirmed that shock may be present with preserved LV systolic function.¹⁶

The hemodynamic hallmarks of RV infarction (Table 18-1) are a decrease in cardiac output, elevation of right atrial pressure (>10 mm Hg), elevation of RV diastolic pressure, and decrease in RV systolic pressure.²⁹⁻³¹ There is diastolic equalization of

RV and LV pressures, as in cardiac tamponade, and the ratio between right atrial and pulmonary capillary wedge pressure increases. This ratio, which normally is less than 0.65, is usually greater than 0.8 in RV infarction.²⁹ The RV tracing reveals a delayed, depressed, and often bifid peak, indicating systolic RV failure.¹⁶ RV diastolic failure is also manifested by a dip and plateau pattern on the RV pressure tracing.

In most studies, hemodynamic tracings showed a blunted x descent with a prominent y descent, suggesting decreased compliance of the right ventricle, as seen in pericardial constriction (Fig. 18-1).^{18,29-33} In contrast, Goldstein and coworkers,¹⁶ when using RV pressure tracings to time hemodynamic events, described a prominent x descent with blunting of the y descent, as seen in tamponade. They also showed that atrial function was of pivotal importance. In some patients, there was an increase in atrial function, as evidenced by augmented a waves. These patients had a better response to therapy and had a better prognosis than patients with depressed atrial function. The latter group was shown to have more proximal RCA occlusion, affecting the atrial branches of the RCA and causing superimposed atrial infarction. Although the hemodynamic criteria for RV infarction are usually present on admission, volume loading may increase the identification of these abnormalities in a few patients.³⁰

Clinical Presentation

Clinically significant RV infarction occurs mainly in patients with concomitant inferoposterior infarction of the left ventricle, and many of the symptoms overlap. Necropsy studies suggest that RV infarction occurs almost exclusively in patients with transmural posteroseptal MI.³⁴ The size of the LV infarct does not correlate with RV infarct size. The size of the RV infarct influences the severity of RV dysfunction and presentation, however.²¹ What is unique to RV infarction is the occurrence of a syndrome of RV diastolic and systolic failure that, in its extreme form, is characterized by a triad of signs: hypotension that can progress to cardiogenic shock, elevated neck veins, and clear lung fields.^{6,12,18,35}

When RV infarction is hemodynamically significant, the physical examination is a sensitive method of detection.

Table 18-1. Hemodynamic Findings in Cases of Right Ventricular Infarction

Elevated right atrial pressure (>10 mm Hg)
Right atrial pressure/pulmonary wedge pressure ratio >0.8
Noncompliant jugular venous pattern (prominent y descent)
Dip and plateau right ventricular diastolic pressure pattern
Depressed and delayed (often bifid) right ventricular systolic pressure
Decreased cardiac output
Hypotension

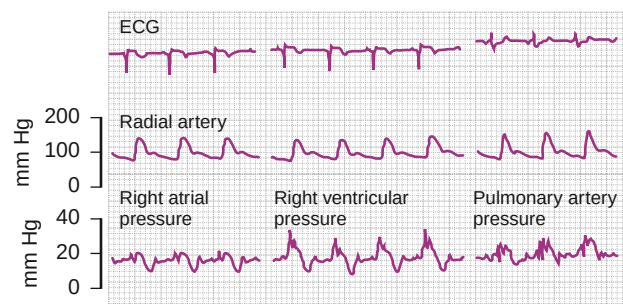


Figure 18-1. Hemodynamic tracings in RV infarction. Noncompliant pattern of RV infarction, with elevated right atrial pressure, a deep y descent in the atrial tracing, a dip and plateau diastolic pattern in the right ventricle, and relatively low pulmonary artery pressure. (From Lorrell B, Leinbach RC, Pohost GM, et al: Right ventricular infarction: clinical diagnosis and differentiation from cardiac tamponade and pericardial constriction. *Am J Cardiol* 1979;43:465-471.)

Dell'Italia and colleagues³⁵ found elevated jugular venous pressure to be 88% sensitive, with a specificity of 69% for inferior wall MI with RV involvement. Kussmaul sign, an inspiratory increase in the jugular venous pressure, was found to be 100% sensitive and specific in the same series, and Bellamy and coworkers³⁶ found it to have a sensitivity of 59% and a specificity of 89%. Other associated findings include a high frequency of bradycardia and atrioventricular (AV) block and atrial arrhythmias, including supraventricular tachycardias and atrial fibrillation or flutter. A right-sided fourth heart sign was described in 11 of 16 patients in one series, with 4 of 16 having a right-sided third heart sound.³⁷ Tricuspid regurgitation may be audible. Pericardial friction rubs may be heard because infarction in the thin right ventricle is usually transmural.³³

The differential diagnosis includes tension pneumothorax, cardiac tamponade, constrictive pericarditis, and pulmonary embolism. When the full triad is present, and ST segment elevations are observed in inferior leads, the diagnosis is straightforward. A potential pitfall is the occurrence of isolated RV infarction, which may manifest with the full clinical picture, but without electrocardiogram (ECG) evidence of MI on the standard 12-lead ECG.²⁷ Pulmonary embolism occasionally mimics RV infarction and may be a predisposing factor,³⁸ leading to occult RV infarction. Conversely, RV infarction with thrombus formation in the right ventricle can lead to pulmonary embolism. Dyspnea is usually more severe in pulmonary embolism, and RV and pulmonary artery pressures and pulmonary vascular resistance are higher than in RV infarction. Cardiac tamponade may be acute and may manifest with a similar triad of elevated neck veins, hypotension, and clear lungs, but it can be distinguished easily at the bedside with echocardiography. Pulsus paradoxus, a hallmark of tamponade, is unusual in RV infarction, which tends to resemble pericardial constriction.³³

Diagnosis

Electrocardiographic Diagnosis

ST Segment

The ECG remains the most useful tool for the diagnosis of RV infarction.³⁹ The hallmark of acute RV ischemia is ST segment elevation in the right precordial leads, a finding first reported in 1976 by Ehrhard and coworkers,⁴⁰ who used lead CR₄₁ located in the fifth intercostal space at the right mid-clavicular line. The importance of obtaining right-sided chest leads on presentation in patients with suspected MI, particularly with evidence of inferior wall involvement, cannot be overemphasized (Fig. 18-2).

Several studies have documented that ST segment elevation of 0.05 mV or greater (0.5 mm when using standard settings of 10 mm/mV) in lead V_{4R} in the setting of inferior MI is sensitive and specific for RV involvement, as documented by postmortem examination⁴¹ or by radionuclide,^{39,42,43} echocardiographic,⁴² hemodynamic,³⁹ or angiographic studies.^{33,43} Braat and colleagues⁴² found that ST segment elevation of 1 mm or greater in lead V_{4R} had a sensitivity of 93% and a specificity of 95% in a series of 67 patients with inferior MI. ST segment elevation in lead V_{3R} was also specific (97%), but less sensitive (69%). In a series of 110 patients with acute inferior MI, Klein and coworkers,⁴⁴ using the 0.5-mV criteria, reported a sensitivity of 83% and a specificity of 77%, with a positive predictive value of 70% and a negative predictive value of 88%. Infrequently, ST segment

elevation in V_{5R} or V_{6R} occurs in the absence of elevation in V_{4R}.^{39,42} Zehender and colleagues^{43,49} confirmed the utility of 0.1-mV ST segment elevation in any of the right precordial leads (V_{4R}-V_{6R}) in a series of 200 patients, showing a sensitivity of 89% and a specificity of 83%.

The ECG findings in RV infarction of right precordial ST segment elevations are the result of a rightward and anteriorly directed vector. Using Grant's method of spatial vector analysis, Hurst⁴⁵ emphasized that the clinician can diagnose RV infarction from the standard 12-lead ECG because the ST segment vector is shifted rightward (>90 degrees) toward the site of infarct. A larger RV infarct would be expected to result in greater rightward ST segment vector deviation (>150 degrees). Andersen and coworkers⁴⁶ showed that ST segment elevation in lead III exceeding that in lead II (i.e., ST segment vector directed rightward) is sensitive (68%) in diagnosing RV infarction. This criterion had a specificity of only 11% and a positive predictive value of 58% in Zehender's series of 200 patients with inferior MI. Andersen's criteria were confirmed as being highly sensitive, however (95% in Zehender's series).

Certain special situations with variant ECG findings that may cause confusion warrant mention. Geft and colleagues⁴⁷ described five patients with ST segment elevations in leads V₁-V₅ who on catheterization were shown to have RCA occlusion and acute RV infarction. All five patients had minimal or absent ST segment elevations in the inferior leads. The authors speculate that in the usual cases of RV infarction, ST segment elevations in leads V₁-V₅ are blocked by the dominant electrical forces of inferoposterior MI, resulting in isoelectric or even depressed ST segments in the left precordium. When these forces are absent, because of isolated RV infarction⁴⁸ or because of minimal posterior involvement, as may be seen in a patient with a codominant circulation,⁴⁷ ST segment elevation in the left precordial leads mimicking anterior wall infarction may be seen. A distinguishing characteristic in RV infarction may be that the ST segment elevations are highest in leads V₁ or V₂ and decrease toward lead V₅, a pattern opposite that seen in anterior MI.⁴⁷

If septal involvement can mimic RV infarction, a left lateral wall infarction or a large true posterior infarction can be expected to cancel right precordial ST segment elevations. Such cases of false-negative findings have been described.^{44,49}

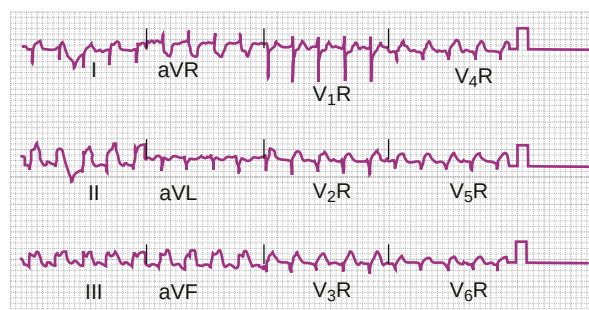


Figure 18-2. ST segment elevations in right precordial leads. A case of RV infarction in a 35-year-old heavy smoker who presented with 1 hour of substernal chest pain. The 12-lead ECG showed an acute inferoposterior infarction. Right-sided leads V_{4R}-V_{6R} show ST elevation, indicating RV involvement.

Most studies of right precordial lead ST segment elevation have been limited to patients with evidence of inferior wall MI. In anterior MI, ST segment elevation in right precordial leads has also been documented and has been found to be predictive of proximal LAD occlusion before the first septal branch, suggesting that the right precordial lead ST segment elevations are the result of septal current of injury.⁵⁰ A distinguishing characteristic in cases of LAD occlusion is that the ST segment elevation has a leftward axis, in contrast to the rightward ST segment in RV infarction, as emphasized by Hurst.⁴⁵ Other causes of right precordial ST segment elevation in the absence of RV infarction include pericardial disease, left anterior hemiblock, and pulmonary embolism.⁵¹

The time course of ST segment elevation in RV infarction warrants emphasis. Braat and colleagues⁴² reported that ST segment elevations in lead V_{4R} resolve within 10 hours after the onset of chest pain in half of patients. Similar findings were reported by Klein.⁴⁴ It is important to obtain a right-sided ECG soon after the patient's presentation.

Q Waves in Right Ventricular Infarction

Because patients may present after the ST segments have returned to baseline, criteria using Q waves in the right precordial leads have been sought. In normal subjects, an rS pattern is always present in V_{3R} and usually (>90%) in V_{4R}. In one series⁵² of patients with autopsy-documented RV infarction, the presence of a Q wave in these leads (as a QS or a QR pattern) was 100% specific and 78% sensitive. The high specificity (>90%) of Q waves was confirmed in Zehender's³⁹ series of 200 patients with inferior wall MI. Early in the course of infarction, Q waves are still absent, and the sensitivity is low, particularly for patients presenting early. In patients admitted late (>12 hours after the onset of symptoms), the sensitivity increases to 95%.

Bundle Branch Block

RV infarction, especially when extensive, has been shown to be associated with an incomplete and often transient right bundle branch block. The block is postulated to occur distally. Because there may also be precordial ST segment elevation in RV infarction, the right bundle branch block may be difficult to detect in lead V₁. Kataoka and coworkers⁵³ pointed to a cove-shaped ST-T elevation in lead V₁ as suggestive of an underlying right bundle branch block.

Atrioventricular Block

Significant AV block is more common in inferior wall MI with RV involvement.⁵⁴ The presence of ST segment elevation in V_{4R} was shown to predict the development of high-grade AV block, with 48% of patients in one series developing AV block during the first 3 days of infarction compared with only 13% without evidence of RV infarction.⁵⁵

After AV block develops in the setting of RV infarction, it has specific implications for therapy. Because cardiac output depends on preload and right atrial function, RV pacing alone may be inadequate. Sequential AV pacing may have a marked salutary effect on cardiac output,^{51,56} and should be considered in patients with RV infarction and AV dissociation. Effective RV transvenous pacing may be more difficult to achieve in RV infarction because of muscle necrosis or scarring. A higher pacing threshold should be anticipated and accepted.^{57,58} Caution should be employed when placing a pacing wire in an area

of infarction because the risk of rupture may be increased. If transvenous pacing fails, transcutaneous external pacing may be successful.⁵⁹

Arrhythmia

Atrial arrhythmias are common in RV infarctions. Because of the propensity for low cardiac output and preload dependence, these arrhythmias are poorly tolerated and should be treated aggressively. Early cardioversion and antiarrhythmic therapy for atrial fibrillation are recommended.⁵¹ One study of patients with RV infarction did not reveal an increase in ventricular arrhythmias compared with patients with inferior infarctions without RV involvement.⁶⁰

Prognostic Implications

ECG findings for RV infarction have marked prognostic implications, even in the absence of hemodynamic abnormalities. In the series of 200 patients by Zehender and associates,⁶¹ ST segment elevation in lead V_{4R} was shown on multiple logistic regression analyses to be the strongest predictor of in-hospital morbidity and mortality. Patients with ST segment elevation in V_{4R} had a mortality rate of 31% compared with 6% for patients without such evidence of RV involvement. Similarly, major complications (e.g., ventricular fibrillation, sustained ventricular tachycardia, cardiogenic shock, cardiac rupture, high-grade AV block, reinfarction) were markedly more common (64% versus 28%; $P < .001$) in patients with ECG evidence of RV involvement. In one series, the presence of AV block in RV infarction was found to be associated with a mortality rate of 41%, whereas the mortality rate for patients with inferior wall infarction with RV infarction but without AV block, and for patients with inferior MI with AV block but without RV infarction was only 11% to 14%.⁵⁸

Echocardiography

Two-dimensional echocardiography is sensitive (80% to 90%) and specific (>90%) in the detection of hemodynamically significant RV infarction.⁶²⁻⁶⁵ The diagnosis rests on the demonstration of RV wall motion abnormality RV dilation, abnormal (paradoxical) septal motion, as and flattening of the septum⁶⁵ and reduced septal thickening.

Echocardiography is particularly useful in assessment of RV infarction because it also provides information on LV function, associated valvular regurgitation, and possible differential diagnoses such as cardiac tamponade. Echocardiography may also detect important complications, such as thrombus formation or pericardial effusion. Two-dimensional contrast echocardiography may help detect right-to-left shunting through a patent foramen ovale.⁶⁶ Because of its noninvasive nature, portability, and the added hemodynamic and morphologic data that it provides, echocardiography is the imaging modality of choice in the Cardiac Intensive Care Unit.

Cardiovascular Magnetic Resonance Imaging

Late enhancement cardiovascular magnetic resonance imaging (MRI) has greater sensitivity at detecting RV infarction than ECG, physical examination, or echocardiography. Late enhancement cardiovascular MRI findings of injury of the right ventricle in the acute phase persist 13 months, suggesting that this imaging modality can predict the extent of irreversible RV injury in the acute phase.⁶⁷

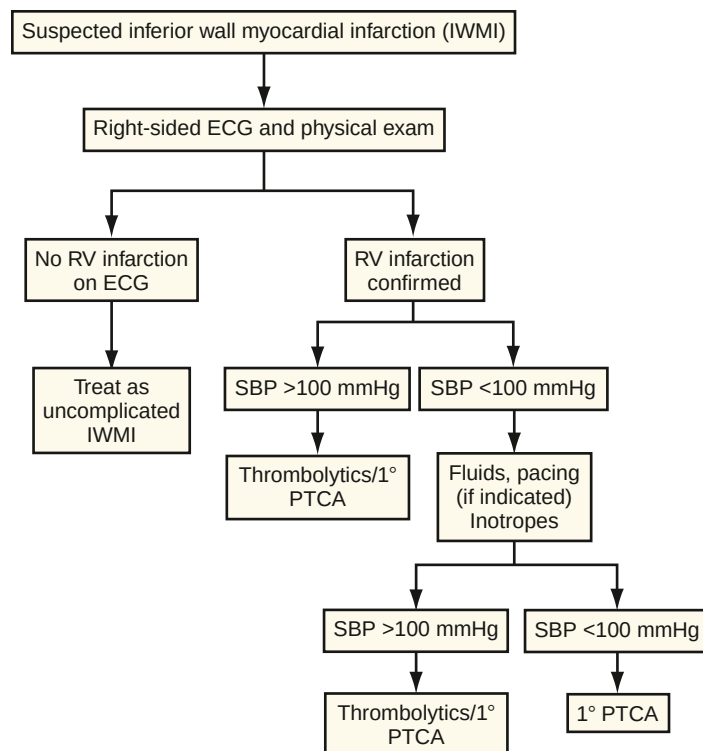


Figure 18-3. Algorithm for evaluation and treatment of RV infarction. PTCA, percutaneous transluminal coronary angioplasty; SBP, systolic blood pressure.

Treatment

Figure 18-3 presents an algorithm for the evaluation and treatment of patients with RV infarction. The goals of therapy are to restore arterial pressure, maintain AV synchrony, and achieve rapid coronary reperfusion.

Reperfusion Therapy

Given the adverse prognostic effect of RV infarction in inferior MI, establishing reperfusion by primary percutaneous coronary intervention (PCI) or thrombolytic therapy is particularly important in this subgroup of patients. Meta-analyses have shown that, overall, PCI results in superior outcomes compared with thrombolysis when performed rapidly by an experienced team.⁶⁸ PCI should be the reperfusion modality of choice where available. If PCI is unavailable, thrombolysis is appropriate therapy that has been shown to reduce mortality. In a nonrandomized trial of therapy in inferior wall MI by Zehender and associates,⁴ the mortality benefit of thrombolytic therapy was limited to the patients with RV involvement, with a reduction in the mortality rate from 42% to 10%. Patients without RV infarction had a similar mortality rate (6% to 7%) with and without thrombolytic therapy. Similarly, in the TIMI II trial, thrombolytic therapy reduced the incidence of RV infarction from 42% to 13% for patients with inferior MI.⁶⁹ Radionuclide studies have confirmed a marked reduction in extent of RV infarction in patients who achieved early reperfusion.^{70,71} Thrombolytic therapy is relatively ineffective, however, in the presence of cardiogenic shock. In the presence of shock not responsive to volume replacement and inotropic therapy, primary PCI is the preferable approach even if the patient requires transfer to another facility.

Volume Infusion

Based on hemodynamic data from dog models,¹⁶ early studies emphasized the importance of volume infusion in RV infarction. The right ventricle is preload-dependent, and in the setting of ischemia with decreased diastolic compliance, the right ventricle may benefit from an augmentation in preload. If hypovolemia is present, there may be a marked improvement with fluid administration. When marked RV dilation has already occurred, however, further increases in RV preload do not result in an increase in RV stroke volume and may impair LV filling further through increased septal shift and increased pericardial constraint.¹⁴ Cardiac output and arterial blood pressure may not increase. In various studies,⁷²⁻⁷⁴ an increase in mean right atrial pressure to 10 to 14 mm Hg was followed by an improvement in stroke volume, but further augmentation was associated with no improvement or a decrease in stroke volume.⁶²⁻⁶⁵ Volume infusion should be used cautiously and only to bring the right atrial pressure to 10 to 14 mm Hg. Invasive hemodynamic monitoring is usually necessary to guide therapy.

Inotropic Support

Dobutamine and dopamine have been evaluated in the setting of severe RV infarction (with right atrial pressure >13 mm Hg) and have consistently been found to increase RV stroke work and cardiac output, where volume loading and nitroprusside were generally ineffective.⁷³ Dobutamine, which also has arteriolar vasodilating effects, usually does not increase mean arterial pressure significantly. Dopamine, by activating dopaminergic and α -adrenergic receptors, increases mean arterial pressure and should be used preferentially when patients are severely hypotensive.¹⁴ After the systolic blood pressure increases

greater than 90 mm Hg, dobutamine may be used, alone or in combination with dopamine. Tricuspid regurgitation has been found to render dobutamine ineffective because the increase in RV contractility was offset by an increase in the regurgitant fraction.⁷⁴

The use of milrinone,⁷⁵ a phosphodiesterase inhibitor, has been shown to be beneficial in chronic right heart failure, increasing myocardial contractility. Milrinone has the advantage of reducing pulmonary vascular resistance and unloading the right ventricle. Its use in RV infarction has not been systematically evaluated, however.

Right Ventricular Assist Devices

More recent reports of the use of percutaneous RV assist devices in patients with shock complicating RV infarction are encouraging. These reports have largely involved the use of the Tandem Heart (Cardiac Assist, Pittsburgh, PA) device. Two 21F cannulae are placed via both femoral veins, one in the right atrium, and the other in the pulmonary artery with assist pumping using an extracorporeal centrifugal pump. The temporary use of such invasive RV assistance is justified by the frequent observation of RV functional recovery over time. This unloading of the right ventricle allows reduction in RV dilation, reducing pericardial pressure and improving LV filling in the setting of shock owing to RV infarction.^{76,77}

Pulmonary Vasodilator Therapy

The use of selective pulmonary vasodilators might be expected to provide afterload reduction for the failing right ventricle without concurrent systemic vasodilation and hypotension, potentially resulting in improved cardiac output. Inhaled nitric oxide acts as a selective pulmonary vasodilator, producing smooth muscle cell relaxation and vasodilation in the pulmonary circulation without systemic vasodilation owing to its active binding to hemoglobin and inactivation in circulating erythrocytes.⁷⁸ Inhaled nitric oxide has been studied and verified to decrease pulmonary vascular tone in adults and children with pulmonary hypertension of varying etiologies.^{79,80}

Ingleiss and colleagues⁸¹ administered short-term inhaled nitric oxide for 10 minutes to 13 patients with RV infarction and cardiogenic shock, and showed temporary beneficial hemodynamic effects reflected by significantly reduced right atrial and mean pulmonary pressures, reduced pulmonary vascular resistance, and increased cardiac indices and stroke volumes. No changes in systemic pressure and pulmonary capillary wedge pressure were noted. Reduced right-to-left shunting by contrast echocardiography was noted in three patients with patent foramen ovale, with subsequent improvement in arterial oxygen-hemoglobin saturations.⁸¹ Further study is necessary to determine if these effects of inhaled nitric oxide used in patients with RV infarction and cardiogenic shock translate into improved survival or early recovery. Uses of other pulmonary vasodilators such as sildenafil or prostacyclin in RV infarction warrant evaluation.

Preload and Afterload Reduction

The right ventricle is sensitive to preload, particularly in the setting of RV infarction. Hypotension provoked by nitroglycerin, morphine sulfate, or diuretics should alert the clinician to the possibility of a preload-sensitive state such as RV infarction. The routine use of these agents should be discouraged in patients

with acute inferior MI until RV involvement is ruled out. Sodium nitroprusside may result in marked afterload reduction, which if ineffective in increasing right-sided output, results in systemic hypotension.⁷³ In some clinical situations, such as combined right and left heart failure with severe LV dysfunction or when fluid administration has been overzealous, the cautious use of vasodilators may be attempted.¹⁴ Invasive hemodynamic monitoring should be used, and the right atrial pressure should be maintained greater than 10 mm Hg.

Hemodynamic Monitoring

In a patient with hemodynamic instability in the setting of RV infarction, the use of a pulmonary artery catheter often helps guide therapy. Extra caution should be employed in the placement of the catheter because a higher incidence of ventricular arrhythmias, including ventricular fibrillation, has been described in the setting of RV infarction (4% versus 0.3% in patients without RV infarction).⁸² Flotation of the catheter under fluoroscopic guidance by a cardiologist or other intensivist may help minimize the risk.

Pacing and Treatment of Arrhythmias

Significant AV block and atrial arrhythmias, particularly atrial fibrillation, are detrimental in the setting of RV infarction because of the importance of AV synchrony and intact atrial contraction to the maintenance of RV and LV stroke volumes.^{14,55,83} High-grade AV block, significant bradycardia, and atrial arrhythmias should be treated aggressively.

Complications

Patients with inferior wall MI and accompanying RV infarction have a much higher rate of complications than patients with inferior wall MI without RV involvement, accounting for part of the adverse prognostic implications of RV infarction (Table 18-2). Some complications may occur in any inferior wall MI, but are more common in the setting of RV infarction; these include AV block, atrial arrhythmias, and pericarditis. The coronary care physician should also be aware of several, less common complications.^{66,84-87}

Patent foramen ovale is present in 25% of the population. In the setting of RV infarction and elevated right-sided pressures, right-to-left shunting may occur, with resulting hypoxemia. Maneuvers that reduce LV pressures, such as afterload reduction, exacerbate this shunting. Percutaneous closure of the patent foramen may be necessary in extreme cases.⁶

Table 18-2. Complications of Right Ventricular Infarction

Atrioventricular block
Atrial tachyarrhythmias
Tricuspid regurgitation
Right-to-left shunting
Right ventricular thrombus
Pulmonary embolism
Paradoxical embolism
Septal rupture
Free wall rupture

As in LV infarction, RV infarction may predispose to thrombus formation in the infarcted ventricle, with possible pulmonary embolism. In the presence of a patent foramen ovale, paradoxical embolization may lead to systemic emboli. Thrombus has been identified in the right ventricle of patients with RV infarction (3 of 33 [9%]) and in patients without RV infarction with posterior wall MI (4 of 106 [4%]).⁸⁸

Severe tricuspid regurgitation secondary to papillary muscle necrosis or severe RV dilation has been described in the setting of RV infarction. In extreme cases, refractory heart failure has necessitated valve replacement.⁸⁹ Other complications include septal rupture,⁸⁷ RV free wall rupture,⁸⁹ and pericarditis, which is common in RV infarction because of the thinness of the RV wall.

Prognosis

RV infarction is associated with markedly increased complication and mortality rates.³⁸ The reduction in mortality by reperfusion therapy is dramatic. Aggressive reperfusion therapy is indicated to maximize survival in the absence of severe mitigating circumstances.

After RV infarct, RV function generally improves.⁹⁰ Long-term prognosis is determined, however, by residual LV rather than RV function, with similar posthospital courses for patients with and without RV infarction.³⁸ A strong correlation exists between the outcome of RV infarction and age.^{34,91} In acute inferior MI, RV infarction substantially increases the risk of death and major complications in elderly patients.³⁴

Conclusion

RV infarction occurs mainly in the setting of inferior wall MI with proximal RCA occlusion. RV involvement in inferior MI has a marked adverse effect on complication rate and prognosis. Patients with RV infarction benefit, however, from reperfusion therapy. Complications such as hypotension, AV block, and atrial tachyarrhythmias should be treated aggressively. Although the short-term prognosis in RV infarction is poor, if the patient survives the acute illness, the long-term prognosis is good.

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Mechanical Complications of Acute Myocardial Infarction

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CHAPTER

19

Free Wall Rupture
Mitral Regurgitation
Ventricular Septal Rupture

Dynamic Left Ventricular Outflow Tract Obstruction
Complicating Acute Myocardial Infarction

MECHANICAL COMPLICATIONS of acute coronary syndromes are associated with very poor prognosis unless prompt diagnosis and aggressive interventions are instituted. In many of these patients, the size of the myocardial infarction (MI) may not be large.^{1,2} Mechanical complications are frequently associated with cardiogenic shock, and approximately 12% of patients with cardiogenic shock have these complications. Early detection and intervention have the potential to improve the otherwise grim prognosis. The mechanical complications of acute MI are outlined in this chapter and summarized in [Table 19-1](#).

Free Wall Rupture

Acute rupture of a free wall is a sudden, usually catastrophic complication of acute MI. It is the second most common cause of post-MI death after cardiogenic shock without mechanical defects.³ More recent studies have reported that free wall rupture accounts for 3% to 20% of all deaths resulting from acute MI.⁴ The overall incidence of free wall rupture is about 2% to 7%, and it accounts for in-hospital mortality of about 15% of all deaths owing to acute MI.⁵ Risk factors for free wall rupture

include female gender, advanced age, single vessel disease, hypertension, transmural MI, and late administration of thrombolytic therapy.⁴⁻⁸ The incidence of rupture for patients with successful reperfusion (0.9%) is less than that without reperfusion treatments (2.7%). The incidence seems to be similar whether reperfusion is achieved by thrombolytic therapy or by angioplasty.

Pathophysiology

The most frequent site of post-MI cardiac rupture is the left ventricular free wall (80% to 90%).^{2,9} Less commonly, the left ventricular posterior wall, right ventricle, or atria may rupture.^{10,11} Rupture may rarely occur at more than one site,¹² and it may be associated with papillary muscle¹² or septal rupture.¹³

Expansion of the infarct area seems to predispose to rupture.¹⁴ When ruptures occur within 24 hours of onset of infarction, however, infarct expansion or infiltration by neutrophils does not seem to contribute to the pathogenesis.¹⁵ The path of the rupture through the wall may be direct (through the center of the necrotic area), but is often serpiginous and often seen at an eccentric position, near the “hinge point” of mobility between the normally contracting and dyskinetic myocardium. These observations suggest that local shear forces contribute to the disruption of tissue.¹⁶ It has been suggested that apoptosis of cardiomyocytes in the region of maximum wall strain contributes to rupture of the ventricular free wall.¹⁷

Infarct expansion and adverse ventricular remodeling has been suggested to contribute to subacute ventricular rupture.¹⁸ Inappropriate changes in the extracellular matrix, in particular, collagen disruption and its inhibition by dysregulation of matrix metalloproteinase metabolism, have been suggested to be important mechanisms in the pathogenesis of ventricular rupture after MI.¹⁹ In experimental animal models, deficiency of local angiotensin type II receptor has been shown to cause decreased collagen deposition and increased incidence of cardiac rupture after MI.²⁰ Angiotensin II induces transforming growth factor- β 1, which promotes fibrogenesis.²¹

Clinical Features

Free wall rupture occurs within 24 hours in 25% to 35% and within the first week in 87% of patients after the onset of acute coronary syndrome.^{22,23} Frequently, rupture occurs in patients

Table 19-1. Mechanical Complications of Acute Myocardial Infarction

Free wall rupture
Acute
Subacute
Mitral regurgitation
Papillary muscle dysfunction without rupture
Papillary muscle rupture
Ventricular septal rupture
Isolated
With free wall
Tricuspid regurgitation
Right ventricular papillary muscle dysfunction
Right ventricular papillary muscle rupture

with uncomplicated MI. There are no specific symptoms or signs of acute or subacute free wall rupture. Patients may present with syncope or signs and symptoms of cardiogenic shock.^{6,10} Sudden onset of severe chest pain during or after some types of physical stress, such as coughing or straining at stool, may suggest the onset of free wall rupture. Some patients have premonitory symptoms, such as unexplained chest pains that are not typical of ischemia or pericarditis-related chest pains,²³ repeated emesis, restlessness, and agitation.²⁴

Rapid onset of tamponade owing to hemopericardium, resulting in severe hypotension and electromechanical dissociation, characterizes acute rupture, and antemortem diagnosis is almost impossible in these patients. In patients with subacute rupture, relatively slower development of tamponade may allow antemortem diagnosis and corrective surgical therapy with salvage of these patients. Elevated jugular venous pressure, pulsus paradoxus, muffled heart sounds, and a pericardial friction rub may indicate subacute rupture. A new systolic, diastolic, or “to-and-fro” murmur may be present in these patients with or without pseudoaneurysm.²⁵

Diagnosis

In acute free wall rupture, the electrocardiogram (ECG) reveals electromechanical dissociation and terminal bradycardia.^{8,26} In subacute rupture, several ECG findings have been described, including presence of Q waves, recurrent ST segment elevation or depression, pseudonormalization of inverted T waves particularly in the precordial leads, persistent ST segment elevation, and new Q waves in two or more leads.^{5,22,24,26,27} None of the ECG findings is specific or sensitive enough, however, to be of value for early diagnosis of impending rupture.

Transthoracic echocardiography should be performed as soon as the subacute rupture is suspected.^{5-7,26} Color flow Doppler may be useful for the diagnosis of the rupture site.²⁸ The most frequent finding is pericardial effusion. The presence of echogenic masses in the fluid and detection of wall defects enhance diagnostic accuracy. Although transesophageal echocardiography may provide a better delineation of these findings, it should not be performed because of the stress of the procedure until absolutely necessary. Contrast echocardiography may show extravasation of the contrast material into the pericardial space, confirming the diagnosis of free wall rupture.^{28,29}

Determination of hemodynamics and contrast ventriculography are unnecessary for diagnosis and should be avoided. If a balloon flotation catheter is already in place, determination of right heart hemodynamics reveals elevated right atrial and pulmonary capillary wedge pressures and equalization of the diastolic pressures.^{5,26}

Management

Surgical repair is the definitive treatment, and for subacute rupture, salvage rates may be considerable. The operative mortality has been reported to be 24% to 35%, and the total in-hospital mortality is 50% to 60%.^{5,7,26} Currently, conservative surgical techniques using simple sutures supported with felt or application of a patch to the epicardial surface with biologic glue are employed.^{24,30} Temporizing measures include pericardiocentesis, volume loading, inotropic support, and intra-aortic balloon support. In very high-risk elderly patients, nonsurgical conservative treatment with adequate control of blood pressure with angiotensin inhibition and the use of β -blocking agents has been suggested.³¹ The treatment

approach of pseudoaneurysm is similar to that of subacute rupture without pseudoaneurysm.

Mitral Regurgitation

Although mild mitral regurgitation is common in patients with acute coronary syndromes, severe mitral regurgitation owing to papillary muscle and left ventricular wall dysfunction with or without rupture of the papillary muscle is much less frequent. The overall incidence of acute mitral regurgitation in patients receiving thrombolytic therapy was 1.73% in the GUSTO-I trial.³² It has been reported that the incidence is significantly lower (0.31%) in patients undergoing primary angioplasty.³³ The reported incidence of mild to moderate mitral regurgitation is variable and is approximately 29% (mild) and 6% (moderate). The incidence of severe mitral regurgitation complicating MI is approximately 10%,³⁴ and the incidence of mitral regurgitation resulting from papillary muscle rupture is 1%.¹

The risk factors for mitral regurgitation with and without papillary muscle rupture seem to be different, although advanced age and female gender are risk factors for both types.³⁵ In patients without papillary muscle rupture, prior MI, relatively large infarct size, multivessel coronary artery disease, recurrent myocardial ischemia, and heart failure on admission are more prevalent. In contrast, in patients with papillary muscle rupture, absence of previous angina, inferoposterior MI, absence of diabetes, and single vessel disease are more common.

Pathophysiology

Several anatomic and functional derangements may cause mitral regurgitation in patients with acute coronary syndromes. Acute transient papillary muscle ischemia is associated with impaired shortening of the muscle, which usually causes only mild mitral regurgitation. Ischemic dysfunction of anterior and posterior papillary muscles may be associated with more severe mitral regurgitation.³⁶ Ischemia of only papillary muscles without involvement of the adjacent left ventricular walls seldom results in severe mitral regurgitation.³⁷ The subendocardial position of the papillary muscles and their characteristic vascular anatomy (supplied by coronary end arteries) predispose them to ischemia.³⁸ The posteromedial papillary muscle receives its blood supply only via the posterior descending coronary artery, whereas the anterolateral papillary muscle receives its blood supply from the left anterior descending and left circumflex coronary arteries.³⁹ Ischemia of posteromedial papillary muscle is more common than ischemia of anterolateral papillary muscle.

A large posterior MI, including the anchoring area of the posteromedial papillary muscle, may be associated with severe mitral regurgitation. The mechanism seems to be asymmetric annular dilation and misalignment of the papillary muscle and the leaflets during systole causing severe leaflet prolapse.⁴⁰ A small inferior or inferoposterior MI with involvement of the posteromedial papillary muscle can also produce severe mitral regurgitation, however, because of severe leaflet prolapse.

Rupture of the posteromedial papillary muscle is 6 to 12 times more frequent than rupture of the anterolateral papillary muscle, explaining the higher incidence of severe mitral regurgitation in patients with inferior MI.³⁴ In approximately 50% of patients with papillary muscle rupture, the infarct size is small.⁴¹

Mild to moderate mitral regurgitation usually does not induce any additional hemodynamic burden. Neither ejection fraction

nor hemodynamics, such as pulmonary capillary wedge and pulmonary artery pressures and cardiac output, is substantially influenced. In contrast, severe mitral regurgitation imposes sudden additional hemodynamic burden on the left ventricular dynamics and function. Sudden large volume overload, resulting from regurgitation to a left atrium with normal compliance and size, causes a marked increase in left atrial and pulmonary capillary wedge pressure, causing severe pulmonary edema. Because of postcapillary pulmonary hypertension, which increases right ventricular afterload, the right ventricle also fails. Left ventricular forward stroke volume decreases, resulting in a reduction in cardiac output and systemic hypotension. All the hemodynamic features of cardiogenic shock develop rapidly and usually abruptly. Left ventricular ejection fraction may increase because of sudden unloading of the ventricle by the mitral regurgitation. The ejection fraction is still less than normal, however, because of the presence of dysfunctional ischemic or infarcted myocardium.

Clinical Features

Mitral regurgitation not resulting from papillary muscle rupture is detected at a median of 7 days (range 5 to 45 days) after MI. Severe mitral regurgitation secondary to papillary muscle rupture occurs at a median of 1 day (range 1 to 14 days) after the onset of the index infarction; approximately 20% of ruptures occur within 24 hours of onset of infarction.^{1,25,42}

In patients with mild mitral regurgitation secondary to papillary muscle dysfunction, the only clinical indication may be the presence of a pansystolic (holosystolic) or more often a late systolic murmur. In patients with rupture of a papillary muscle, the clinical presentation is characterized by an abrupt onset of severe respiratory distress resulting from flash pulmonary edema. Hypotension and reflex tachycardia rapidly develop. Other clinical features of preshock or shock are also present. A sudden appearance of a pansystolic or an early systolic murmur, radiating to the left axilla or to the base or both, is also a characteristic physical finding. A palpable thrill is uncommon. In some patients, the murmur may be abbreviated or absent. The abbreviation of the murmur results from a rapid decrease in the pressure gradient between the left atrium and the left ventricle.²⁵ "Bubbling" rales of pulmonary edema are present bilaterally and make auscultation difficult.

Diagnosis

The ECG most frequently reveals recent inferior or inferoposterior MI (55%); however, location of the index infarction is anterior (34%) and posterior (32%) in patients with severe mitral regurgitation and cardiogenic shock.³⁴ In occasional patients, only ST-T abnormalities of "shell infarct" are present. Radiographic evidence of acute severe pulmonary edema is invariably present.

Doppler and transthoracic echocardiography should be performed in all patients. Transthoracic echocardiography is less sensitive than transesophageal echocardiography for visualization of the disrupted mitral valve (45% to 50% versus 100%),⁴³⁻⁴⁵ but it is 100% sensitive for the detection by color Doppler echocardiography of the resultant severe mitral regurgitation (Fig. 19-1A).^{43,46}

Echocardiography shows the underlying regional left ventricular wall motion at the site of ischemia/infarction and excludes ventricular septal or free wall rupture.^{43,47} A partial papillary muscle rupture may be detectable by two-dimensional

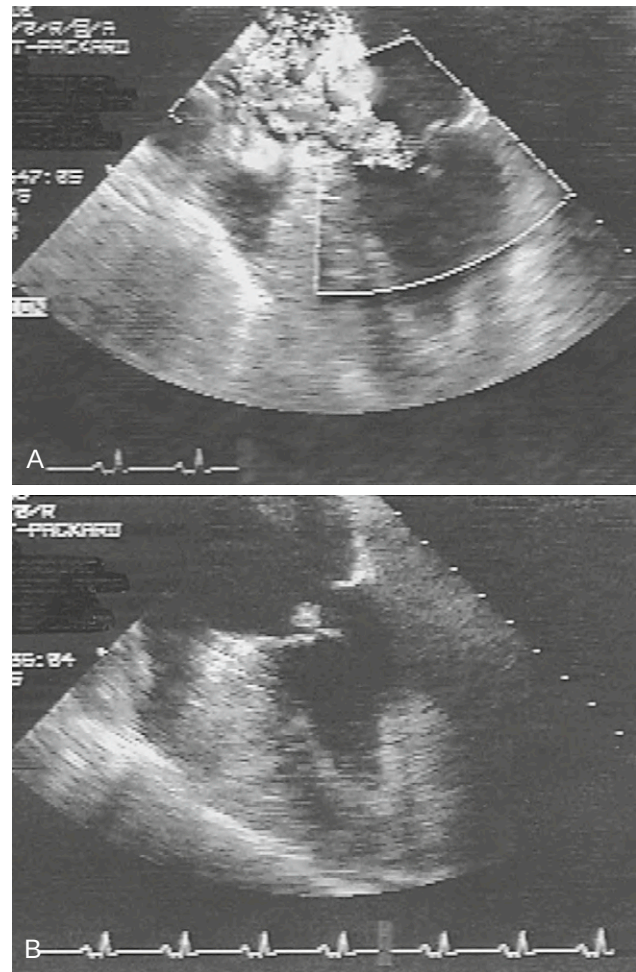


Figure 19-1. **A**, Systolic frame Doppler image of a patient with rupture of the posteromedial papillary muscle. There is a large eccentric jet of severe mitral insufficiency, directed anteriorly, seen as a conspicuous color mosaic. **B**, Two-dimensional transesophageal echocardiogram (vertical plane image of left ventricle) of a complete rupture of the posteromedial papillary muscle. A mobile mass (ruptured papillary muscle head) attached to the posterior mitral leaflet is seen in the left atrium in this systolic frame. Also seen is segmental dilation of the area of the basal and mid-inferior wall infarction.

echocardiography. A complete rupture is diagnosed when the head of the papillary muscle is seen as a freely moving mobile mass attached to the mitral valve chordae (Fig. 19-1B).^{44,46,48-50}

Right heart catheterization with the use of balloon flotation catheters is unnecessary for the diagnosis of severe mitral regurgitation. If it is undertaken, however, it reveals giant v waves in the pulmonary capillary wedge pressure tracing (Fig. 19-2). Giant v waves may also be present in patients with ventricular septal rupture. In ventricular septal rupture, increased pulmonary venous return owing to the large left-to-right shunt to a left atrium with normal size and compliance is associated with an accentuated v wave. The presence of a reflected v wave in a pulmonary artery pressure tracing is diagnostic of acute or subacute severe mitral regurgitation.⁵¹ For the diagnosis of left-to-right shunt, step-up in oxygen saturation in the pulmonary artery is detected. In some patients with severe acute mitral

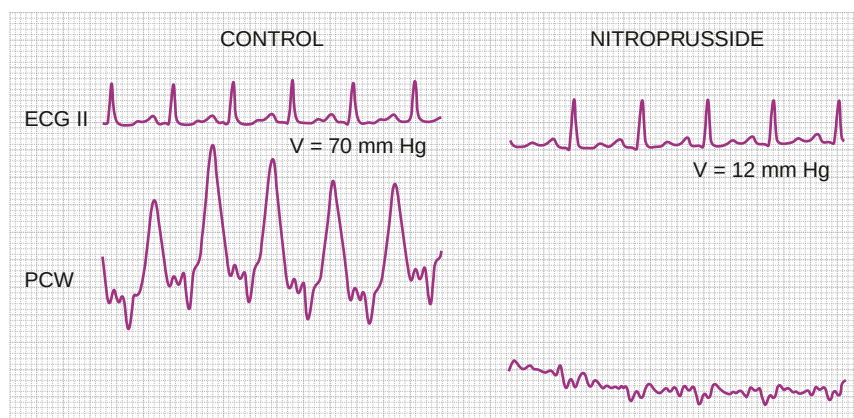


Figure 19-2. Acute mitral regurgitation. *Left tracings*, Large v waves in the pulmonary capillary wedge (PCW) tracing. *Right tracings*, Reduction in magnitude of the v wave during sodium nitroprusside infusion.

regurgitation, reflux of the oxygenated pulmonary venous blood occurs in the distal pulmonary artery branches. For the diagnosis of ventricular septal rupture, oxygen saturation should be determined in the proximal pulmonary arteries.

Management

Patients with mild mitral regurgitation do not require surgical intervention. After adequate reperfusion therapy, appropriate adjunctive treatments, such as angiotensin-inhibiting agents, β -adrenergic antagonists, aldosterone antagonists, antiplatelet agents, and lipid-lowering agents, should be employed to decrease the risk of development of heart failure, for reverse ventricular remodeling, and to improve prognosis. Even in patients with mild mitral regurgitation diagnosed during the acute phase of MI, the long-term prognosis is unfavorable, although immediate prognosis is not affected.^{52,53} Aggressive post-MI adjunctive therapies are essential.

Severe mitral regurgitation complicating acute MI with cardiogenic shock requires surgical intervention for mitral valve replacement or repair. In the SHOCK registry, in-hospital mortality without valve surgery was 71% versus 40% with surgery, indicating a significant improvement in immediate prognosis.³⁴

Supportive and stabilizing treatments consist of mechanical ventilation, diuretics, vasodilators, inotropic agents, and, if possible, intra-aortic balloon pump. Vasodilator drugs such as sodium nitroprusside reduce regurgitant volume, decrease pulmonary capillary wedge and pulmonary artery pressures, and increase forward stroke volume and cardiac output.⁵⁴ Hypotension precludes the initial use of vasodilators, but they can be used after institution of intra-aortic balloon pump. Intra-aortic balloon pump reduces left ventricular ejection impedance and maintains perfusion pressure concurrently. The therapeutic approach for mitral regurgitation complicating MI is outlined in Table 19-2.

Ventricular Septal Rupture

The incidence of ventricular septal rupture complicating acute MI is approximately 0.2% in the era of reperfusion.⁵⁵ Before the introduction of reperfusion therapy for MI, the reported incidence was 0.5% to 2%.^{38,56} The clinical risk factors seem to be older age, female gender, lower incidence of diabetes, and history

Table 19-2. Suggested Management of Mitral Regurgitation Complicating Acute Myocardial Infarction

Mild Mitral Regurgitation

Reperfusion treatments

Adjunctive treatments

Angiotensin-inhibiting agents, β -adrenergic antagonists, aldosterone antagonists, lipid-lowering agents, antiplatelet agents

Severe Mitral Regurgitation

Corrective valve surgery

Stabilizing and supportive treatments

Mechanical ventilation, diuretics, intra-aortic balloon pump, vasodilators, vasopressors, inotropic agents

Adjunctive treatments in survivors

Angiotensin-inhibiting agents, β -adrenergic antagonists, aldosterone antagonists, lipid-lowering agents, antiplatelet agents

of smoking.⁵⁷ Although it was previously thought that the incidence of septal rupture increased with thrombolytic therapy, placebo-controlled thrombolytic trials failed to confirm the increased risk of rupture with thrombolytic therapy.^{58,59} Early occurrence of ventricular septal rupture has been observed, however, after thrombolytic therapy.⁶⁰ Whether a history of hypertension increases the risk of ventricular septal rupture remains controversial.⁶¹

Pathophysiology

Most commonly, ventricular septal rupture occurs after a first infarction.^{13,61} In the SHOCK registry trial, the incidence of first infarction was only 17%.⁵⁷ The rupture usually occurs in thin akinetic areas, and it may be direct or “complex.” The complex rupture forms a dissection plane in a serpiginous path in the septum.⁶² Complex ruptures may be associated with concurrent ruptures of other structures, such as ventricular free wall or papillary muscle.¹³ Lack of septal collateral flow, regional distortion, and infarct expansion seem to be important factors for

the development of a ventricular septal rupture.^{14,61} Ventricular septal rupture seems to occur with almost equal frequency in anterior and inferior MI,⁶³ and single or double vessel disease is more common.⁵⁷

Ventricular septal rupture produces a usually large, left-to-right shunt (pulmonary-to-systemic flow >3:1) that places a volume load on the right ventricle, pulmonary circulation, left atrium, and left ventricle. The left ventricular performance, which is depressed by ischemia, is compromised further by the volume overload. In the SHOCK trial registry, the range of ejection fraction in patients with post-MI ventricular septal rupture was 25% to 40%.⁵⁷ Left ventricular forward stroke volume declines, but right ventricular stroke volume and pulmonary flow increase. There is reflex increase in heart rate and systemic vascular resistance, which increases left ventricular ejection impedance, further increasing the magnitude of left-to-right shunt. Right ventricular performance also declines because of the volume load and postcapillary pulmonary hypertension.

Clinical Features

In more than 70% of patients, the clinical presentation is characterized by circulatory collapse with hypotension, tachycardia, and low cardiac output and other clinical features of shock that may develop abruptly or within a few hours after the occurrence of a new systolic murmur.⁴³ The murmur is best heard over the left lower sternal border and may be associated with a palpable thrill. Right-sided and left-sided S₃ gallops with accentuated pulmonary component of S₂ are often present along with findings of tricuspid regurgitation. Pulmonary edema is less abrupt and fulminant than that seen with papillary muscle rupture.

The chest x-ray shows a combination of pulmonary edema and increased pulmonary flow. The ECG shows evidence of MI with or without evidence for ischemia.

Diagnosis

Echocardiography and Doppler echocardiography are mandatory in all patients with suspected ventricular septal rupture. Two-dimensional echocardiography reveals the septal defect in most cases, and shows regional wall motion abnormalities and changes in right and left ventricular function. Doppler echocardiography increases the diagnostic yield by showing transseptal flow (Fig. 19-3).^{43,47} Color flow imaging during echocardiography is very sensitive for diagnosing and characterizing ventricular septal rupture.^{28,43,47} Agitated saline is also used to identify the defect, and it may show negative contrast in the right ventricle. Doppler echocardiography is also performed to estimate the magnitude of left-to-right shunt and right ventricular and pulmonary artery systolic pressures.

Right heart catheterization with the use of balloon flotation catheters is not required for the diagnosis of ventricular septal rupture. If it is undertaken, however, it shows a step-up in oxygen saturation in the right ventricle and pulmonary artery compared with right atrial saturation (Fig. 19-4). The ratio of pulmonary to systemic flow can be calculated, and the hemodynamics can be determined.

Management

Urgent surgical repair of the ventricular septal rupture is a class I indication by the American College of Cardiology/American Heart Association guideline committee.⁶⁴ In the SHOCK

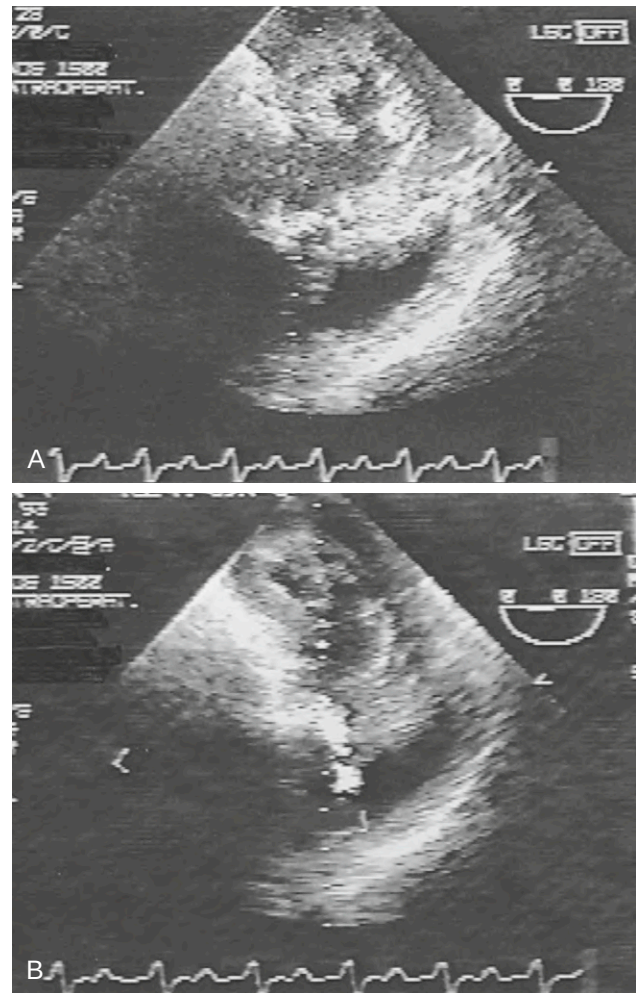


Figure 19-3. **A**, Two-dimensional transesophageal echocardiogram (transgastric basal short-axis plane) of a postinfarction ventricular septal rupture. The left ventricle is displayed above and the right ventricle below. Complex disruption of the interventricular septum is apparent in the midportion of the septum. **B**, Systolic frame color Doppler image of the same patient. There is a mosaic jet through the area of disruption of the interventricular septum, representing transseptal flow. Also seen is the eccentric contraction of the left ventricle, with dilation and dyskinesis of the infarct area involving the septum.

trial registry,⁵⁷ surgical repair of ventricular septal rupture was undertaken in 31 of 55 patients with cardiogenic shock, and 21 of these 31 patients also had concomitant coronary artery bypass graft surgery. Three of these patients also had aneurysmectomy. The overall mortality in the surgical group was 81%. Only 1 of 24 patients not undergoing surgery survived (almost 100% mortality). In the GUSTO-I trial, patients with cardiogenic shock were excluded; mortality for surgical versus medical treatment was 47% versus 94%.³² The results of these studies suggest that surgical repair should be considered if not absolutely contraindicated.

In a few patients, catheter-based percutaneous closure of the ventricular septal rupture has been performed with success.⁶⁵ This technique is promising and may be used for stabilization of patients who cannot undergo surgery urgently.

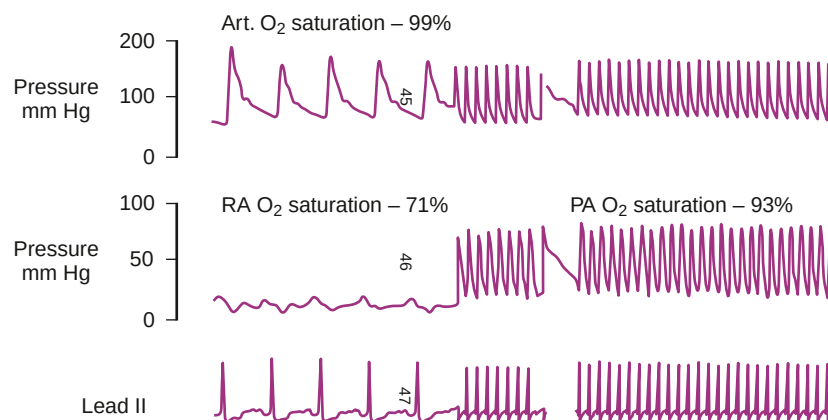


Figure 19-4. Ventricular septal defect. Oxygen saturation step-up between the right atrium (RA) and pulmonary artery (PA).

Survivors of surgery usually have improved functional class and a favorable late mortality rate.^{66,67} A 10-year survival rate of 50% has been observed after surgical repair.⁶⁸

Medical therapy is required to stabilize patients before surgery. The goal of medical therapy is to reduce the magnitude of the left-to-right shunt, improve cardiac output and systemic perfusion, and decrease pulmonary congestion. The magnitude of the left-to-right shunt in ventricular septal defect is determined by the resistance at the defect and the relative resistances in the pulmonary and systemic vascular beds. When the size of the defect is large, as in patients with post-MI ventricular septal rupture, the magnitude of the left-to-right shunt is principally determined by the ratio of pulmonary to systemic resistance.

Vasodilators such as sodium nitroprusside may increase the magnitude of left-to-right shunt owing to vasodilation of the pulmonary artery. Vasodilators with less vasodilatory effects on the pulmonary vascular bed but significant systemic vasodilatory effect, such as hydralazine or phentolamine, may be more effective in reducing the magnitude of left-to-right shunt. The most effective nonsurgical treatment to decrease the magnitude of left-to-right shunt is an intra-aortic balloon pump, which selectively reduces left ventricular ejection impedance. Inotropic agents and vasopressors are ineffective, although they are used frequently to maintain blood pressure. Diuretics are required to decrease pulmonary congestion. The therapeutic approach for the management of ventricular septal rupture is outlined in Table 19-3.

Dynamic Left Ventricular Outflow Tract Obstruction Complicating Acute Myocardial Infarction

Left ventricular outflow tract obstruction is a rare mechanical complication of acute MI.⁶⁹ It should be considered in the differential diagnosis of a new systolic murmur in a patient with acute MI.⁷⁰ Some patients with this syndrome develop hypotension and other features of cardiogenic shock. The mechanism of the outflow obstruction in these patients is very similar to that in patients with hypertrophic obstructive cardiomyopathy. A marked systolic anterior motion of the mitral valve obstructs the left ventricular outflow tract, reduces forward stroke volume and cardiac output, and causes hypotension and reflex

Table 19-3. Suggested Therapeutic Approach for Patients with Postinfarction Ventricular Septal Rupture

Corrective surgery as soon as feasible if not contraindicated
Intra-aortic balloon pump to decrease magnitude of left-to-right shunt
Vasopressors and inotropic agents
Arteriolar dilators
Diuretics
Survivors—angiotensin-inhibiting agents, β -adrenergic antagonists, aldosterone antagonists, lipid-lowering agents, antiplatelet agents

tachycardia. This dynamic obstruction of the left ventricular outflow tract also is the cause of the systolic murmur, which has the same characteristics of hypertrophic obstructive cardiomyopathy. This complication often occurs in patients with apical MI with hypercontraction of the basal septum.

Diagnosis

Echocardiography and Doppler echocardiography are the investigations of choice. Echocardiography shows systolic anterior motion of the mitral valve and the degree of outflow tract obstruction. The echocardiographic findings are similar to findings in patients with hypertrophic obstructive cardiomyopathy.

Management

The treatment is medical and is to reduce the outflow obstruction. Volume expansion, rather than diuretics, and β -adrenergic antagonists, rather than inotropic agents, are indicated.^{70,71} Vasopressors may be required to maintain blood pressure and to reduce outflow obstruction.^{71,72} There is no indication for intra-aortic balloon pump or surgical therapy in these patients even with cardiogenic shock.

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Ventricular and Supraventricular Arrhythmias in Acute Myocardial Infarction

Judith A. Mackall, Mark D. Carlson

CHAPTER 20

Supraventricular Arrhythmias Ventricular Arrhythmias

Prevention of Sudden Cardiac Death Conclusion

CARDIAC RHYTHM abnormalities occur in 72% to 95% of patients with acute myocardial infarction (MI) (Table 20-1).¹⁻³ Because arrhythmias are more likely to occur early, and frequently occur before hospitalization, some cardiologists have suggested that the true incidence of arrhythmias associated with acute MI may be 100%.⁴ Arrhythmias associated with acute MI may occur because of re-entry, abnormal conduction or automaticity, and triggered activity. Several factors, including myocardial ischemia, infarct size, impaired hemodynamics, electrolyte abnormalities, and abnormalities of autonomic nervous system control, may influence these mechanisms and aggravate or cause arrhythmias.^{2,5,6}

Arrhythmias may result in cardiac arrest, syncope, angina, heart failure, palpitation, or no symptoms at all. Whether of supraventricular or ventricular origin, arrhythmias associated with acute MI require treatment when they impair hemodynamics, aggravate myocardial ischemia, or predispose to life-threatening arrhythmias. Timely recognition and therapy for arrhythmias decreases morbidity and mortality associated with MI. This chapter reviews the mechanisms, diagnosis, and therapy for supraventricular and ventricular arrhythmias that occur in acute MI. Conduction disturbances in the setting of acute MI are discussed in Chapter 22.

Supraventricular Arrhythmias

Sinus Tachycardia

Sinus tachycardia is present in approximately 30% of patients with acute MI (see Table 20-1).⁷ This arrhythmia usually represents an increase in sympathetic activity and is more commonly seen in patients with anterior wall MI. Sinus tachycardia that persists beyond the initial 4 hours suggests that other causes of tachycardia may be present. Sinus tachycardia may be an early manifestation of heart failure, and in this setting is a poor prognostic sign. An underlying cause of the tachycardia should be determined (e.g., fever, pericarditis, pain, heart failure, anemia) and treated in an attempt to decrease myocardial oxygen demand. Specific therapy to slow the heart rate in the setting of anxiety and increased sympathetic activity includes administration of a β blocker (Table 20-2).

Atrial Arrhythmias

Atrial arrhythmias occur in 20% to 54% of patients with acute MI.⁵⁻¹¹ Several studies have shown that patients with inferior MI are more likely to develop atrial arrhythmias early in their hospital course, but that patients with anterior MI tend to manifest atrial arrhythmias 12 hours to 4 days after MI.^{12,13} Several factors have been implicated in the pathogenesis of atrial arrhythmias,

Table 20-1. Incidence of Arrhythmias in Acute Myocardial Infarction

Arrhythmia	Incidence (%)
Sinus bradycardia	10-55
First-degree AV block	4-15
Second-degree AV block	
Mobitz type I	4-10
Multilevel AV block	2
Mobitz type II	Rare
Third-degree or complete AV block	
Inferior infarction	12-17
Anterior infarction	5
Asystole	1-10
Sinus tachycardia	30
Premature atrial contractions	54
Supraventricular tachycardia	<5
Atrial fibrillation	9-20
Atrial flutter	1-2
Premature ventricular contractions	90-100
Accelerated idioventricular rhythm	8-20
Ventricular tachycardia	10-40
Ventricular fibrillation	4-18

AV, atrioventricular.

Table 20-2. Antiarrhythmic Agents for Acute Myocardial Infarction*

Class	Drug	Indications	Dosage	Elimination Half-Life	Adverse Effects
IA	Procainamide	AVRT, VT	Intravenous—15 mg/kg at 20 mg/min (load), then 1-6 mg/min (maintenance); oral—50 mg/kg/day in 4 divided doses	2.5-4.7 hr	Hematologic—marrow suppression, lupus-like illness; proarrhythmia; hypotension (with intravenous infusion)
IB	Lidocaine	VT, PVCs, in setting of ischemia	Intravenous—1 mg/kg bolus, then 1-4 mg/min (maintenance)	1.5-2 hr	CNS—drowsiness, agitation, disorientation, tremulousness
II	Esmolol	Short-term rate control of AF, AFL, treatment of AVNRT, AVRT, MAT	Intravenous—500 µg/kg over 1 min (load), then 50 µg/kg/min (maintenance)	2 min	Hypotension; CNS—dizziness, somnolence, headache; bronchospasm at higher doses
	Metoprolol	Rate control of AF, AF; treatment of AVNRT, MAT	Oral—25-100 mg q6h; intravenous—5 mg every 5-15 min up to 15 mg	3-4 hr	As above
	Atenolol	As above	Oral—25-200 mg qd [†]	6-7 hr	As above
	Propranolol	As above	Intravenous—0.5-3 mg, repeat in 2-5 min, then q4h; oral—10-30 mg q6-8h	2 hr (initial dose); 3, 4-6 hr	As above; bronchospasm owing to β ₂ -antagonist activity
III	Amiodarone	VT, VF	Oral—800-1600 mg/day for 1-3 wk (load), 200-400 mg qd (maintenance); intravenous—150 mg/min over 10 min, then 1 mg/min for 8 hr, then reduce to 0.5 mg/min (maintenance)	9-11 days	Conduction disturbances—sinus bradycardia, heart block; abnormalities of thyroid function, liver function; pulmonary toxicity; hypotension more likely to occur with intravenous administration
IV	Diltiazem	Rate control of AF, AFL; treatment of AVNRT, MAT	Intravenous—0.25 mg/kg over 2 min; if no response in 15 min, 0.35 mg/kg over 2 min, then 5-15 mg/hr (maintenance); oral—30-125 mg tid, 120-300 mg CD qd	3.5-10 hr	Hypotension; potentiation of sinus node dysfunction
	Verapamil	As above	Intravenous—5-10 mg, may repeat in 15-30 min with 10 mg; oral—80-120 mg q6-8h or 120-240 mg SR q12-24h	2 hr (intravenous); 4.5-12 hr (oral)	Cardiac effects—congestive heart failure owing to negative inotropic effect, hypotension; gastrointestinal effects—constipation
Other	Digoxin	Rate control of AF, AFL; treatment of AVNRT	Intravenous/oral—0.5 mg (initial), 0.25 mg q4-8h to total of 1 mg (load); 0.125-0.375 mg qd (maintenance) [†]	30 min (intravenous), 34-44 hr (oral)	Toxic side effects—nausea, accelerated functional rhythm, high-grade AV block
	Adenosine	Termination of AVNRT, AVRT, occasionally MAT, and exercise-mediated VT	Intravenous—6 mg rapid bolus, may repeat with 12 mg in 1 min, and then 18 mg	9.5 sec	Dyspnea, chest pain, flushing, sinus tachycardia
	Magnesium	Torsades de pointes	Intravenous—1-2 g (load); 1-7.5 mg/min (maintenance) [†]	—	Hypotension

*The dosages and indications listed are based on current practice standards and therefore are subject to change in the future.

[†]The dosage should be adjusted in the presence of renal insufficiency.

AF, atrial fibrillation; AFL, atrial flutter; AT, atrial tachycardia; AV, atrioventricular; AVNRT atrioventricular nodal re-entry tachycardia; AVRT, atrioventricular re-entry tachycardia; CNS, central nervous system; MAT, multifocal atrial tachycardia; PVCs, premature ventricular contractions; VF, ventricular tachycardia; VT, ventricular tachycardia.

including atrial distention owing to underlying left or right ventricular dysfunction, pericarditis, and atrial infarction.

In a small series of patients with documented inferior MI, Rechavia and colleagues¹² found that there was a significantly higher occurrence of premature atrial contractions and atrial fibrillation in patients with right ventricular dysfunction. It is unclear whether right atrial distention resulting from right ventricular dysfunction caused the premature atrial contractions and atrial fibrillation, or if there was associated right atrial infarction. Studies showing a higher incidence of atrial fibrillation in patients with atrial infarction and in patients with some extent of atrial infarction in right ventricular MI¹⁴ suggest that both factors may play a role.¹⁵ Atrial arrhythmias that occur late in the hospital course have been attributed to underlying left ventricular dysfunction. In these patients, treatment of congestive heart failure may prevent recurrence.^{12,16}

Premature Atrial Contractions

Premature atrial contractions are the most common atrial arrhythmias, occurring in 54% of patients with acute MI (see Table 20-1).^{8,11} These beats may result from heightened sympathetic activity owing to pain or anxiety, or they may result from atrial distention, pericarditis, atrial infarction, or atrial ischemia. Although premature atrial contractions may precipitate other atrial arrhythmias, they are usually asymptomatic and are of no hemodynamic significance. Because premature atrial contractions are not associated with increased mortality, medical therapy to suppress these beats is not indicated.¹¹

Paroxysmal Supraventricular Tachycardia

Paroxysmal atrial tachycardia and other re-entrant supraventricular tachycardias occur in less than 5% of patients (see Table 20-1).^{12,17} Most of these arrhythmias are transient, but the rapid ventricular rate is frequently associated with symptoms. Management of tachycardia should be directed at control of the ventricular rate. This control can be achieved promptly with intravenous administration of a β blocker or calcium channel blocker (see Table 20-2). These drugs or adenosine may terminate the tachycardia if the atrioventricular node is an integral part of the re-entry circuit. Adenosine may also terminate atrial tachycardia; however, it has the potential to result in atrial fibrillation.¹⁸ Caution should be used when administering any agent if symptoms of hypotension and congestive heart failure are present.

In patients with hemodynamic instability, synchronized DC cardioversion is the safest and the most expedient method to terminate the tachycardia. Treatment of underlying heart failure may prevent recurrences.¹²

Atrial Fibrillation and Flutter

Atrial fibrillation occurs in 9% to 20% of patients and is associated frequently with atrial infarction (see Table 20-1).^{8,12,14,19-21} Atrial flutter is uncommon in MI, occurring in only 1% to 2% of patients.^{11,12} There is no association between the occurrence of atrial or supraventricular arrhythmias and outcome.²²⁻²⁴ Earlier studies showed an increased mortality associated with supraventricular arrhythmias in the setting of acute MI.^{15,24,25} A later study designed to determine the prognostic value of supraventricular arrhythmias in the late phase of MI (13 to 19 days) found, however, that left ventricular ejection fraction was the only independent predictor of mortality.¹¹ Serrano and coworkers¹²

determined the short-term and long-term outcomes of patients with supraventricular arrhythmias after MI. Although patients with arrhythmias during the late phase of MI (12 hours to 4 days) had significantly higher mortality rates at 1 month and 47 months, the presence of supraventricular arrhythmias was not an independent predictor of mortality. The increased mortality was not related to left ventricular function, but correlated with the presence of more extensive coronary artery disease.

Patients with atrial fibrillation frequently develop symptoms owing to the loss of atrial contribution to cardiac output associated with these arrhythmias, and owing to the rapid ventricular rates. In the presence of hemodynamic instability, restoration of normal sinus rhythm can be achieved promptly with synchronized DC cardioversion. For a hemodynamically stable patient with atrial fibrillation, the ventricular rate can be controlled with intravenous administration of a β blocker or a calcium channel blocker. Conversion to normal sinus rhythm often occurs spontaneously, but DC cardioversion may be necessary. No data are available on the use of ibutilide, a class III antiarrhythmic drug, in the post-MI period.

Patients with atrial flutter typically have 2:1 conduction, and control of the ventricular rate may be difficult. DC cardioversion or pace termination via temporary atrial transvenous or epicardial wires can be performed to terminate the tachycardia. Recurrent episodes of atrial fibrillation or flutter may be prevented with administration of amiodarone. Patients with recurrent atrial fibrillation who meet current guidelines for anticoagulation should be started on warfarin therapy.²⁶ Clopidogrel (Plavix) and aspirin do not prevent or reduce the risk of thromboembolism from atrial fibrillation.²⁷

Ventricular Arrhythmias

Ventricular tachyarrhythmias are potentially the most dangerous arrhythmias associated with acute MI, occurring in 10% to 50% of patients.^{1,28} These arrhythmias are observed more frequently soon after the onset of MI. In experimental animals, factors that determine the occurrence of ventricular tachyarrhythmias include the size of the ischemic area,²⁹ stress,³⁰ preconditioning,^{31,32} increased heart rate,^{33,34} and autonomic nervous system influences.^{35,36} The occurrence of more than one factor may increase the risk for arrhythmias. Ischemia and sympathetic stimulation are more arrhythmogenic than either factor alone.^{37,38}

Considerable evidence indicates that factors that influence arrhythmias in experimental models also influence the occurrence of ventricular tachyarrhythmias in humans. The incidence of ventricular tachyarrhythmias is related to infarct size and the presence of heart failure.^{36,39,40} Patients with an absolute increase in sympathoadrenal stimulation or decreased vagal efferent activity are at increased risk for sudden cardiac death and ventricular tachyarrhythmias.⁴¹⁻⁴⁴ Acute MI causes several changes in the autonomic nervous system that may facilitate initiation of ventricular arrhythmias. Activation of cardiac mechanoreceptors and cardiopulmonary and carotid baroreceptors results in increased circulating catecholamine levels and increased efferent sympathetic activity. Ischemic damage to cardiac adrenergic neurons results in the release of catecholamines. Transmural MI denervates viable myocardium distal to the infarct site.⁴⁵ Ischemic and denervated viable myocardium are hypersensitive to circulating catecholamines.⁴⁴ Sympathetic

stimulation also enhances automaticity in Purkinje fibers. These effects result in inhomogeneities of repolarization and enhance automaticity.

Electrolyte abnormalities, including hypokalemia and hypomagnesemia, are potentially correctable causes of ventricular arrhythmias associated with MI. Hypokalemia is an independent risk factor for ventricular arrhythmias early in MI.⁴⁶ Hypomagnesemia often accompanies hypokalemia and may result in polymorphic ventricular tachycardia (VT). The use of thrombolytic drugs to treat patients with acute MI has renewed interest in arrhythmias associated with coronary reperfusion. These arrhythmias were observed in 1881, when ventricular fibrillation (VF) was seen within seconds after restoration of coronary flow.⁴⁷ Coronary reperfusion may cause isolated premature ventricular contractions, accelerated idioventricular rhythm (AIVR), VT, or VF, presumably by enhancing automaticity of ischemic myocardium.⁴⁸ The severity of the arrhythmia induced by reperfusion is related to the duration of myocardial ischemia.

The presence of certain antiarrhythmic drugs at the time of MI may facilitate initiation or maintenance of ventricular arrhythmias. This proarrhythmic effect is thought to occur because of changes in the electrophysiologic action of the drugs in the setting of myocardial ischemia. In a canine model, flecainide facilitated induction and sustenance of VT, particularly at shorter cycle lengths.⁴⁹ The effect seemed to result from slowing of conduction in ischemic myocardium. Although less well studied, ischemia-induced proarrhythmia may occur with type IA or type III antiarrhythmic drugs.

Ventricular Premature Beats

Ventricular premature beats occur in almost all patients with acute MI⁵⁰ (see Table 20-1), and are rarely a cause of myocardial ischemia or systemic hypotension. Previously, these beats were thought to be important because of their potential to trigger VT or VF. Early studies suggested that the frequency and timing of ventricular premature beats was associated with the risk for life-threatening arrhythmias.⁵¹ Early ventricular premature beats (R on T phenomenon) were thought to initiate VF because they depolarized the ventricle during the vulnerable period when ventricular refractoriness was inhomogeneous, and re-entry was more likely to occur. Data from animal models and human studies indicate, however, that frequent and complex ectopy is neither a sensitive nor a specific predictor for development of sustained ventricular tachyarrhythmias early after MI.^{28,52-57}

The incidence of frequent ventricular premature beats and the R on T phenomenon is similar between patients who develop VF and patients who do not develop VF.²⁸ Studies of animals and humans have shown that most VT episodes⁵⁸ and 41% to 45% of VF episodes^{52,53} are initiated by late-coupled ventricular premature beats (after the T wave), suggesting that early beats are not required to initiate the arrhythmia. VF occurs in the absence of preceding ventricular ectopy in 40% to 83% of patients.^{52,53}

Ventricular Tachycardia

VT is defined as three or more consecutive ventricular ectopic beats at a rate greater than 100 beats/min. This arrhythmia may be classified as nonsustained (i.e., terminating spontaneously within 30 seconds) or sustained (i.e., requiring intervention or of >30 seconds' duration), as monomorphic or polymorphic (depending on the QRS complex morphology), and as early or late (i.e., occurring <24 hours or >48 hours after the onset of MI).

Table 20-3. Electrocardiographic Criteria That Support the Diagnosis of Ventricular Tachycardia

QRS complex width >0.14 sec
Left-axis deviation
Configuration of QRS complex
In RBBB: monophasic or biphasic complex in lead V ₁
In LBBB: Q wave in lead V ₂
Concordance in the precordial leads
AV dissociation*
Absence of an RS complex in the precordial leads*
If RS complex is present, an RS interval >0.10 sec*

AV, atrioventricular; LBBB left bundle branch block; RBBB, right bundle branch block.

*100% specific for ventricular tachycardia.

From Mackall JA, Buchler CM, Thames MD. The pharmacological approach to the management of the cardiac surgical patient. In Baue AE, (ed): Glenn's Thoracic and Cardiovascular Surgery. East Norwalk, CT, Appleton & Lange, 1998, p 1613.

VT appears on the surface 12-lead electrocardiogram (ECG) as a wide QRS complex tachycardia. Although several criteria and algorithms have been proposed to differentiate this arrhythmia from supraventricular tachycardia with aberrant ventricular conduction, the diagnosis sometimes remains uncertain (Table 20-3).^{59,60} When a definitive diagnosis is impossible, a wide QRS complex tachycardia associated with acute MI should be considered ventricular in origin until proved otherwise.

Additional measures may differentiate VT from supraventricular tachycardia with aberrant ventricular conduction. Vagal stimulation (with a Valsalva maneuver or carotid sinus massage) or administration of adenosine may transiently slow or terminate supraventricular tachycardia, but does not affect most VT.⁶¹ Intracardiac electrograms may be recorded from temporary pacemaker wires to show the relationship of atrial and ventricular activation. The presence of atrioventricular dissociation during a wide QRS complex tachycardia is almost always diagnostic of VT. Administration of lidocaine may be diagnostic and therapeutic because lidocaine has no activity in atrial tissue.

VT occurs in 10% to 40% of patients with acute MI (see Table 20-1).^{1,28} The timing of VT has important implications regarding the mechanism and prognosis of the arrhythmia. VT that occurs late in the course of MI (after 48 hours) is more common in patients with transmural infarction and left ventricular dysfunction.^{1,62} When it occurs late, is sustained, and results in hypotension, VT is likely to recur and is associated with increased in-hospital and long-term mortality rates.⁶²⁻⁶⁴ VT that occurs early is more likely to have reversible causes (e.g., ischemia, reperfusion, autonomic nervous system influences) and is less likely to recur.

Sustained monomorphic VT most often results from re-entry, usually within a single circuit.⁶⁵ Patients with this arrhythmia, even when it occurs less than 48 hours after the onset of acute MI, should undergo a thorough evaluation to determine the risk for recurrence and the need for therapy. VT resulting from reperfusion often occurs within the first hour after administration of thrombolytic therapy, is often associated with a slower rate, and is less likely to recur.

Polymorphic VT differs from monomorphic VT in that the QRS complex morphology varies from beat to beat. This arrhythmia has been reported to occur in 0.7% to 2% of patients hospitalized for acute MI.^{66,67} Although the mechanism for the arrhythmia is unknown, polymorphic VT is not thought to be associated with a stable re-entrant circuit. When the arrhythmia occurs early (within 6.5 hours of the onset of symptoms), it is often associated with coronary reperfusion and a good prognosis.⁶⁷ When it occurs late (2 to 13 days after acute MI), the arrhythmia is associated with recurrent ischemia and a poor prognosis.⁶⁶

Torsades de pointes is a specific type of polymorphic VT, and is usually caused by a proarrhythmic effect of antiarrhythmic drugs. Drugs that prolong ventricular refractoriness (class IA antiarrhythmic drugs and the class III drugs sotalolol, dofetilide, and ibutilide) may prolong the Q–T interval and predispose the patient to this arrhythmia. In this situation, torsades de pointes is thought to result from triggered activity induced by early afterdepolarizations. Early afterdepolarization amplitude depends on heart rate; increased heart rate decreases the amplitude and the probability that the afterdepolarization will reach a threshold potential and “trigger” torsades de pointes. Faster heart rates shorten repolarization and suppress early afterdepolarizations.

Ventricular Fibrillation

VF is caused by multiple electrical activation wave fronts that depolarize the ventricles in a disorganized and chaotic fashion. By definition, this arrhythmia does not terminate spontaneously and is lethal unless converted quickly. The absence of organized ventricular electrical activation results in the absence of QRS complexes and an irregular undulating baseline on the surface ECG.

VF is the leading cause of death early during the course of MI, occurring in 4% to 18% of hospitalized patients (see Table 20-1).^{50,52} The arrhythmia is more likely to occur in patients with a large MI. The incidence of VF is lower among patients with non-Q wave than with Q wave MI. VF occurs with similar frequency, however, in patients with anterior and inferior Q wave MI.²⁸ Although VF that occurs early (≤ 48 hours) is associated with an increased in-hospital mortality, it does not increase long-term mortality.⁶⁸

When associated with acute MI, VF has been classified as primary or secondary. Primary VF occurs early and unexpectedly in the absence of heart failure or other apparent causes. Approximately 50% of these episodes occur within 1 hour, 60% to 80% occur within 4 hours, and 80% occur within 12 hours of the onset of symptoms.^{1,54,66} Secondary VF occurs as a result of severe heart failure or cardiogenic shock and can occur at any time during the course of MI.¹

Whether VF occurs early or late, myocardial ischemia should be considered as the underlying cause, particularly when the arrhythmia recurs frequently. VF may also result from coronary reperfusion. When caused by reperfusion, the occurrence of VF, rather than AIVR or VT, is related to the duration of myocardial ischemia.⁷⁰ In animal models, the incidence of VF increases when ischemia is prolonged from 5 to 20 minutes, but decreases when reperfusion is delayed beyond 30 minutes.

Sudden cardiac death and VF may be the presenting symptoms in patients with acute MI. In these patients, the cause of the arrhythmia or the MI is often unclear. In many patients, VF may be the cause, rather than the result, of MI. In others,

particularly patients with previous MI, VF may have occurred as a result of sustained VT. These are important considerations when evaluating the risk for recurrent ventricular tachyarrhythmias and the need for electrophysiologic testing and long-term antiarrhythmic therapy.

Accelerated Idioventricular Rhythm

AIVR is defined by its rate (60 to 100 beats/min) and is sometimes referred to as slow VT. AIVR occurs in 8% to 20% of patients, usually during the first 2 days after MI. The arrhythmia occurs with equal frequency in patients with anterior or inferior MI and may be provoked by spontaneous or induced coronary reperfusion.^{71,72} AIVR may begin with a premature ventricular beat or may occur as a result of sinus slowing or an increase in the ventricular “escape” rate. Similarly, AIVR may terminate abruptly because the sinus rate increases or because the ventricular escape rate slows. Variation in the rate of this arrhythmia is common.

In humans, AIVR is the most common arrhythmia following coronary reperfusion.^{63,74} Most cases of AIVR probably occur as a result of enhanced automaticity in Purkinje fibers on the endocardial surface near or within the infarction zone.⁷⁴ In vitro studies, using a model of coronary artery reperfusion, have shown AIVRs that were caused by triggered activity associated with delayed afterdepolarization.⁷⁵ Rapid VT with a rate twice that of the AIVR has been observed in some patients, suggesting re-entry with episodic exit block as another possible mechanism for the arrhythmia.^{76,77}

Therapy

Ventricular tachyarrhythmias should be treated when they adversely affect hemodynamics, cause myocardial ischemia, or predispose to life-threatening arrhythmias. Depending on the indication, the goal of therapy may be to convert the arrhythmia, to suppress the arrhythmia, or to prevent a life-threatening arrhythmia.

Reversible causes may be responsible for ventricular arrhythmias and should be addressed in every patient. Acid-base status, systemic arterial oxygen saturation, and serum electrolytes should be evaluated, and abnormalities should be corrected at the time of admission to the cardiac intensive care unit. Proarrhythmia caused by an antiarrhythmic drug may necessitate discontinuation of the drug and additional specific therapy, depending on the offending agent. These and other reversible causes of arrhythmia should be reconsidered when arrhythmias occur.

Recurrent or incessant ventricular tachyarrhythmias are often caused by and may be the only manifestation of myocardial ischemia. In such cases, recognition of myocardial ischemia as the cause of ventricular arrhythmias is particularly important because antiarrhythmic drugs are often ineffective and are more likely to cause proarrhythmia in this setting. Appropriate diagnostic measures and vigorous anti-ischemic therapy should be instituted. Intra-aortic balloon pump counterpulsation or percutaneous coronary intervention, or both, may be required to suppress incessant ventricular arrhythmias.

Cardioversion and Defibrillation

Ventricular Tachycardia

Rapid conversion of VT is imperative because of its adverse hemodynamic effects and its potential to deteriorate into VF. When possible, a 12-lead ECG should be obtained before

conversion of VT. This is important to ensure proper diagnosis and therapy for the arrhythmia.

VT that is associated with hypotension should be treated promptly with a synchronized DC shock. The shock should be administered with paddles placed on conductive pads near the apex and base of the heart. VT sometimes can be terminated with 20 J of external DC energy. When the arrhythmia is associated with hemodynamic collapse and loss of consciousness, the initial shock energy should be 200 J or more with a monophasic shock and 120 to 200 J with a biphasic shock.

Hemodynamically stable VT sometimes can be cardioverted by antiarrhythmic drugs. Chemical cardioversion is usually more time-consuming and is less reliable than electrical cardioversion. Administration of antiarrhythmic drugs is not associated with pain, however, and does not require sedation. Chemical cardioversion is appropriate when VT is hemodynamically well tolerated and is not associated with myocardial ischemia. An external cardioverter-defibrillator should be available if hypotension occurs⁷⁸.

Amiodarone, procainamide, and sotalol can be used to convert VT. Sotalol given orally is often impractical because steady state would not be reached for several days. Intravenous amiodarone, 150 mg over 10 minutes followed by a maintenance infusion (see Table 20-2) and repeating the bolus as necessary, is very effective at converting VT. Intravenous amiodarone may result in hypotension; in case of hypotension, either lidocaine bolus or DC cardioversion should be available.

Lidocaine is safe to use with amiodarone because it has no adverse hemodynamic effects and does not cause Q-T prolongation. Lidocaine has a rapid onset of action and may terminate or suppress ventricular arrhythmias within minutes. The drug can be administered intravenously as a bolus of 50 to 100 mg, followed by a continuous infusion of 1 to 4 mg/min. Because of a significant first-pass effect in the liver, a second bolus can be administered 20 to 30 minutes after the initial dose to maintain a therapeutic serum drug level.

Procainamide is also effective for cardioversion, but requires a longer period to infuse and is sometimes associated with hypotension because of negative inotropic effects and vasodilation. The drug prolongs refractoriness in atrial and ventricular myocardium. Procainamide can be administered intravenously and can be titrated to achieve the therapeutic effect. Procainamide undergoes acetylation in the liver to *N*-acetyl procainamide; both forms have antiarrhythmic activity. Serum concentrations of procainamide can be determined by a bioassay and correlate with efficacy and with toxicity. Because it prolongs ventricular refractoriness, procainamide prolongs the Q-T interval on the surface ECG. It can be used in patients unable to tolerate amiodarone. Because of its Q-T prolonging effect, it should be used cautiously if amiodarone has been given. Q-T prolongation to greater than 550 ms is associated with an increased risk for torsades de pointes, and may be an indication to decrease the dose or discontinue the drug.

Pacing, similar to antiarrhythmic drug therapy, may terminate VT. Pace termination of VT is effective in certain patients with relatively slow and hemodynamically well-tolerated VT. Patients with temporary endocardial ventricular pacing wires and patients with temporary epicardial electrode wires placed during cardiac surgery are ideal candidates for this therapy. Synchronized pacing is performed at a cycle length that is 90% or less than that of the VT. In some cases, VT can be terminated by

a single synchronized beat. More often, 5 to 15 seconds of pacing is required to terminate the arrhythmia. Burst pacing can be repeated if the initial attempt is unsuccessful. Pacing should not be performed at a rate greater than 300 beats/min because of the risk for accelerating the arrhythmia or inducing VF. Pacing should not be performed unless a defibrillator is available. Ramp pacing (i.e., a beat-to-beat decrease in the pacing cycle length) is often successful when bursts at a single cycle length do not terminate VT.

Procainamide may facilitate pace termination of VT by slowing the rate of the arrhythmia and by favorably influencing the re-entrant circuit. In some cases, antiarrhythmic drugs may adversely influence the re-entrant circuit, however, decreasing the effectiveness of pacing despite slowing the rate of the tachycardia.

β blockers are useful in preventing recurrent VT in the setting of ischemia. Calcium channel blockers should not be used in patients with wide QRS tachycardia because they can promote hemodynamic collapse and death in the setting of VT.

Ventricular Fibrillation

The treatment of VF is direct electrical countershock. Because time to definitive therapy for this arrhythmia is directly related to outcome, electrical countershock should be delivered as quickly as possible and should not be delayed by administration of a precordial thump or antiarrhythmic drugs.

Although cardioversion of VT may be accomplished with 20 J of DC electricity, defibrillation usually requires substantially greater energy. Generally, 360 J (monophasic) or 200 J (biphasic) should be delivered at each attempt. Cardiopulmonary resuscitation (CPR) should be initiated whenever electrical countershock cannot be delivered immediately. If defibrillation may be delayed more than 5 minutes, CPR should be performed for 1½ to 3 minutes before shock delivery.⁷⁹ In the setting of hypoxemia, myocardial ischemia, severe heart failure, and acid-base disturbances, VF is likely to recur.

The advanced cardiac life support protocol should be followed giving continuous chest compressions with interruptions of less than 10 seconds for shock delivery. Drugs should be infused during chest compressions. Intravenous amiodarone, 300 mg, should be administered, and a 150-mg dose may be repeated in 3 to 5 minutes if necessary. Lidocaine can be given if amiodarone is unavailable or ineffective.

Special Cases

In patients with frequent or incessant ventricular tachyarrhythmias, adhesive conductive patches should be placed on the back and the precordium and attached to an external cardioverter-defibrillator. This configuration allows for more rapid treatment of the arrhythmia.

Patients with implantable cardioverter-defibrillators represent a small but growing population of individuals admitted to cardiac intensive care units with MI. These devices may be programmed to recognize and treat ventricular tachyarrhythmias automatically either by a countershock or by antitachycardia pacing. This is an appropriate strategy for hospitalized patients with episodes of VT that can be reliably terminated by antitachycardia pacing. Patients with frequent ventricular tachyarrhythmias who are susceptible to multiple shocks are better treated by deactivating the device temporarily and suppressing the arrhythmias with antiarrhythmic drugs.

Suppression

Ventricular Premature Beats

When coronary care units were first developed, therapy focused on suppression of so-called warning arrhythmias (i.e., frequent and complex ventricular ectopy, including R on T ventricular premature beats). Many investigators advocated antiarrhythmic drug therapy for all patients early after MI when it became apparent that the warning arrhythmias were neither sensitive nor specific predictors for VF. Several studies have evaluated the routine administration of antiarrhythmic drugs (e.g., lidocaine, quinidine, procainamide, disopyramide) to all patients with acute MI.^{80,81} These studies have shown that antiarrhythmic drugs suppress ventricular ectopy, and in the case of lidocaine sometimes prevent VF.^{80,82,83} No study has shown, however, that routine administration of these drugs prolongs life.⁸⁴⁻⁸⁷

Fifty percent of patients experience side effects from lidocaine, including slurred speech, confusion, tremor, and seizures.⁸⁸ Compared with the limited number of patients who may benefit from therapy, routine administration of lidocaine to all patients is not justified. When promptly terminated in the cardiac intensive care unit, primary VF has little effect on the prognosis of patients with acute MI.⁸⁹

Because suppression of ventricular premature beats is not associated with improved survival, these beats should be suppressed only when they aggravate myocardial ischemia or adversely affect hemodynamics. Intravenous administration of antiarrhythmic drugs allows for rapid onset of drug activity and titration of the dose to optimize efficacy and minimize side effects. Lidocaine remains the first-line therapy, primarily because of its favorable benefit-to-risk ratio.

Ventricular Tachycardia

Nonsustained VT, similar to ventricular premature beats, should be treated when the arrhythmia aggravates myocardial ischemia and adversely affects hemodynamics. Treatment of asymptomatic nonsustained VT remains controversial because there is little evidence that this strategy improves mortality or morbidity. Sustained VT should be suppressed when it occurs late or frequently. When it occurs early and as a single episode, however, sustained VT is not likely to recur, and suppression with antiarrhythmic drug may not be indicated.

Amiodarone can be administered orally or intravenously to suppress recurrent, sustained VT. An oral loading dose of 1200 to 1600 mg/day is usually administered until a 6- to 10-g load is complete.⁹⁰⁻⁹² If recurrent hemodynamically unstable VT and VF occur, intravenous amiodarone has been shown to reduce the frequency of events during the first 24 hours of infusion.⁹³ The recommended starting dose for intravenous amiodarone is approximately 150 mg over 10 minutes followed by 0.5 to 1 mg/min the first 24 hours of therapy, but may vary according to individual necessity and tolerance. Mean daily doses greater than 2100 mg are associated with an increased risk of hypotension. A maintenance infusion of 0.5 mg/min may be administered for 3 weeks. Experience with infusions longer than 3 weeks is limited.

Lidocaine and procainamide, administered intravenously, are also effective antiarrhythmic drugs for suppression of sustained monomorphic VT. These drugs may be administered alone or in combination with one another. Neither lidocaine nor procainamide transitions easily to oral maintenance therapy. Atrial or ventricular pacing may suppress sustained monomorphic VT

in some patients with monomorphic VT, particularly when the arrhythmia is aggravated by bradycardia.

Torsades de Pointes

Suppression of this arrhythmia depends on increasing the heart rate and eliminating the offending agent. Increased heart rate (usually 90 to 110 beats/min) shortens ventricular repolarization time and suppresses the arrhythmia. Intravenous atropine or isoproterenol (or both) can be administered. Insertion of a temporary atrial or ventricular pacing wire may be necessary. Magnesium, which may shorten ventricular repolarization, has been administered intravenously to treat this arrhythmia.

Ventricular Fibrillation

Intravenous amiodarone is the first-line therapy for recurrent VF. Lidocaine should be administered when amiodarone is ineffective or associated with side effects. Repeat boluses of amiodarone may be given if the arrhythmia proves to be recurrent. Pacing may be an effective adjuvant therapy when the arrhythmia is associated with bradycardia or pauses. If arrhythmia associated with bradycardia or pauses occurs in the setting of ongoing ischemia, severe left ventricular dysfunction, or cardiogenic shock, intra-aortic balloon pump or the need for emergent cardiac catheterization, or both, should be considered.

Prevention of Sudden Cardiac Death

Coronary Care Unit

The institution of coronary care units resulted in a significant decline in mortality for acute MI during the last 3 decades (from 30% to <15%), principally because primary arrhythmias were virtually eliminated as a cause of death.²⁸ These units provide continuous ECG monitoring and access to therapy and trained personnel, allowing immediate detection and treatment of arrhythmias.⁹⁴ Coronary care units provide an environment for delivery of therapies that may decrease the long-term risk for arrhythmias by decreasing myocardial ischemia or limiting infarct size (i.e., early percutaneous intervention, thrombolytic drugs, intravenous nitroglycerin, heparin, and intra-aortic balloon counterpulsation).

The duration of continuous ECG monitoring depends on the risk for a life-threatening arrhythmia. Patients with a large and complicated MI (i.e., heart failure, recurrent myocardial ischemia, or hemodynamically significant arrhythmias) are at the highest risk for early sudden cardiac death and should be monitored continuously for 5 to 7 days. Patients with small uncomplicated MI may not require continuous monitoring for more than 3 days after the event.

Thrombolytic Therapy

Administration of thrombolytic agents has complex effects on the incidence of ventricular arrhythmias after MI. Studies of the influence of thrombolytic therapy on ventricular arrhythmias in acute MI have yielded conflicting results.⁹⁵⁻¹⁰¹ Thrombolytic therapy is associated with coronary reperfusion, which has been shown to cause AIVR, VT, and VF, depending on the duration of ischemia. The incidence of ventricular arrhythmias early after MI may be similar, if not increased, for patients who receive thrombolytic therapy or have patent infarct-occluded arteries. Arrhythmias that occur late are more likely the result of recurrent myocardial ischemia or re-entry related to scar. Early

percutaneous intervention or administration of thrombolytic agents, by decreasing ischemia and infarct size, may decrease the incidence of these arrhythmias.

β -Adrenoceptor Antagonists

Several studies have shown that early administration of intravenous β -adrenoceptor antagonists reduces the incidence of VF during evolving MI,^{102,103} and may reduce the long-term risk for sudden death in these patients.^{104,105} β -adrenoceptor antagonist may prevent ventricular arrhythmias by limiting infarct size, by decreasing heart rate, or by direct antiarrhythmic effects.^{34,40}

Implantable Cardioverter-Defibrillators

Several studies have shown that prophylactic implantation of implantable cardioverter-defibrillators improves survival in patients who are status post MI and have depressed left ventricular systolic function (left ventricular ejection fraction <0.30 to 0.35).¹⁰⁶⁻¹⁰⁹ These studies have generally enrolled patients at least 40 days after MI. The prophylactic use of implantable cardioverter-defibrillators for patients with depressed ejection fraction has not shown a mortality benefit in the acute post-MI period (≤ 40 days)¹¹⁰ or in the acute postrevascularization period (≤ 3 months).¹¹¹

Conclusion

Cardiac arrhythmias are observed frequently in the setting of acute MI because of electrophysiologic alterations that result from myocardial ischemia and necrosis. These arrhythmias, whether supraventricular or ventricular, may precipitate hemodynamic collapse or death. Efforts should be made to identify and correct factors such as electrolyte abnormalities, hypoxia, heart failure, and ischemia, which increase the risk for developing an arrhythmia. The mortality associated with acute MI has been greatly reduced because of the early recognition and prompt treatment of arrhythmias.

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Conduction Disturbances in Acute Myocardial Infarction

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CHAPTER 21

Anatomy Incidence Specific Conduction Abnormalities

Mortality Management

THE IMPACT of infarction on myocardial conduction tissue can be dramatic and pivotal in altering the consequences of an acute myocardial infarction (MI), and could affect the basic management of a patient presenting with occlusion of a coronary artery. Immediate recognition of emergence of conduction disturbances between the sinoatrial node and the right atrium and between the atrium and the ventricles in the acute phase of MI is of prognostic and therapeutic significance. The nature of conduction disturbance not only can give clues to the location of the infarct, but also aid in prioritizing the management of MI, including, but not limited to, potential need for temporary pacemaker support. Autonomic imbalance and ischemia or necrosis seem to induce these disturbances.

Anatomy

The sinus node, sinoatrial conduction system, atrioventricular (AV) node, bundle of His, right bundle, left bundle dividing into anterior and posterior fascicle, and myocardial Purkinje fibers form components of the conduction system. The sinoatrial node is supplied by the atrial branch of the proximal right coronary artery (RCA) in 55% of cases and the proximal left circumflex artery in 45% of cases.¹ The RCA perfuses the AV node and the proximal portion of the His bundle in most cases (left circumflex artery in 10% of cases). The septal branches of the left anterior descending artery supply the distal part of the His bundle, the right bundle branch, and the anterior fascicle of the left bundle branch. The posterior fascicle of the left bundle is supplied by septal branches from both the left anterior descending artery and the RCA.

Incidence

The overall incidence of conduction disturbances, including bundle branch and fascicular block, during acute MI is approximately 10% to 20%. The incidence of complete heart block may be lower with thrombolytic therapy compared with the prethrombolytic era.

Based on multicenter retrospective reviews in the prethrombolytic era, left bundle branch block (LBBB) was the most common block, occurring in 38% of patients who had preexisting or new intraventricular conduction delay.^{2,3} This statement is controversial, however, because in 1975, Lie and coworkers⁴ found that complete LBBB secondary to acute MI is rare. Right bundle

branch block (RBBB) with left anterior fascicular block (LAFB) was also common, occurring in 34% of patients who developed an intraventricular conduction delay. RBBB, RBBB with left posterior fascicular block (LPFB), and “alternating bundle branch block” occurred in 11%, 10%, and 6% of patients with new intraventricular conduction delay; isolated LAFB and LPFB were uncommon. Twenty-two percent of patients developed high-grade AV block or complete heart block.

In the thrombolytic era, the available data suggest that the incidence of complete heart block in acute MI may be lower with thrombolytic therapy at 4% to 5%,⁵ and the combined end point of complete heart block or second-degree AV block is 7% to 10%. The onset of complete heart block occurred within the first 2 days after MI in 81% of patients who developed complete heart block.

Specific Conduction Abnormalities

Sinoatrial Node

Sinus Bradycardia

Sinus bradycardia is the most common arrhythmia in inferior MI and three times more common in inferoposterior than anterior MI.⁶ Possible mechanisms include increased vagal tone (common), neurologic reflexes, and infarction or ischemia of the sinus node or the surrounding atrium.

Sinoatrial Block and Sinus Arrest

Grade 2 or complete sinoatrial block suggests a proximal occlusion of the RCA or left circumflex artery and is often accompanied by atrial infarction. This is a sign of a large MI, and coronary reperfusion therapy should be initiated rapidly.⁷

Atrioventricular Node

Prolongation of the P–R interval (so-called first-degree block) can arise in the AV node, the bundle of His, or the bundle branches. AV nodal delay is usually seen in cases of occlusion of the RCA proximal to the right ventricular branch.⁸ This conduction abnormality may also manifest as second-degree AV block or complete AV block.

Below the Atrioventricular Node

The various forms of conduction abnormalities known to occur below the AV node include Mobitz II second-degree AV block, 2:1 AV block, and RBBB with or without left anterior or posterior

fascicular block. RBBB is much more common than complete LBBB owing to dual supply of various fascicles of the left bundle and a wide area of distribution within the myocardium. The clinical prognosis is worse when RBBB plus LAFB is the result of the MI, predicting early death owing to pump failure.⁹

Complete heart block with inferior MI generally results from an intranodal lesion. It is associated with a narrow QRS complex, and develops in a progressive fashion from first-degree to second-degree to third-degree block (Fig. 21-1). It often results in asymptomatic bradycardia (40 to 60 beats/min) and is usually transient, resolving within 5 to 7 days. LBBB occurs as a form of aberration during bradycardia—either sinus bradycardia or AV block with a junctional escape mechanism. Complete heart block with anterior MI generally occurs abruptly in the first 24 hours. It can develop without warning or may be preceded by the development of RBBB with either LAFB or LPFB (bifascicular

or trifascicular block) (Fig. 21-2).³ The escape rhythm is wide and unstable, and the event is associated with a high mortality (approximately 80%) from arrhythmias and pump failure. Heart block in this setting is thought to result from extensive necrosis that involves the bundle branches traveling within the septum.

Inferior Wall Myocardial Infarction versus Anterior Wall Myocardial Infarction

High (second or third) degree AV block associated with inferior wall MI is located above the His bundle in 90% of patients.¹⁰ For this reason, complete heart block often results in only a modest and usually transient bradycardia with junctional or escape rhythm rates greater than 40 beats/min (Fig. 21-3). It is common, however, for the junctional pacemaker that controls the ventricles to accelerate greater than 60 beats/min. The QRS is narrow in this setting and is associated with a low mortality.



Figure 21-1. Mobitz type I atrioventricular block and inferior myocardial infarction. (Courtesy of Ary Goldberger, MD.)

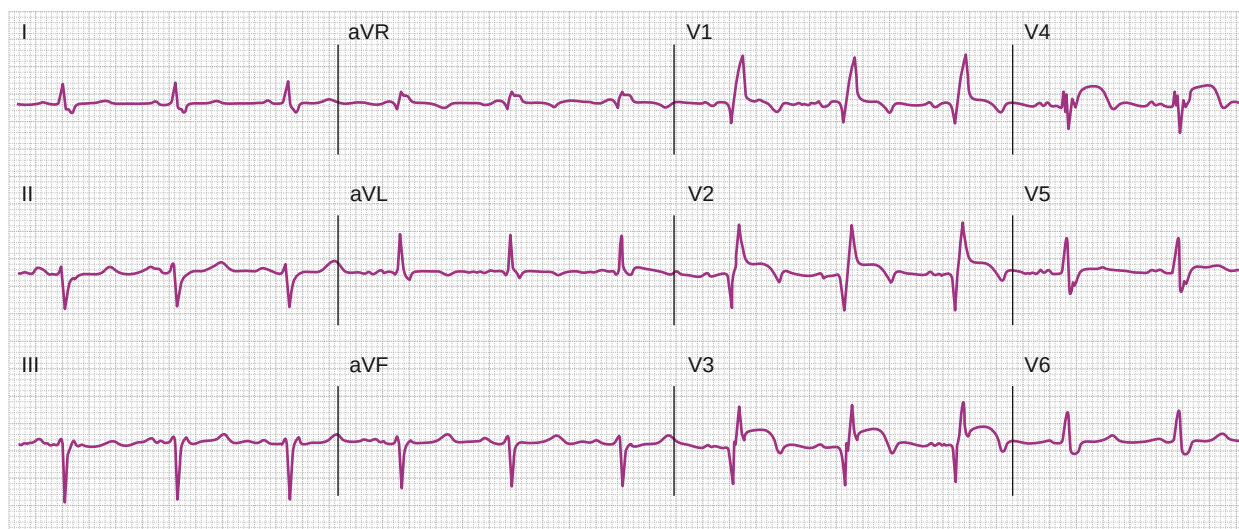


Figure 21-2. The 12-lead ECG from a patient with a history of an anteroseptal myocardial infarction (Q waves seen in lead V₁-V₃) shows a typical right bundle branch block and left anterior fascicular block.

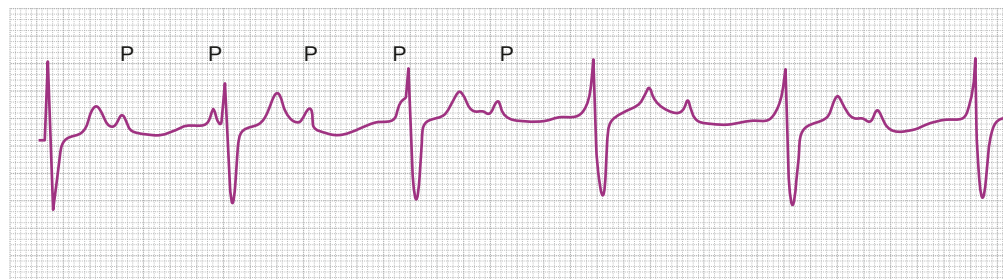


Figure 21-3. Sinus rhythm with high-grade atrioventricular block. (Courtesy of Ary Goldberger, MD.)

High-degree AV block associated with anterior MI is more often located below the AV node (more frequently within the His bundle or proximal bundle branches).¹¹ It is usually symptomatic and has been associated with a mortality rate approaching 80% largely because of greater loss of functioning myocardium. The current mortality may be less because of improvements in the management of congestive heart failure and cardiogenic shock, but the risk remains substantial.

Mortality

High-degree AV block is associated with increased mortality in patients with inferior or anterior MI. Most of the increased risk is within the first 30 days.¹² High-degree AV block in patients with an anterior wall MI is associated with a greater increase in in-hospital and 30-day mortality than seen with an inferior wall MI, probably because of more extensive myocardial involvement and a higher incidence of hemodynamic complications.¹³

The presence of a fascicular or bundle branch block during an acute MI is associated with an increased in-hospital and long-term mortality. The 30-day mortality is significantly increased only in patients with a RBBB at baseline and an anterior MI and in patients with a new LBBB or new RBBB with an anterior MI. Piotrowicz and colleagues¹⁴ noted that patients with LBBB, RBBB, or indeterminate ventricular conduction disturbances show longer repolarization duration than patients without these conduction disturbances. Q-T and J-T intervals (as measured by Rautaharju Q-T and J-T (R-R) formulas) significantly and independently predict mortality in patients after MI with conduction disturbances. The authors have noted no evidence of LBBB among 200 consecutive cases of left anterior descending artery percutaneous coronary intervention in the setting of anterior acute MI (personal observation).

Management

Patients with two or more of the following new findings are at 25% to 36% risk of progression to complete heart block: P-R prolongation, second-degree AV block, left anterior or posterior fascicular block, LBBB, and RBBB.¹⁵

Acute Management

In case of ventricular asystole, which is quite rare, prompt resuscitative measures, including chest compressions, atropine, vasopressin, epinephrine, and temporary pacing, should be administered.

Temporary Pacemaker

The purpose of temporary transvenous pacemaker insertion is to maintain circulatory integrity by providing for standby pacing should sudden complete heart block ensue, to increase heart rate during periods of symptomatic bradycardia, and occasionally to control sustained supraventricular or ventricular tachycardia.¹⁶ Whether ventricular or AV pacing should be used depends on hemodynamic considerations. Performance of AV temporary pacing requires additional experience and can be considerably more difficult from a technical standpoint. Because temporary pacemakers are manufactured by many different vendors, physicians credentialed to insert temporary pacemakers should be familiar with the insertion equipment, leads, and external generator used in their own hospitals.

Class I indications for temporary pacing during ST segment elevation myocardial infarction (STEMI) include any complete heart block or alternating LBBB/RBBB, Mobitz II second-degree AV block during anterior STEMI in the presence of fascicular block plus RBBB or new bundle branch block. Class IIa indications during STEMI include any second-degree AV block with new bundle branch block or fascicular block plus RBBB. STEMI with old bundle branch block in the presence of Mobitz II second-degree AV block, and anterior STEMI with fascicular block and Mobitz II second-degree AV block are also class IIa indications. Contraindications to the procedure are few and include the patient's inability to cooperate and lack of therapeutic benefit because of advanced disease. Several approaches to the central venous system have been used, including internal jugular vein, subclavian vein, and femoral vein. Most complications are infrequent and usually minor. Life-threatening complications are rare. Minor complications, such as nonsustained arrhythmias and local phlebitis, are common.

Atrioventricular Nodal Blockers

β blockers are not contraindicated in the presence of prolonged AV conduction (the dose should be decreased), but are a relative contraindication in patients with second-degree block or higher degrees of block. Drugs are usually "related" to the conduction disturbances, but are not the "cause."

Permanent Pacemaker

Indications for permanent pacing are described in detail in Table 21-1.¹⁷

Standard Indications

There is general agreement that placement of a permanent pacemaker after an acute MI is appropriate in the following circumstances:

1. Third-degree AV block within or below the His-Purkinje system
2. Persistent second-degree AV block in the His-Purkinje system, particularly with evidence of extensive conduction disease in the His-Purkinje system (e.g., RBBB with LAFB, RBBB with LPFB, or alternating RBBB and LBBB)
3. Transient advanced infranodal AV block in association with a bundle branch block that is believed to be due to the infarction
4. Symptomatic and persistent second-degree or third-degree AV block at any level

Indications for permanent pacing after STEMI in patients experiencing AV block are related in large measure to the presence of intraventricular conduction defects. In contrast to some other indications for permanent pacing, the criteria for patients with STEMI and AV block do not depend on the presence of symptoms. The requirement for temporary pacing in STEMI does not by itself constitute an indication for permanent pacing. There is general agreement that pacemakers are unnecessary in the following situations:

1. Transient AV block, with or without associated conduction defects (e.g., LAFB). These transient phenomena usually occur in the setting of inferior MI. In the less common situation when transient AV block occurs after an anterior MI, pacemaker implantation may be considered.
2. Acquired LAFB in the absence of AV block
3. P-R prolongation in the presence of bundle branch block that is not believed to be caused by MI

Table 21-1. Use of Permanent Pacemakers**Permanent Pacing for Bradycardia or Conduction Blocks Associated with ST Segment Elevation Myocardial Infarction (STEMI)****Class I**

1. Permanent ventricular pacing is indicated for persistent second-degree AV block in the His-Purkinje system with bilateral bundle branch block or third-degree AV block within or below the His-Purkinje system after STEMI (*level of evidence: B*)
2. Permanent ventricular pacing is indicated for transient advanced second-degree or third-degree infranodal AV block and associated bundle branch block. If the site of block is uncertain, an electrophysiologic study may be necessary (*level of evidence: B*)
3. Permanent ventricular pacing is indicated for persistent and symptomatic second-degree or third-degree AV block (*level of evidence: C*)

Class IIb

1. Permanent ventricular pacing may be considered for persistent second-degree or third-degree AV block at the AV node level (*level of evidence: B*)

Class III

1. Permanent ventricular pacing is not recommended for transient AV block in the absence of intraventricular conduction defects (*level of evidence: B*)
2. Permanent ventricular pacing is not recommended for transient AV block in the presence of isolated left anterior fascicular block (*level of evidence: B*)
3. Permanent ventricular pacing is not recommended for acquired left anterior fascicular block in the absence of AV block (*level of evidence: B*)
4. Permanent ventricular pacing is not recommended for persistent first-degree AV block in the presence of bundle branch block that is old or of indeterminate age (*level of evidence: B*)

Sinus Node Dysfunction after STEMI**Class I**

1. Symptomatic sinus bradycardia, sinus pauses >3 sec, or sinus bradycardia with heart rate <40 beats/min and associated hypotension or signs of systemic hemodynamic compromise should be treated with an intravenous bolus of atropine, 0.6 to 1 mg. If bradycardia is persistent and maximal (2 mg) doses of atropine have been used, transcutaneous or transvenous (preferably atrial) temporary pacing should be instituted (*level of evidence: C*)

AV, atrioventricular.

From Antman EM, Anbe DT, Armstrong PW, et al: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: executive summary: a report of the ACC/AHA Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines on the Management of Patients with Acute Myocardial Infarction). *J Am Coll Cardiol* 2004;44:671-719.

When a permanent pacemaker is being considered for a post-STEMI patient, the clinician should address two additional questions regarding the patient: Is there an indication for biventricular pacing, and is there an indication for implantable cardioverter-defibrillator use? There are well-established criteria for patients who need implantable cardioverter-defibrillators and biventricular pacemakers more than several months after MI, but the criteria are not established for patients who need pacemakers within 1 month after MI. In patients with MI who presented with bifascicular block with or without complete heart block, if they survived cardiogenic shock, there was a 30% incidence of aneurysm formation associated with increased frequency of ventricular tachycardia and ventricular fibrillation several weeks after MI.

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Complications of Percutaneous Interventional Procedures

Diagnosis and Treatment of Complications of Coronary and Valvular Interventions

Htut K. Win, Neal S. Kleiman

CHAPTER 22

Characteristics Predictive of High Risk for Adverse Outcome
Classification of Complications
Perforation
Management
Abrupt Vessel Closure
Preventive Measures
Diagnosis and Management of Abrupt Closure

Air Embolism
Distal Embolization
Stent Infection
Contrast-induced Nephropathy and Other Contrast Toxicities
Metformin
Complications of Valvular Interventions

SINCE THE advent of percutaneous transluminal coronary angioplasty (PTCA), percutaneous coronary intervention (PCI) procedures have become part of daily clinical practice.¹⁻⁵ Currently, more than 1 million procedures are performed in the United States annually. The immediate success rates of PCI are greater than 95 percent.⁶⁻⁸ Adverse outcomes after PCI have declined significantly over the last 15 to 20 years because of improvement in adjunctive pharmacotherapies and device technologies. The incidence of emergent coronary artery bypass graft (CABG) surgery after PCI decreased significantly to 0.14% in 2000.⁹ In the American College of Cardiology (ACC)–National Cardiovascular Data Registry PCI database, of more than 550,000 PCIs performed between January 2001 and December 2004 for reasons other than ST segment elevation myocardial infarction (MI), the observed frequencies of death, MI, unplanned CABG surgery, and major cardiovascular complications were 0.76%, 1.1%, 0.6%, and 2.4%.¹⁰ Observations from Europe were similar with an overall unadjusted mortality of less than 2% in all patients and mortality of 0.36% to 3.25% in nonemergency compared with emergency cases.¹¹

Not every adverse clinical outcome during and after PCI is a complication of the procedure itself. Adverse events are often the result of the natural history of the disease that initially led to the intervention. This notion is exemplified by the extremely low rate of adverse events in young patients with normal left ventricular function compared with greater than 50% mortality in older patients presenting with cardiogenic shock.^{12,13}

Any attempt at unraveling the risks associated with PCI must deal with the complex interplay of factors relating to the procedure itself and the natural history of the underlying disease occurring in a patient with unique baseline clinical characteristics. Numerous risk models that quantified the risk of major complications have been developed and validated to identify a group of patients with underlying higher risks associated with PCI by using readily available clinical and angiographic characteristics from large databases.¹⁴⁻²⁰ Various scoring systems have been derived from these models allowing clinicians and patients to appreciate the risks in a semiquantitative manner before the procedure (Table 22-1).

Table 22-1. Odds Ratios* for Significant Independent Risk Factors† for Short-term Mortality Related to Percutaneous Coronary Intervention

	New York State	Northern New England	Michigan BMC2	ACC-NCDR	ACC-NCDR Update		COAP
No. patients	50,046	15,331	10,796	100,253	No acute MI (142,817)	Acute MI (30,926)	19,358
Incidence (%)	0.58	1.1	1.6	1.4	NA	NA	1.6
Years	2003	1994-1996	1997-1999	1998-2000	1998-2001	1998-2001	1999-2000
Clinical							
Acute MI <12-24 hr	8.6	5.5	2.8	1.3			+‡
Age	+	+	+	+	+	+	+
Cardiac arrest			3.7				
CHF	3.2	8.6					1.6
COPD				1.3	1.7	1.5	1.8
Diabetes				1.4	1.25		
Female	1.5		1.8				1.4
Pre-IABP		26.2		1.7		1.9	
Peripheral vascular disease	2.6	3.3	1.6				1.6
Prior CABG surgery	1.4						
Priority (salvage, emergent urgent, elective)		+		+	+	+	+
Renal insufficiency	3.1	6.4	5.5	3.0	3.5	2.0	3.5
Shock	22.1	32.2	11.5	8.5	9.8	8.8	9.8
Anatomic							
ACC lesion score, C		2.9					
Ejection fraction	+	+		+	+	+	+
LMT lesion				2.0	1.5	2.1	
No. diseased vessels	+		+				
Proximal LAD lesion				2.0	1.3	1.3	+
SCAI lesion score				+	+	+	
Thrombus				+			
Procedural							
Lytic use				1.4		1.25	
Nonstent use				1.6	1.6	1.4	
C-statistic	0.905	0.88	0.90	0.89	0.85	0.87	0.87

*Values are odds ratios for binary variable unless otherwise noted.

†Specific definitions of risk factors may vary from series to series.

‡+ indicates relationship exists for continuous or ordinal variables (61-66).

ACC-NCDR, American College of Cardiology National Cardiovascular Data Registry; BMC2, Blue Cross Blue Shield of Michigan Cardiovascular Consortium; CABG, coronary artery bypass graft; CHF, congestive heart failure; COAP, clinical outcome assessment program; COPD, chronic obstructive pulmonary disease; IABP, intra-aortic balloon pump; LAD, left anterior descending; LMT, left main trunk; MI, myocardial infarction; NA, Not available; SCAI, Society for Cardiovascular Angiography and Interventions.

From King SB 3rd, Aversano T, Ballard WL, et al; American College of Cardiology Foundation; American Heart Association; American College of Physicians Task Force on Clinical Competence and Training (Writing Committee to Update the 1998 Clinical Competence Statement on Recommendations for the Assessment and Maintenance of Proficiency in Coronary Interventional Procedures): ACCF/AHA/SCAI 2007 update of the clinical competence statement on cardiac interventional procedures: a report of the American College of Cardiology Foundation/American Heart Association/American College of Physicians Task Force on Clinical Competence and Training (Writing Committee to Update the 1998 Clinical Competence Statement on Recommendations for the Assessment and Maintenance of Proficiency in Coronary Interventional Procedures). J Am Coll Cardiol 2007;50:82-108.

Table 22-2. Characteristics of American College of Cardiology/American Heart Association Lesions Type A, B, and C Classifications

Type A Lesions (High Success, >85%, Low Risk)	Type B Lesions (Moderate Success, 60% to 85%, Moderate Risk)	Type C Lesions (Low Success, <60%, High Risk)
Discrete (<10 mm length)	Tubular (10-20 mm length)	Diffuse (>2 cm length)
Concentric	Eccentric	Excessive tortuosity of proximal segment
Readily accessible	Moderate tortuosity of proximal segment	Extremely angulated segments, >90 degrees
Nonangulated segment <45 degrees	Moderately angulated segment, 45-90 degrees	Inability to protect major side branches
Smooth contour	Irregular contour	Degenerated vein grafts with friable lesions
Little or no calcification	Moderate to heavy calcification	
Less than totally occlusive	Total occlusion <3 mo old	Total occlusion >3 mo old
Non-ostial in location	Ostial in location	
No major branch involvement	Bifurcation lesions requiring double guidewires	
Absence of thrombus	Some thrombus present	

Note: Success rate reported is expected rate of success at the time the system was first presented.

From Ellis SG, Vandormael MG, Cowley MJ, et al: Coronary morphologic and clinical determinants of procedural outcome with angioplasty for multivessel coronary disease: implications for patient selection. Multivessel Angioplasty Prognosis Study Group. *Circulation* 1990;82:1193-1202.

These risk models confer good relative predictive accuracy and discriminatory ability in identifying increased risk associated with PCI for the overall cohort from which they were derived. Most of these models, however, lack serial external calibration over time to ensure their continued reliability in contemporary cohorts. The incidence of abrupt vessel closure, one of the dreaded complications in the early years of PTCA, now occurs in less than 1% of all procedures. During this period, potentially fatal complications, such as stent thrombosis, which occurs at a later point in time than abrupt vessel closure, came into existence as a result of novel technologies.²¹⁻²³

Characteristics Predictive of High Risk for Adverse Outcome

Patient Clinical Characteristics

Clinical factors associated with an increased risk of an adverse outcome after PCI as identified by all the models include advanced age, poor left ventricular systolic function, acute coronary syndrome, chronic renal insufficiency, heart failure, peripheral vascular disease, and multivessel coronary disease. Of these characteristics, cardiogenic shock is the most powerful predictor of death after PCI. Patients with impaired renal function, particularly in the presence of diabetes, are at increased risk for contrast-induced nephropathy.²⁴

Target Lesion Anatomic Factors

Particular lesion morphologic characteristics that are predictive of immediate outcome with PCI in these models include multivessel disease, presence of thrombus, left main coronary artery disease, left main intervention, and ACC/American Heart Association (AHA) type C lesion classification (Table 22-2).²⁵ More recent experience indicates that improved devices and techniques have higher success rates in more complex lesions.^{26,27} As a result, lesion morphology is now less predictive of complications than it had been in the past. The Mayo Clinic risk score offers significantly better prediction for cardiovascular

complications than the ACC/AHA classification. Lesion classification by ACC/AHA classification is a better predictor for angiographic success, however.²⁸ In the current PCI device era, the simpler Society for Cardiovascular Angiography and Interventions (SCAI) classification using the seven variables listed earlier predicted interventional success and complications better than the ACC/AHA classification (Table 22-3).²⁹

Classification of Complications

The American College of Cardiology Foundation/AHA/SCAI clinical competence statement proposed classification of complications related to PCI into eight basic outcome categories and three mechanistic categories.³⁰

Outcome Categories

For the purpose of assessing clinical competence, complications may be divided into eight basic outcome categories, as follows:

1. Death—related to the procedure, regardless of mechanism
2. Stroke
3. MI—related to the procedure, regardless of mechanism
4. Ischemia requiring emergency CABG surgery—resulting from either procedure failure or a procedure complication
5. Vascular access site complications
6. Contrast agent nephropathy
7. Excessive bleeding, requiring treatment
8. Other (e.g., coronary perforation and tamponade)

Mechanistic Categories

The three mechanistic categories of complications are as follows:

1. *Coronary arterial injury* can occur when devices are introduced into coronary vessels or result from embolization of thrombotic or atherosclerotic material. Examples include coronary dissection, thrombosis, perforation, and embolization.
2. *Other vascular events* are caused by injury to a peripheral vessel by catheter insertion, manipulation, or removal, or

Table 22-3. Society for Cardiovascular Angiography and Interventions (SCAI) Lesion Classification Types I through IV

SCAI I (Highest Success Expected, Lowest Risk)	SCAI II	SCAI III	SCAI IV
Does not meet criteria for ACC/AHA type C lesion	Diffuse (>2 cm length)	Does not meet criteria for ACC/AHA type C lesion	Diffuse (>2 cm length)
Patent	Excessive tortuosity of proximal segment	Occluded	Excessive tortuosity of proximal segment
	Extremely angulated segments, >90 degrees		Extremely angulated segments, >90 degrees
	Inability to protect major side branches		Inability to protect major side branches
	Degenerated vein grafts with friable lesions		Degenerated vein grafts with friable lesions and occluded or
	Patent		Occluded >3 mo

ACC/AHA, American College of Cardiology/American Heart Association.

From Krone RJ, Shaw RE, Klein LW, et al; ACC-National Cardiovascular Data Registry: Evaluation of the American College of Cardiology/American Heart Association and the Society for Coronary Angiography and Interventions lesion classification system in the current “stent era” of coronary interventions (from the ACC-National Cardiovascular Data Registry). *Am J Cardiol* 2003;92:389-394.

by embolization of thrombotic or atherosclerotic material. Examples include false aneurysm, retroperitoneal hemorrhage, arteriovenous fistula, and stroke.

3. *Systemic nonvascular adverse events* are caused by the procedure, but are not due to vascular injury. They include all the systemic hazards of cardiovascular radiographic angiography procedures. Examples include contrast agent–induced nephropathy, anaphylactoid reactions, and acute pulmonary vascular congestion.

Recognizing and stratifying risk factors associated with adverse clinical outcomes in an individual patient, and prompt diagnosis and treatment of these complications are integral to daily practice of interventional cardiology. This chapter discusses mechanistic complications of PCI, which together constitute one facet of potential adverse outcomes of PCI (Table 22-4).

Perforation

Perforation or vessel rupture associated with PCI is a rare complication that can potentially result in a catastrophic clinical outcome, particularly if it is not recognized. The incidence has remained constant over the years, ranging from 0.2% to 0.8%.³¹⁻³⁵ Coronary artery perforation accounts for 20% of emergent CABG surgery after PCI.³⁶ The clinical spectrum of perforation extends from small extraluminal extravasation of blood to frank rupture of the epicardial coronary vessels leading to cardiac tamponade and acute hemodynamic collapse. Device oversizing, wire trauma, and atherectomy have been the most frequent causes of perforations since the early days of angioplasty.³⁷⁻³⁹

Coronary perforations are traditionally classified according to the morphologic appearance and degree of extravasations present on the coronary angiogram. Ellis and associates³¹ proposed the following classification: type I, crater extending outside the lumen only in the absence of linear staining suggestive of a dissection; type II, pericardial or myocardial blush without a visible exit hole (≤ 1 mm); type III, frank streaming of contrast material

through an exit hole greater than 1 mm, and perforation into an anatomic cavity chamber such as the coronary sinus or the right ventricle (Table 22-5).

The mortality and morbidity of perforations vary according to the severity of the perforation. The rates of 19% mortality and 63% cardiac tamponade have been reported after type III perforations.³¹ Mortality of 60% has been associated with rapidly developing pericardial tamponade that occurs within the first 20 minutes.⁴⁰ In a more recent series, overall mortality from perforation ranged from 2.5% to 8%.^{34,41} Mortality after type III perforations seemed to remain high over the years (22% to 44%).^{42,43}

Cardiac tamponade after PCI may often be delayed and can occur outside the catheterization suite.⁴⁴ Not all cases of cardiac tamponade owing to hemopericardium are attributable to vessel perforations, however. Spontaneous bleeding into the pericardium after the use of anticoagulants even in the absence of PCI has been described, as has perforation of the right ventricle by percutaneous temporary pacemakers.^{45,46}

Perforations can occur as a result of guidewires, balloons, stents, or atherectomy devices (rotational and directional). One study reported that type 1 and 2 perforations are predominantly caused by hydrophilic or stiff guidewires and rarely require pericardial drainage or surgical intervention, whereas type 3 perforations are more often associated with stent and device use.⁴² The following factors have been associated with this complication in observational data from large consecutive series of patients.

Complex Coronary Anatomy

PCI of chronic total occlusions is arguably the most common angiographic characteristic associated with coronary perforation in contemporary practice. It has been reported that PCI of chronic total occlusions is responsible for 17% of all coronary perforations.⁴⁷ Complex coronary anatomy including calcifications, chronic total occlusion, tortuosity of the vessel, and ostial location is also associated with coronary perforations. Lesions

Table 22-4. Types of Percutaneous Coronary Intervention Complications

Acute Procedural Complications
Perforation/vessel rupture (coronary)
Wire
Balloon
Stent
Temporary pacemaker
Air or clot embolization
Access vessel
Bleeding
Femoral
Retroperitoneal
Thrombosis
Arterio-arterial embolization
Deep vein thrombosis
False aneurysm
Dislodgment of closure device
Infection
Arteriovenous fistula
Nerve injury
Device-related coronary events
Abrupt closure
Embolization
Side branch entrapment
No-reflow
Valvuloplasty related
Perforation of myocardium
Embolization
Valvular regurgitation
Pharmacologic complications
Contrast-induced nephropathy and other contrast toxicities
Pulmonary edema
Sedation-related
Chronic complications
Stent infection
Radiation lesions
Late stent thrombosis
Frequency
Etiology
Risk factors
Association with clopidogrel

located on bends and bifurcation are predisposed to perforation, especially after atherectomy procedures.⁴⁸ Traditionally, perforation of part of the venous bypass grafts or of the native vessel beyond the grafts is said to be less likely to be associated with cardiac tamponade secondary to mediastinal scar related to postoperative reaction.³² Occurrence of cardiac tamponade after perforation of a saphenous vein graft has been reported, however.⁴⁹⁻⁵¹

Table 22-5. Anticipated Clinical Outcomes Based on Type of Perforation

Ellis Type	Cardiac Tamponade (%)	MI (%)	CABG Surgery (%)	Death (%)
I	6-8	0-29	15-24	0-6
II	5-13	13-29	0-24	0-6
III	20-63	0-30	50-60	19-21

CABG, coronary artery bypass graft; MI, myocardial infarction.

From Klein LW: Coronary artery perforation during interventional procedures. Cathet Cardiovasc Interv 2006;68:713-717.

Devices

Hydrophilic guidewires and extra-stiff guidewires are most often associated with perforation.^{33,42} Witzke and colleagues³⁴ reported that of 39 cases of coronary perforation among 12,658 patients undergoing PCI during the period 1995-2003, 20 cases (51%) were due to guidewires. Oversizing of the balloon or stents in relation to the vessel diameter is also an important cause of perforation.⁴¹ Since they were first introduced, debulking devices, such as rotablation, directional coronary atherectomy, and laser atherectomy, are associated with a higher incidence of perforation compared with balloon angioplasty.^{31,34,52}

Glycoprotein IIb/IIIa Inhibitors

Even though there were concerns that glycoprotein (GP) IIb/IIIa inhibitors, which are potent antiplatelet drugs, would increase the clinically apparent incidence of perforation during PCI, no studies show an association of increased incidence of perforation or higher adverse events after perforation with these agents. Nonetheless, when perforation is diagnosed, GP IIb/IIIa inhibitors should be discontinued, and platelet transfusions should be implemented if there is evidence of hemodynamic compromise.

Management

Management of patients with coronary artery perforation depends on the extent of the perforation. When coronary perforation is recognized by angiography, treatment strategies are dictated by the extent of perforation and hemodynamic status of the patient. Treatment strategies consist of isolating the perforation and stopping the bleeding, and treating cardiac tamponade. Boluses of intravenous fluid or pressors or both should be started, especially when a decrease in blood pressure is observed, to provide higher venous filling pressure of the right heart chambers. Inotropic agents are not usually helpful because the left ventricle is already hyperdynamic.

Echocardiography to evaluate the extent and physiology of tamponade must be done without delay. Right heart catheterization may also be useful in this setting for continuous monitoring. Pericardiocentesis should be performed promptly for any hemodynamically significant effusion.

Cardiac tamponade may be immediate, and urgent pericardiocentesis may be necessary. Consequently, a pericardiocentesis tray should be made available as soon as a perforation is recognized. Tamponade may be delayed, however, and it is crucial that patients who were seemingly successfully managed

after coronary perforation be closely monitored after the procedure. Occasionally, follow-up angiography to confirm that the communication is sealed may be helpful. In patients with tamponade, serial echocardiography to exclude reaccumulation of pericardial fluid is prudent. In the catheterization laboratory, anticoagulation is discontinued, and prolonged low-pressure balloon inflations are performed in an effort to “seal” the perforation. In limited perforations, this approach was successful for most patients.⁵³ In contrast, larger perforations that often result in tamponade and ischemia frequently require emergency surgical intervention.

Clinical symptoms of perforation include severe chest pain, tachycardia, and hypotension if tamponade ensues. Vagal-mediated symptoms such as nausea and vomiting may occur because of acute increases in pericardial pressure. Persistence of ST segment elevation after balloon inflation is often observed. Occasionally, perforations that occur during balloon inflation are characterized by abrupt expansion of the balloon and rapid decrease in the inflation pressure. In type I perforations, hemodynamic compromise is uncommon. Deployment of a stent is useful over the perforation in vessels larger than 2 mm in diameter followed by close monitoring of patients with repeat echocardiography in a few hours. In smaller vessels, observation alone may be sufficient.^{35,54}

When cardiac tamponade occurs as a result of larger perforation, wire position must be retained, and balloon tamponade of the vessel proximal to or overlying the site of perforation should be carried out without delay. Prolonged inflation of the balloon (10 to 15 minutes) along with cessation of anticoagulation is occasionally sufficient to arrest the bleeding in moderate-sized perforations.

Covered Stents

When the above-described measures fail, placement of a polytetrafluoroethylene (Dacron)-covered stent usually offers a quick, effective solution even for large perforations. The GraftMaster (JoMed, Abbott Vascular, IL, USA) is one such stent. It is made of two stainless steel stents with a layer of polytetrafluoroethylene in between. Because of its larger profile, a 7F guide catheter is required. The available sizes range from 3 to 5 mm in diameter and 12 to 26 mm in length. Postdilation with a noncompliant balloon is essential to ensure the full deployment of the inner stent. Intravascular ultrasound may be useful in this setting to guide optimal stent apposition.

Although initial retrospective studies did not show a decreased incidence of adverse events with this approach,⁴³ multicenter retrospective series have subsequently reported a 97% procedure success rate in a selected population.⁵⁵ Long-term data are not yet available to assess postdischarge thrombosis, restenosis, and vessel reocclusion and endoleak owing to jailing of side branches. Long-term therapy with dual antiplatelet therapy consisting of aspirin and thienopyridines is empirically recommended.

Other Mechanical Measures

Distal vessel embolizations (as in some guidewire perforations) performed with thrombin injection, absorbable gelatin sponge (Gelfoam) particles, polyvinyl alcohol particles, or microcoils have also been described, especially for small vessels.⁵⁶⁻⁵⁹ The incremental advantage, if any, of these techniques remains unknown.

Emergency Coronary Artery Bypass Graft Surgery

Most perforations can be treated without cardiac surgery. The need for emergent CABG surgery and futility of continuing a nonsurgical approach must be promptly recognized, however. Timely referral for bail-out emergent CABG surgery should be made before protracted hemodynamic compromise renders the condition into an irreversible downward spiral, and not as a last-ditch rescue effort to save the various available percutaneous options that have been exhausted.

Abrupt Vessel Closure

Periprocedural vessel occlusion is an important source of morbidity and mortality after percutaneous revascularization. It occurs primarily as a result of acute coronary dissection, thrombosis, or, most often, a combination of both. About 2% to 11% of patients in the early angioplasty era, depending on definitions used and populations studied, have been reported to experience complications.^{60,61} From the 1985-1986 National Heart, Lung, and Blood Institute (NHLBI) Angioplasty Registry comprising 1801 patients, 20% of procedure-related deaths, 40% of MIs, and 25% of all emergency CABG operations occurred in the 6.8% of patients who sustained abrupt closure.⁶² Late adverse events are also increased in patients with successfully treated closure.⁶³ By 6 months, 45.9% of these patients had CABG surgery, 41% had MIs, and 6.6% had died. Following the routine use of intracoronary stents and aggressive periprocedural antiplatelet therapies, the incidence of abrupt closure has decreased in recent years to less than 1% for all PCIs. This low rate seems to have remained unchanged in the era of drug-eluting stents.⁶⁴

Mechanisms, Timing, and Risk Factors Associated with Threatened Acute Coronary Closure

Two important mechanisms of abrupt closure—acute thrombus formation and coronary dissection—often occur together. The underlying mechanism is probably multifactorial, involving a combination of vessel dissection, elastic recoil, local thrombosis, activation of proinflammatory cytokines, vasospasm, and formation of intramural hematomas. The relative contribution of each of these factors varies from patient to patient, and probably varies with the coronary revascularization technology being applied. Abrupt closure is often preceded by either dissection or thrombus formation before distal coronary flow ceases completely, and this condition is termed *threatened acute coronary closure*.

About 75% of abrupt vessel closures occur during the PCI, and most of the remainder occur within the first 24 hours after the procedure. In the early days of PTCA, the incidence of closure was 4.9% to 5.6% within the laboratory, decreasing to less than 2% after the patient leaves the laboratory.⁶⁵ Because most patients are discharged within 24 hours after PCI, ascertainment of late abrupt closure may be less reliable. A vulnerable period for abrupt closure is during and after sheath removal, when anticoagulation has been withdrawn, and vagal-mediated hypotension and hemorrhagic volume depletion may occur.^{66,67}

Numerous investigators have attempted to identify clinical, angiographic, and procedural factors that are associated with abrupt closure in the present era.⁶⁸⁻⁷⁰ Those studies identified many clinical, preangiographic and postangiographic findings and lesion characteristics predictive of abrupt closure. From these studies, the strongest predictor of abrupt closure was the

angiographic finding of preexisting presence of a thrombus.⁷¹ Unstable angina, acute coronary syndrome, and acute MI were also shown to be predictive of abrupt closure. Other clinical risk factors included female sex, diabetes mellitus, and high surgical risk. Angiographic features such as multivessel disease, multiple stenoses in the same vessel, long lesions, severe angulations (>45 degrees), and lesion at branch point were also identified as high risk. In addition, postintervention angiographic observations, such as presence of intimal dissection, residual thrombus, or postprocedure stenosis greater than 35%, were shown to be associated with the complication.

Preventive Measures

Preventive measures consist of mechanical measures to prevent or limit dissection and pharmacologic measures to prevent intracoronary thrombus formation, sometimes as “foundation antithrombotic therapy” and sometimes as adjuncts after a dissection has occurred.

Mechanical Measures

Coronary dissection can occur as a result of guide catheter or wire trauma, but it occurs most frequently after balloon inflation. The presence of dissection is usually sufficient indication for placement of a coronary stent in current practice. Before the availability of intracoronary stents, not all dissections led to abrupt vessel closure. There is a morphologic classification of acute coronary dissection designed with a view to predicting the chance of development of abrupt closure.⁷² This information is still relevant in the current era because the situation may arise where stent placement is not technically feasible or indicated (Table 22-6).

The introduction of coronary stenting for treatment of acute threatened closure after PTCA resulted in reduction in need for emergency CABG surgery after failed angioplasty.^{73,74} This initial success rate of 93% to 98% in treatment of acute threatened closure or abrupt closure by using early-generation stents was at first offset by subacute stent thrombosis, which was reported to occur in 8% to 16% of patients. Over the ensuing years, improvement in adjunctive pharmacotherapies and device technologies seemed to reduce the need for urgent CABG surgery to less than 1% in contemporary series.⁷⁵⁻⁸³

Diagnosis and Management of Abrupt Closure

The management of abrupt closure or acute threatened closure requires prompt diagnosis followed by restoration of blood flow of the affected vessel. When coronary blood flow becomes compromised, accompanying electrocardiogram (ECG) changes, chest pain, fluctuation in blood pressures, and arrhythmias usually follow, depending on underlying clinical conditions of the patients and degree of acute compromise of blood flow to the dependent myocardium. For patients who develop symptoms consistent with abrupt closure after the procedure, emergency coronary angiography is indicated. In 104 patients with abrupt vessel closure, clinical manifestations included recurrent chest pain (97%), ST segment elevation (77%), ST segment depression (13%), hypotension (20%), and ventricular fibrillation (10%).⁶⁵

Table 22-6. Classification of Dissection

Type	Description	Acute Closure (%)
A	Minor radiolucencies within lumen during angiography without dye persistence	0-2
B	Parallel tracks or double lumen separated by radiolucent area during angiography without dye persistence	2-4
C	Extraluminal cap with dye persistence	10
D	Spiral luminal filling defects	30
E	New persistent filling defects	9
F	Non-A-E types that lead to impaired flow or total occlusion	69

From Huber MS, Mooney JF, Madison J, Mooney MR: Use of a morphologic classification to predict clinical outcome after dissection from coronary angioplasty. *Am J Cardiol* 1991;68:467-471.

When the diagnosis is confirmed, the occluded coronary segment must be recrossed with a guidewire, which can be technically challenging because the wire may follow a dissection plane into the false lumen. It is imperative to maintain the activated coagulation time (ACT) within the “therapeutic range.” The target ACT should be in the range of 250 to 300 seconds with HemoTec device (Medtronic, MN, USA) and 300 to 350 second with HemoChron device (ITC, NJ, USA). For patients who are receiving concomitant GP IIb/IIIa antagonists, a target ACT of 200 to 225 seconds is adequate for both devices.

The mainstay of treatment includes restoration of the patency of the lumen followed by stenting if feasible. Often when flow is restored, a previously unidentified dissection at the margin of a stent or in a balloon-dilated area is recognized. In cases when a stent cannot be delivered to the site of the occlusion, such as in tortuous or rigid vessels, balloon angioplasty of the occluded segment using multiple and prolonged inflations is often successful, although the success rates are lower than for stent placement.^{84,85}

Treatment of Symptoms and Maintaining Stable Hemodynamics

Adequate analgesia should be given at all times while maintaining adequate blood pressure and oxygenation. If blood pressure support is necessary, intravenous boluses of crystalloids or colloid solutions are given initially. Inotropes or pressors may be required. In patients who are hypotensive, it is important to exclude hemorrhage and cardiac tamponade as causes of the hypotension. When sympathomimetic agents such as dopamine or epinephrine are needed, the risk of increasing myocardial oxygen demand must be taken into consideration. Although intracoronary nitroglycerin may be used as a diagnostic test to exclude coronary spasm, there are no data to support the use of intravenous nitroglycerin in this setting. The deleterious effects of vasopressors may be more pronounced in the presence of severe valvular lesions such as mitral regurgitation. Intra-aortic balloon pump counterpulsation may be useful to reduce

myocardial oxygen demand and promote coronary and cerebral perfusion during diastole.

Emergency Coronary Artery Bypass Graft Surgery

Although restoration of coronary flow by percutaneous means is often successful, in cases where the PCI operator knows a priori that no further interventions are likely to succeed, proceeding directly to CABG surgery may be elected.

Air Embolism

Angiographically or clinically evident air embolism occurs in 0.1% to 0.3% of cardiac catheterizations, and it may result in a serious and fatal outcome.⁸⁶⁻⁸⁸ Entrapment of air within the catheters during device introduction or withdrawal, incomplete aspiration of catheters, or aspiration of air through loose connections may result in inadvertent injection of air into the coronary artery. Other mechanisms include balloon rupture and mechanical or structural failures of the equipment. Massive air embolism can also occur during mechanical injection into the left ventricle or aortic root.⁸⁹

Treatment consists of supportive measures with inhalation of 100% oxygen. Oxygen facilitates the outward diffusion of nitrogen from the air bubble by creating a diffusion gradient and improves ischemia. Use of pressors to increase blood pressure so that bubbles are compressed is also recommended. Mechanical interventions such as aspiration and forceful saline injection with successful outcomes have been reported.⁹⁰ In the case of prolonged cardiac arrest, full hemodynamic support with the use of cardiopulmonary bypass has been successfully employed. In this case, the membrane oxygenator may facilitate removal of air from the blood.

Distal Embolization

Distal embolization during PCI ranges from frank distal migration of a visible thrombus or grumous material in a saphenous vein graft to microscopic embolization of atherosclerotic debris.⁹¹ Angiographic distal embolization is believed to be a key mechanism underlying postprocedural non-Q wave MI.⁹²⁻⁹⁵

The term *no-reflow* was originally coined to describe a post-thrombolytic phenomenon in dogs per se, and it has never been characterized precisely in humans.⁹⁶ In the terminology of PCI, the *no-reflow phenomenon* loosely refers to a failure to restore blood flow despite successful treatment of the luminal obstruction. It has been reported to occur in 2% to 3% of PCIs, and is more likely during intervention for acute MI and in saphenous vein grafts.⁹⁷ It is an independent predictor of death and MI.⁹⁸ Numerous factors account for no-reflow, such as microvascular vasoconstriction, reperfusion injury, and endothelial damage, in addition to embolization of atheromatous and thrombotic debris to the microcirculation.

Several strategies to limit the degree of embolization and no-reflow have been examined. Embolic protection devices have been shown to improve clinical outcomes in PCI within saphenous venous grafts. The landmark SAFER trial, examining balloon-occlusive distal protection devices, showed that the primary end point—a composite of death, MI, emergency bypass, or target lesion revascularization by 30 days—was 16.5% in the control group versus 9.6% in the embolic protection device group. This 42% relative reduction in major adverse cardiac

events was largely a consequence of reduction in MI and in the no-reflow phenomenon.⁹⁹ This trial has served as a standard according to which other embolic protection devices have been judged.^{100,101} Conversely, embolic protection devices have not been shown to improve clinical outcomes in PCI for ST segment elevation MI.¹⁰²⁻¹⁰⁴ There is no evidence to advocate routine use of these devices in PCI outside the realm of saphenous vein graft intervention.

Another strategy includes removal of thrombus by mechanical devices such as catheters and rheolytic thrombectomy directly from the coronary vessels. Several such thrombectomy devices are available, including AngioJet (Possis Medical, Minneapolis, MN), Export Catheter (Medtronic, Santa Rosa, CA), Diver CE (Invatec, Roncadelle, Italy), and Pronto Catheter (Vascular Solution, Minneapolis, MN). Numerous studies consistently showed favorable outcomes in surrogate end points such as improved myocardial blood flow, improvement in ST segment changes, and lower incidence of angiographic evidence of distal embolization and no-reflow.¹⁰⁵⁻¹⁰⁷ In the DEAR-MI study, 148 consecutive patients with ST segment elevation MI who underwent primary PCI were randomly assigned to manual thrombus aspiration using the Pronto Catheter or standard treatment. Complete ST segment resolution (68% versus 50%), myocardial blush grade III (88% versus 44%), corrected TIMI frame count (17.3 ± 6 versus 21.5 ± 12), no-reflow (3% versus 15%), angiographic embolization (5% versus 19%), and peak creatine kinase-MB (790 ± 132 $\mu\text{g/L}$ versus 910 ± 128 $\mu\text{g/L}$) all were in favor of aspiration catheter.¹⁰⁸

In a similar context, contrast-enhanced magnetic resonance imaging (MRI) was performed to evaluate microvascular damage and infarct size at days 3 and 30 in patients presenting with ST segment elevation MI (<9 hours from symptom onset) with angiographically confirmed occlusive thrombus. Seventy-five patients were randomly assigned to either thrombus aspiration followed by stenting or conventional stenting. A reduction in microvascular damage and infarct size at 30 days compared with the acute evaluation at day 3 was observed only in the thrombus aspiration group.¹⁰⁹

Although this strategy of adding mechanical thrombectomy seems attractive for improving reperfusion and survival after primary angioplasty for ST segment elevation MI, the definitive clinical benefit of this approach remains inconclusive. Most early studies failed to show any substantial clinical benefits, such as reduction of infarct size, improvement of left ventricular performance, or reduction in adverse cardiac events, by using various forms of this adjunctive approach in ST segment elevation MI even in the presence of a visible thrombus at least in the short-term follow-up.¹¹⁰⁻¹¹³

In the single-center TAPAS study, 1071 patients were randomly assigned to the thrombus aspiration group or the conventional PCI group before undergoing coronary angiography. Aspiration with the Export Catheter was considered to be successful if there was histopathologic evidence of atherothrombotic material. A myocardial blush grade of 0 or 1 was in 17.1% of the patients in the thrombus aspiration group versus 26.3% of patients in the conventional PCI group. Complete resolution of ST segment elevation occurred in 56.6% of patients in the thrombus aspiration group versus 44.2% of patients in the conventional PCI group. At 30 days, the rates of death in patients with a myocardial blush grade of 0 or 1, 2, and 3 were 5.2%, 2.9%, and 1%, and the rates of adverse events were 14.1%, 8.8%, and 4.2%.

This landmark study showed that thrombus aspiration is applicable in most patients with MI with ST segment elevation, and it resulted in better reperfusion and clinical outcomes than conventional PCI regardless of clinical and angiographic characteristics at baseline.¹¹⁴ These findings suggest there may be incremental late benefit associated with mechanical reduction of thrombus burden over and above the routinely employed strategy of primary PCI along with aggressive antiplatelet and antithrombin therapies by further improving perfusion at tissue level during the acute phase.

Treatment

It is important that an adequate ACT be maintained, and GP IIb/IIIa inhibitors can be used as a bailout measure. Although intracoronary nitrates are not shown to have any role in the treatment of no-reflow, they may be given as first-line therapy to relieve vasospasm of epicardial vessels. Intracoronary verapamil, adenosine, and nitroprusside are the first-line drugs for no-reflow because arteriolar vasodilation may allow embolized material to track further downstream, lessening the area subtended by the occluded vessels.

Piana and colleagues¹¹⁵ showed that verapamil (50 to 900 µg) improved intracoronary flow in 89% of patients. Other studies showed similar successful results in degenerated vein grafts and after rotational atherectomy.^{116,117}

Bolus doses of adenosine, 10 to 20 µg, have also been used in this setting as a distal arteriolar vasodilator.^{118,119} Intracoronary sodium nitroprusside in boluses of 50 to 200 µg have been reported to be useful despite a relative paucity of objective evidence.¹²⁰ Intracoronary administration of epinephrine (50 to 200 µg) has been used successfully in refractory cases.¹²¹ Data from post-hoc analysis of pivotal trials have not suggested that GP IIb/IIIa antagonists effectively prevent no-reflow during saphenous vein graft intervention. Embolization of non-thrombotic material may cause elevation in creatine kinase-MB, however, masking an effect of GP IIb/IIIa on decreasing events. A more recent study suggested there is an incremental beneficial role of GP IIb/IIIa in addition to routine use of an embolic protection device during saphenous vein graft intervention.¹²² Other agents given through the intracoronary route, including diltiazem, papaverine, nicardipine, and nicorandil, have been assessed with variable results.¹²³⁻¹²⁷ Intracoronary heparin and thrombolytics (e.g., urokinase, tissue plasminogen activator) have been proven to be of limited use even with the combination of GP IIb/IIIa inhibitors.^{128,129}

Stent Infection

Infection of a coronary stent is extremely rare.¹³⁰ Infection is typically manifest within 1 month of stent placement, with persistent fever and positive blood cultures suggesting endovascular infection. The patient may also complain of chest pain. There are typically no ECG changes or elevation in cardiac enzymes. This complication has been described after placement of bare metal stents, covered stents, or drug-eluting stents.¹³¹⁻¹³³ *Staphylococcus aureus* has been reported as the responsible pathogen in most cases.¹³⁴ Other organisms, such as coagulase-negative staphylococci, *Pseudomonas aeruginosa*, and *Candida*, have also been implicated.^{135,136}

Infective processes of the stent site often result in mycotic aneurysm formation.¹³⁷ Other complications include abscess

formation and suppurative pericarditis.^{138,139} Stent infection may also lead to septic systemic embolism.¹⁴⁰ Various imaging modalities, such as coronary angiography, MRI, computed tomography, and transesophageal echocardiography, are useful to make the diagnosis.¹⁴¹ Prolonged treatment with intravenous antibiotics alone is usually insufficient, and the condition often necessitates surgical intervention for drainage or resection of a false aneurysm and removal of the stent. The mortality has been reported to be 40%.¹³⁰ There is no evidence to support benefit for a preventive strategy beyond compliance with the current standards of prevention of infection, and routine use of prophylactic antibiotics is not indicated.

Contrast-induced Nephropathy and Other Contrast Toxicities

Currently available ionic contrast agents include hyperosmolar media, such as diatrizoate (Hypaque, Renografin), and the low-osmolar agent, ioxaglate (Hexabrix). Nonionic agents consist of low-osmolar agents, such as iohexol (Omnipaque), iopamidol (Isovue), and ioversol (Optiray), and iso-osmolar agents, such as iodixanol (Visipaque). Complications related to contrast agents can be classified into anaphylactoid reaction, nephrotoxicity, and hemodynamic complications (Table 22-7).

Anaphylactoid Reaction

Severe anaphylactoid reaction is the rarest but most severe contrast-related toxicity. Although the exact etiology of this reaction remains unknown, it is thought to result from mast cell degranulation resulting in activation of complement and kinin release through mechanisms independent of IgE.¹⁴² It may occur on first exposure to contrast agents.¹⁴³ The incidence has been reported as 5% for all reactions (including mild ones) and 0.1% for severe reactions. The risk of a repeat reaction can be 15% in patients with a history of anaphylactoid reaction to an iodinated contrast agent.¹⁴⁴

Clinical features of anaphylactoid reaction range from relatively mild reactions, such as generalized pruritus and urticaria, to bronchospasm, angioedema, vasodilation, and hypotension. Progression to hemodynamic collapse or total airway obstruction may occur in severe cases.

The cornerstone of management of anaphylactoid reaction is prevention: identifying patients at risk and appropriate use of prophylactic pharmacologic agents. Although there are studies suggesting that pretreatment with corticosteroids and antihistamines in unselected patients significantly reduces the incidence of reactions, the usefulness of applying this strategy routinely remains doubtful because numerous patients would need to receive premedication to prevent each potentially serious reaction.^{145,146} This notion was reinforced more recently by a meta-analysis that included nine trials with a total of 10,011 adults. In two trials, 0.4% of patients who received oral methylprednisolone, 32 mg twice, or intravenous prednisolone, 250 mg, had laryngeal edema compared with 1.4% of controls. In two other trials, 0.2% of patients who received oral methylprednisolone, 32 mg twice, had shock, bronchospasm, or laryngospasm compared with 0.9% of controls. In one trial, 0.5% of patients who received intravenous clemastine, 0.03 mg/kg, and cimetidine, 2 to 5 mg/kg, had angioedema compared with 8 of 194 (4.1%)

Table 22-7. Types of Contrast Agents

Product	Type of Contrast Agent Concentration	mg (I/mL)	Osmolality (mOsm/L)
Monomers			
Iohexol (Omnipaque)	Nonionic LOCM	350	844
Iopamidol (Isovue)	Nonionic LOCM	370	796
Ioxilan (Oxilan)	Nonionic LOCM	350	695
Iopromide (Ultravist)	Nonionic LOCM	370	774
Ioversol (Optiray)	Nonionic LOCM	350	792
Dimers			
Iodixanol (Visipaque)	Nonionic IOCM	320	290
Ioxaglate (Hexabrix)	Ionic LOCM	320	600

Note: Ultravist is a registered trademark of Berlex Laboratories. Isovue is a registered trademark of Bracco Diagnostics. Omnipaque and Visipaque are registered trademarks of GE Medical, Inc. Optiray is a registered trademark of Mallinckrodt Medical, Inc. Oxilan and Hexabrix are registered trademarks of Guerbet, S.A.

IOCM, iso-osmolar contrast media; LOCM, low-osmolality contrast media.

Adapted from Kozak M, Robertson BJ, Chambers CE: Cardiac catheterization laboratory: diagnostic and therapeutic procedures in the adult patient.

In Kaplan JA (ed): Kaplan's Cardiac Anesthesia, 5th ed. Philadelphia, Saunders, 2006, p 307.

controls. None of the studies exclusively included patients with a prior history of anaphylactoid reaction.¹⁴⁷

There are no randomized data evaluating the role of prophylactic medications exclusively in patients with a prior history of reaction to contrast media. In a nonrandomized series, only 10.8% experienced reactions after pretreatment with prednisone and diphenhydramine. Transient hypotension occurred in only 0.7% of these patients. The addition of ephedrine to the regimen was associated with an incidence of 5%.¹⁴⁸ Lasser and coworkers¹⁴⁵ showed that methylprednisolone given as two doses, 12 hours and 2 hours before ionic dye exposure, was associated with fewer reactions compared with one dose of corticosteroid 2 hours prior. Based on these studies, treatment with diphenhydramine, cimetidine, or ranitidine before the procedure and preferably two doses of corticosteroids at 12 hours and 2 hours before the procedure is advocated empirically for patients with a previous history of reaction to intravenous contrast agents.

Management of a mild or moderate reaction includes administration of H₁- and H₂- histamine antagonists and fluid resuscitation. In patients who developed a more severe form of reaction during the procedure such as wheezing, laryngospasm, or hypotension, intravenous treatment with 1:10,000 epinephrine, 0.5 to 1 mg intravenously; hydrocortisone, 100 to 200 mg; and intravenous H₁- and H₂- antagonists is indicated. In cases of severe laryngospasm with acute or impending airway compromise, endotracheal intubation or surgical control of the airway may be required.

Contrast-induced Nephrotoxicity

Contrast-induced nephropathy is responsible for 11% of hospital-acquired renal insufficiency, and is the third leading cause of hospital-acquired renal failure. It is associated with significant morbidity and mortality.^{149,150} In 7586 patients undergoing cardiac catheterization, an absolute increase of 0.5 mg over the baseline level of creatinine occurred in 3.3% of patients overall, and in 25% of patients with a baseline serum creatinine greater than 2 mg/dL.¹⁵¹ The serum creatinine becomes elevated on day 2 or 3 after exposure to contrast medium, although the peak usually occurs on day 5 or 6. The creatinine usually returns to the baseline value within 2 weeks.^{152,153} Renal function may not return to its baseline level, however, and development of renal failure after PCI is independently associated with increased mortality.^{154,155}

Moderate to severe chronic kidney disease is the most important risk factor for the development of contrast-induced nephropathy.¹⁵⁶ Other major risk factors include advanced age, diabetes mellitus, higher dose of contrast agent, recent contrast agent administration, concurrent use of nephrotoxic drugs, dehydration, and any other condition associated with decreased effective circulating blood volume and reduced renal blood flow.¹⁵⁷⁻¹⁵⁹ Serum creatinine overestimates actual creatinine clearance, particularly in elderly patients. Treatment of this condition is expectant with conservative measures. Approximately 5% to 10% of patients may require transient dialysis, and about 1% need long-term renal replacement therapy.

Metformin

The insulin-sensitizing drug metformin carries a risk of causing lactic acidosis of 0.03 per 1000 cases per year. Lactic acidosis in this setting is associated with a mortality rate of 50%. Metformin is excreted unmetabolized by the kidneys and may accumulate in patients with renal failure. The half-life of metformin is 2 to 6 hours in healthy individuals. Although metformin use is not a risk factor for nephropathy, there is a concern that the likelihood of lactic acidosis may be higher after contrast-induced nephropathy in patients who are taking metformin.^{160,161} It is recommended that metformin be withheld perhaps at least 6 hours before the procedure, and it is recommended not to resume the therapy until it is clear that renal function has not significantly deteriorated.^{162,163}

Complications of Valvular Interventions

Mitral Balloon Valvuloplasty

Percutaneous mitral balloon valvuloplasty is an effective means of nonsurgical treatment of selected patients with mitral stenosis.¹⁶⁴ Short-term and intermediate-term outcomes of single and double balloon valvuloplasty compare favorably with results of closed and open surgical mitral commissurotomy.¹⁶⁵⁻¹⁶⁹ Mitral valve area is often increased twofold with this procedure, and most patients experience marked alleviation of symptoms.¹⁷⁰ The combined incidence of major events (death, surgery, new percutaneous mitral balloon valvuloplasty) is low in the first 5 years. The frequency of events progressively increases thereafter, however, reaching a total of 47.2% at 15-year follow-up.¹⁷¹

Complications

Complications after mitral valvuloplasty occur primarily as a result of cardiac tamponade, mitral regurgitation, or embolization. In 787 patients enrolled into the NHLBI mitral balloon angioplasty registry, the global incidence of major complications was 12% with a mortality rate of 1.6% at 30-day follow-up.¹⁷² Other series subsequently reported the mortality rate 0% to 3%.¹⁷³

Hemopericardium

The incidence of hemopericardium and cardiac tamponade, at average rates of 1% to 3%, is related to transseptal puncture or perforation of the left ventricular apex by the guidewire or by the balloon itself.¹⁷⁴⁻¹⁷⁶ Left ventricular laceration produces immediate hemodynamic deterioration and requires emergency corrective surgery.^{177,178}

The most frequent complication of valvuloplasty is worsening of preexisting mitral regurgitation. Among reported series of patients, mitral regurgitation develops or worsens in 30% to 40%.¹⁷⁹ Severe mitral regurgitation was an infrequent complication of percutaneous balloon mitral valvuloplasty (7.5% of 280 patients) and resulted from disruption of the valve integrity, including chordal rupture (43%) and leaflet tearing (30%). Heavily calcified posterior leaflets may be at greater risk of tearing, and most patients who develop severe regurgitation (77%) ended up requiring nonemergency mitral valve replacement.¹⁸⁰

Kaul and associates¹⁸¹ performed a retrospective analysis of 3650 patients (median age 26 years). Significant mitral regurgitation (moderate or severe) occurred in 8.4% of patients, of whom 116 (3.2%) required mitral valve replacement urgently or on follow-up. All patients whose mitral regurgitation was due to rupture of valve leaflets (usually the posterior one) required urgent valve replacement.

The occurrence of severe mitral regurgitation depends more on the location and distribution of the morphologic changes of the valve than on underlying severity, rendering prediction of development of severe mitral regurgitation difficult on an individual basis, and echocardiographic scoring systems do not predict the development of mitral regurgitation.¹⁸² Characteristics associated with development of severe mitral regurgitation have been described as heterogeneous valve thickening with thick areas adjacent to normal ones, involvement of the subvalvular apparatus, and discrete calcification in one or both commissures.¹⁸³ In the valves with heavily diseased commissures, the leaflets ruptured at the least affected portions.¹⁸⁴

Residual Left-to-Right Shunting

After successful atrial puncture, a residual atrial septal defect with left-to-right shunting is detectable in 87% of patients by color flow Doppler ultrasound, but only 1% to 2% of patients with atrial septal defect by echocardiography have hemodynamic evidence of significant shunting (ratio between systemic and pulmonary flow >1.5:1).¹⁸⁵ Most of these shunts resolve as left atrial pressure decreases after the procedure and are of no clinical consequence. Large residual atrial septal defects with significant shunting are rare, usually resulting from inadvertent balloon inflation across the interatrial septum.¹⁸⁶ With recurrent valve stenosis, defects may reappear as the left atrial pressure increases, creating a variation of Lutembacher syndrome.¹⁸⁷

Systemic Embolism

The rate of systemic embolism is 0.5% to 3%. Systemic embolism very seldom causes permanent disability, and even more seldom leads to death.¹⁸⁸

Aortic Valvuloplasty

Percutaneous balloon valvuloplasty for aortic stenosis partially improves valvular stenosis and functional status of patients, but is associated with very high restenosis rates.¹⁸⁹ It is usually reserved for elderly, severely symptomatic patients who are not thought to be surgical candidates. These critically ill patients, who often have multiple comorbid illnesses, are at increased risk for procedural complications. Earlier, vascular complication rates were 15% largely because of the large-bore femoral artery access (12F to 14F) required for the valvuloplasty balloons. Access site complications have decreased significantly with the current generation of catheters, however, and following the use of percutaneous closure devices including preclose technique, wherein placement of surgical sutures percutaneously and progressive dilation are undertaken before the placement of the large-bore sheath.^{190,191}

Hemodynamic instability resulting from these complications may be poorly tolerated by these patients. Other potential complications include severe aortic regurgitation (1% to 2%), systemic embolization (1% to 5%), cardiac perforation with tamponade (1% to 4%), MI (1%), and death (2% to 5%). These rates remain unchanged.¹⁹²⁻¹⁹⁵

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Vascular Complications after Percutaneous Coronary Intervention

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CHAPTER 23

**Arterial Access and Sheath Removal
Techniques
Hemorrhagic Complications**

**Arteriovenous Fistula
Thrombotic Complications
Infectious Complications**

VASCULAR ACCESS complications are the most common complications (2% to 6%) after diagnostic cardiac catheterization and coronary interventions despite their significant decline over the last decades.^{1,2} Care providers in the coronary care unit (CCU) should be familiar with the incidence, clinical presentation, and appropriate management of these complications. Critically ill patients admitted to the CCU are at high risk for access complications because of the presence of comorbidities such as peripheral vascular disease, renal failure, and advanced age. These patients are also more likely to be heavily anticoagulated, and to have had high-risk, technically demanding procedures on an emergency basis.^{2,3}

In addition, patients are occasionally admitted to the CCU for management of vascular access complications. A thorough understanding of vascular access issues and prompt recognition of these complications are essential to minimize the substantial morbidity and mortality associated with them.

The complications can be categorized as hemorrhagic or thrombotic/occlusive. Hemorrhagic complications include access site bleeding, retroperitoneal hematoma, pseudoaneurysm, arteriovenous fistula, and vessel laceration. Thrombotic complications include arterial thrombosis, distal embolization, dissection, and rarely venous thrombosis or pulmonary embolism. Risk factors include advanced age, female gender, obesity, peripheral vascular disease, use of large arterial sheaths, intensity of anticoagulation including the use of glycoprotein (GP) IIb/IIIa inhibitors, recent thrombolysis, intra-aortic balloon pump counterpulsation, and prolonged duration of time that the sheath remained in place.⁴⁻⁶ Meticulous technique during cardiac catheterization and during the removal of the sheath is essential in reducing the complications rate.

Arterial Access and Sheath Removal Techniques

A focused but detailed clinical examination of the access site before the patient is taken to the catheterization laboratory is essential. The femoral and distal pulses are palpated, and their presence or absence is documented; the groin is auscultated for bruits and inspected for the presence of infections and surgical

scars that point to prior peripheral vascular bypass procedures. In radial artery cases, a modified Allen test is performed using the waveform of the pulse oximeter to detect distal perfusion.

The femoral approach is the site of choice for most operators. The common femoral artery is the point of entry. In most patients, the bifurcation of the common femoral artery is at the level of the mid third of the femoral head.⁷ Time should be taken to palpate the femoral pulse at the site of maximal impulse. This should be 2 cm below the inguinal ligament, which runs across a line connecting the anterior superior iliac spine and the symphysis pubis. We also strongly recommend the use of fluoroscopy to identify the mid third of the head of the femoral bone as an additional point to assist with orientation; this is particularly important in obese patients in whom the skin landmarks can be deceiving. The additional time required for this extra step is worthwhile, and fluoroscopy should be performed even under the most emergent circumstances. Arterial entry above the inguinal ligament predisposes to retroperitoneal hematomas, whereas low entry predisposes to formation of pseudoaneurysms and arteriovenous fistulas.⁸

Front wall technique should be used. The use of the smallest arterial sheaths that would allow for optimal performance of the percutaneous coronary intervention should be used because it has been shown that larger sheaths are associated with higher incidence of hemorrhagic and occlusive/thrombotic complications.⁹ Patients after fibrinolysis and patients who have been heavily anticoagulated should be catheterized by the most experienced operators. Patients anticoagulated with warfarin should ideally wait until the international normalized ratio (INR) is less than 1.5, although in emergency situations with good access technique and careful sheath removal or the use of closure devices by experienced operators, an INR of 2 to 3 is not an absolute contraindication to the procedure.¹⁰

Patients with severe peripheral vascular disease often are a challenge. Femoral artery atherosclerosis and calcification, iliac tortuosity, and stenosis make arterial access difficult and pose problems to wire advancement, sheath insertion, and catheter manipulation. In situations such as this, when there is any question regarding the intraluminal position of the 0.035-inch wire (resistance, buckling, trapping), we strongly recommend against use of force and further advancement of the wire and against

the introduction of a large sheath. A 4F introducer can be slowly inserted, and after pressure transduction a gentle contrast injection is used to confirm the intraluminal position and to define the vascular anatomy. Stiff hydrophilic wires are useful to negotiate calcified tortuous iliac arteries, but their use should be restricted to experienced operators.

When the sheath is introduced, we use the over the wire exchange technique with the tip of the catheter in the proximal abdominal or distal thoracic aorta. In addition, we often use long, stiff sheaths to facilitate catheter manipulation because otherwise it might be impossible to have control of the coronary diagnostic or guiding catheters. We routinely perform catheter exchanges and observe the wire under fluoroscopy as we advance it in the iliac artery to get a sense of the tortuosity and elasticity of the artery, which determines the use of appropriate equipment to optimize the chances of a successful intervention.

Sheaths should be removed as soon as it is safe after a procedure depending on the anticoagulation regimen used for the intervention. The use of bivalirudin compared with the use of heparin plus GP IIb/IIIa inhibitors is associated with a reduction of vascular complications.³ For anticoagulation with heparin, an activated coagulation time of less than 180 seconds¹¹ is considered the criterion for safe sheath removal. If a GP IIb/IIIa inhibitor is used, some clinicians advocate an activated coagulation time of less than 150 seconds. With bivalirudin use, sheaths can be removed 2 hours after discontinuation of the bivalirudin.³

Throughout the time of sheath removal, the patient's vital signs should be monitored closely, the access site should be assessed for the development of oozing or hematoma formation, and the distal pulses and color of the skin should be continuously assessed to ensure adequate perfusion of the limb. We strongly recommend the presence of at least two experienced nurses (or physicians) during sheath removal, frequent (every few minutes) measuring of the blood pressure, continuous telemetry and pulse oximetry monitoring, the availability of at least two reliable peripheral intravenous access sites, and atropine and normal saline available in the room.

Vagal episodes are common with compression of the femoral artery and are characterized by nausea, vomiting, hypotension, and bradycardia. These episodes usually respond promptly to intravenous fluids and atropine, 0.6 to 1 mg intravenously. If the pressure decreases again, and if there are other signs or symptoms such as flank or abdominal pain or palpable hematoma, the situation should be readdressed quickly because these are warning signs of potentially more serious complications, such as retroperitoneal hematoma or groin bleeding. It is a common mistake to misdiagnose significant bleeding episodes as "vagal episodes" with detrimental delays in appropriate management.

In patients with peripheral bypass grafts, we avoid total occlusion of the femoral artery, and we use continuous Doppler monitoring of the distal pulses to ensure uninterrupted blood flow through the graft. We generally recommend 15 minutes of manual compression for 6F sheaths, and we add 5 minutes for each French increase in size (i.e., 20 minutes for 7F and 25 minutes for 8F sheaths). Alternatively, mechanical compression devices can be used (C-clamp, fem-stop); although more convenient for the staff, these devices have a learning curve and still require the presence of staff members during the application. Closure devices are advocated because they are more comfortable for the patient allowing faster ambulation. In the past, there were concerns that bleeding or thrombotic/occlusive complications

might be increased.¹²⁻¹⁴ With the exception of Vasoseal,¹⁵ however, the complication rate with closure devices is similar to the rate with manual sheath removal except for a slight increase in infectious complications.

Hemorrhagic Complications

The need for transfusion during or after percutaneous coronary intervention is associated with in-hospital and long-term increase in mortality.¹⁶⁻¹⁸ The explanation for this finding is unclear, but could be related to hemodynamic alterations associated with blood loss, the discontinuation of anticoagulation, or the adverse effect of blood transfusion per se.¹⁹

Groin Hematoma

Groin hematoma is a common complication that can occur shortly after sheath removal if there is inability to control the femoral artery. The incidence of access site bleeding requiring transfusion was found to be 1.8% in one study.¹⁸ Heparin is no longer administered routinely after intervention, and this has led to significant reduction in the bleeding complications rate. Newer anticoagulation regimens using bivalirudin and clopidogrel without the use of GP IIb/IIIa inhibitors have also reduced the rate of access site bleeding.^{3,20,21}

Risk factors include obesity, anticoagulation, large sheaths, premature ambulation, and peripheral vascular disease. Poor hemostatic technique increases the risk of localized bleeding further. A common mistake is application of hemostatic pressure on the site of the skin incision, whereas the actual point of entry into the artery is a couple of centimeters above the skin nick, and so pressure should be applied more proximally. Another common mistake is short duration of manual compression and subsequent dislodgment of the immature thrombus. The clinical management depends on the severity of bleeding. In most cases, the bleeding can be controlled with additional manual compression or the use of mechanical hemostatic devices. Reversal of anticoagulation and discontinuation of GP IIb/IIIa inhibitors are indicated. Particularly in obese patients, a significant amount of blood loss can occur in the femur resulting in hemodynamic compromise requiring transfusion. Surgical repair is usually not required, and the hematoma resolves over the ensuing days or weeks.

Retroperitoneal Hematoma

Retroperitoneal bleeding complicates cardiac interventions in less than 1% of the cases.²² High femoral and back-wall sticks above the inguinal ligament are risk factors. The usual clinical presentation is sudden onset of flank or abdominal pain with fullness, guarding, and hypotension. Prompt recognition and immediate aggressive resuscitation with intravenous fluids or blood or both are required. Emergency vascular surgery consultation should be obtained. Manual compression is of little use because the bleeding site is high in the pelvis where the artery is noncompressible.

Prompt hemodynamic stabilization and reversal of anticoagulation are indicated. Heparin can be reversed with protamine (1 mg/100 U of heparin intravenously up to 50 mg maximum). Low-molecular-weight heparin can be partially reversed with protamine as well (1 mg/100 anti-factor Xa U). If fibrinolytics have been used, fresh frozen plasma (15 mL/kg), cryoprecipitate (1 bag per 10 kg), and aminocaproic acid (5 g during the

first hour followed by 1 to 1.25 g/hr for approximately 8 hours or until bleeding stops) are indicated.²³ GP IIb/IIIa inhibitors should be discontinued. Platelet transfusion can be used to reverse the effects of abciximab. The effect of tirofiban or eptifibatide wears off after approximately 4 hours. Ongoing bleeding despite the aforementioned measures is an absolute indication for emergency surgical or endovascular repair. In the endovascular approach, arterial access is obtained from the contralateral side, and the bleeding site can be identified angiographically and occluded with balloon inflation. Options thereafter include either covered stent placement or open surgical repair.

Pseudoaneurysm

A pseudoaneurysm is the formation of a hematoma contained by the surrounding tissues. It is called a *pseudoaneurysm* because there is no aneurysmal sac that contains all the layers of the vessel wall. It manifests as a painful, palpable, pulsatile mass accompanied by a systolic bruit. Pseudoaneurysms less than 2 cm in diameter may resolve spontaneously. If they are greater than 2 cm in diameter, if there are signs of expansion of the hematoma, or if the patient requires anticoagulation, the pseudoaneurysm should be closed.

There are different methods of closure depending on the anatomy and the local expertise.²⁴ Surgical repair with suturing the hole on the arterial wall is the traditional approach and is indicated in cases of rapidly expanding pseudoaneurysms, massive bleeding, and hemodynamic compromise. Alternatively, thrombin injection under ultrasound guidance has a high success rate (Fig. 23-1).²⁵ Meticulous technique is mandatory to avoid

injecting the thrombin in the actual artery, particularly when the neck of the pseudoaneurysm is wide and short. The distal pulses should be examined before the procedure. The pseudoaneurysm is localized by ultrasound and entered with the needle perpendicular to the ultrasound beam. When the sac is entered (the needle can be visualized on ultrasound), a saline bubble injection is performed to ensure that bubbles do not enter the femoral artery. Subsequently, the thrombin is injected slowly, and there should be immediate obliteration of the sac. Bed rest is recommended for 2 hours. The groin ultrasound scan is usually repeated the next morning.

An alternative technique is direct prolonged compression of the pseudoaneurysm with the ultrasound probe. This technique is time-consuming and uncomfortable for the operator and the patient, but series have been described in the literature with reasonably good results.²⁶ It might be suited for relatively small pseudoaneurysms with short “necks” (Fig. 23-2). Endovascular repair with coils has also been described.²⁷ Stent grafting is an option that might be limited by technical considerations such as subacute stent thrombosis, occlusion of major side branches, and compromise of future access.²⁸

Vascular Perforation

Perforation of the iliac arteries is a catastrophic complication that manifests as abdominal pain and hypovolemic shock. Unless promptly recognized and treated, it can be lethal (Fig. 23-3). Reversal of anticoagulation is indicated as soon as it is recognized. Emergency vascular surgery consultation is recommended simultaneously with aggressive resuscitation and hemodynamic support. The bleeding can be controlled with

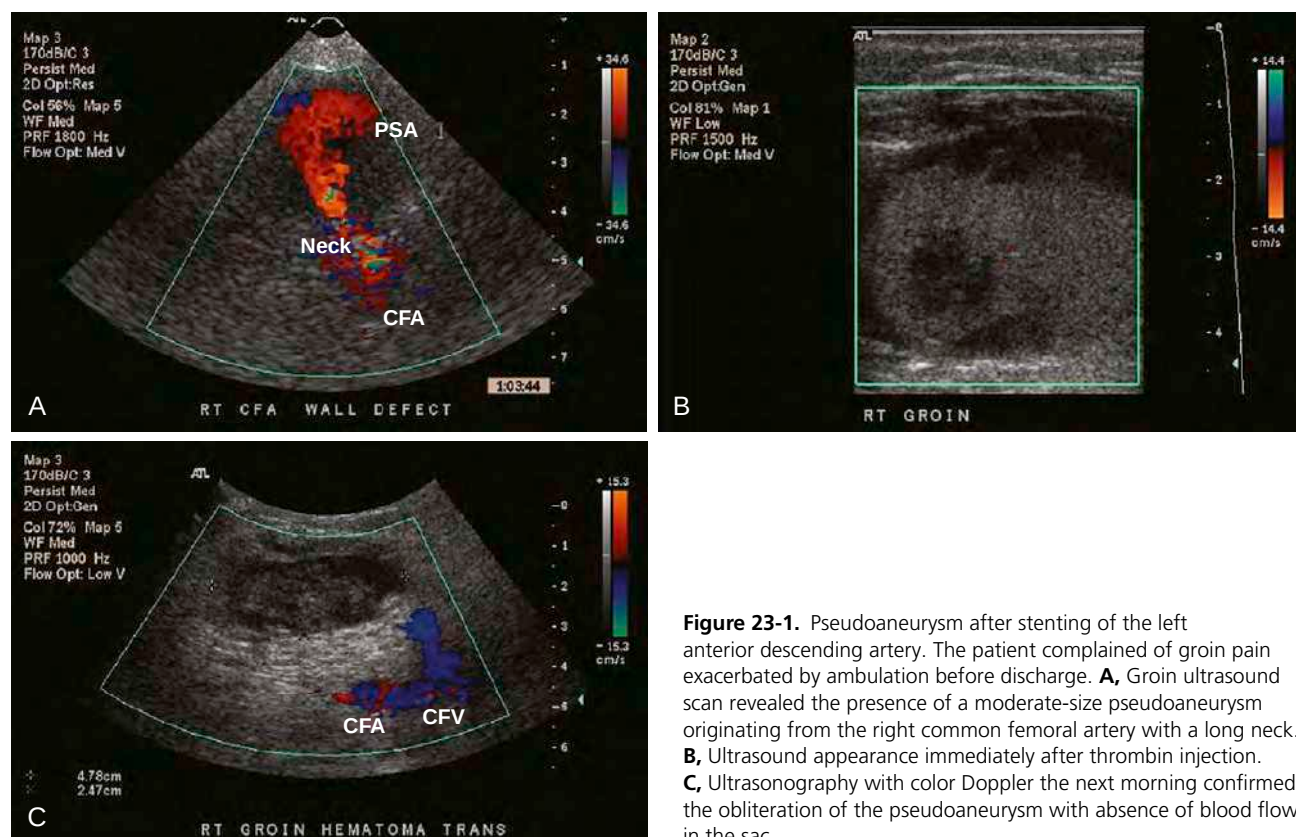


Figure 23-1. Pseudoaneurysm after stenting of the left anterior descending artery. The patient complained of groin pain exacerbated by ambulation before discharge. **A**, Groin ultrasound scan revealed the presence of a moderate-size pseudoaneurysm originating from the right common femoral artery with a long neck. **B**, Ultrasound appearance immediately after thrombin injection. **C**, Ultrasonography with color Doppler the next morning confirmed the obliteration of the pseudoaneurysm with absence of blood flow in the sac.

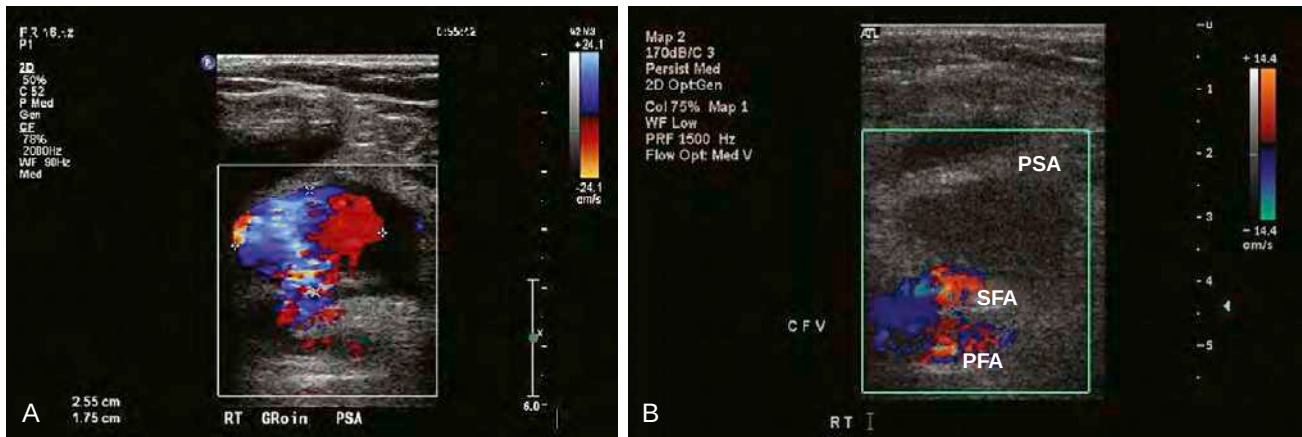


Figure 23-2. Pseudoaneurysm after stenting of the right coronary artery. **A**, Groin ultrasound scan revealed a small pseudoaneurysm with a short neck in close proximity to the superficial femoral artery. Given these anatomic characteristics, it was treated with prolonged ultrasound-guided compression. **B**, Complete obliteration of the pseudoaneurysm is shown in follow-up ultrasonography.

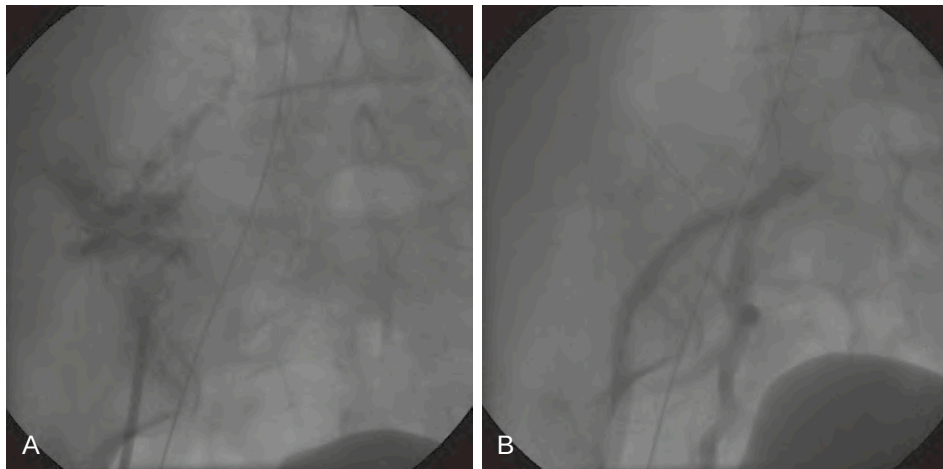


Figure 23-3. Right external iliac artery perforation in a patient with inferior ST segment elevation myocardial infarction and slow flow after right coronary artery stenting. Eptifibatide (Integrilin) was initiated, and the decision was made to place an intra-aortic balloon pump. There was resistance with wire advancement, and the patient complained of abdominal pain and became hypotensive. **A**, Iliac angiography via the sheath revealed massive extravasation of the dye. The wire was repositioned in the true lumen, and the lesion was treated with prolonged balloon inflation for immediate control of bleeding. **B**, Final angiography after deployment of a covered stent with complete sealing of the perforation.

prolonged balloon inflations followed by stent graft deployment or open surgical repair.

Dissection

Most retrograde dissections are due to wire entering the subintimal plane. Because the blood flow is from the opposite direction, these dissections usually heal spontaneously. In cases of acute or threatened vessel closure, repair is needed, which can be accomplished with catheter-based techniques and stenting usually by access from the contralateral groin.

Arteriovenous Fistula

Fistulas occur in approximately 0.4% of interventional cases when there is simultaneous puncture of the artery and the vein and the formation of a track, or if ongoing bleeding from the artery is decompressed to the adjacent vein.²⁹ Predisposing

factors are poor access technique and high and low access of the superior femoral artery. Clinically, it is recognized by the presence of a continuous bruit or palpable thrill because the pressure in the artery is higher than in the vein throughout the cardiac cycle. Repair of an arteriovenous fistula is rarely an emergency; however, close follow-up is indicated because fistulas tend to enlarge with time, and repair is eventually required. Other options for repair include coil embolization and endovascular repair with covered stents.

Thrombotic Complications

Arterial thrombosis can occur in any vessel that is accessed for cardiac catheterization. Risk factors include pre-existing peripheral vascular disease, prolonged sheath insertion, and use of large sheaths.³⁰ The classic presentation is the sudden onset of pain and paresthesia, and clinical signs include the loss of distal

pulses. The affected limb is cold and pale. Prompt recognition is essential because restoration of flow is crucial for limb salvage. Urgent vascular surgery consultation is indicated. Angiography confirms the diagnosis. Treatment options include surgical embolectomy and percutaneous thrombectomy.

Occasionally, with sheath insertion, transient limb ischemia can occur because of pre-existing peripheral vascular disease or spasm; it resolves with sheath removal or vasodilator therapy. The risk of distal embolization during sheath removal can be decreased by applying pressure distal to the insertion site and by allowing transient bleeding from the arteriotomy site. We routinely perform this maneuver in cases of radial and brachial access, and after the removal of large femoral artery sheaths and intra-aortic balloon pumps. Femoral vein thrombosis and pulmonary embolism are rare complications and their incidence may be underestimated because they are often clinically silent.³¹

Infectious Complications

Infection is a rare but potentially serious complication, especially if it is not limited to the skin (cellulitis) and involves deep tissues and the artery itself. Meticulous attention to sterile technique is mandatory. If infection occurs, it manifests with fever and systemic signs of infection and local pain, erythema, induration, and swelling. Treatment for superficial infections includes antibiotics that should cover *Staphylococcus* species. Deep tissue infections often require surgical débridement.

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Noncoronary Diseases: Diagnosis and Management

SECTION

IV

Acute Heart Failure and Pulmonary Edema

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CHAPTER

24

Pathophysiologic Considerations

Clinical Presentation of Acute Heart Failure
Diagnosis and Evaluation of Acute Heart Failure

Treatment of Acute Heart Failure Choice of Therapeutic Regimen

ACUTE HEART failure (AHF) is a clinical syndrome of new or worsening signs and symptoms of heart failure (decompensated), often leading to hospitalization or a visit to the emergency department. Patients with AHF represent a heterogeneous population with high postdischarge readmission rates.¹⁻⁵ Most hospitalized patients have significant volume overload, and congestive symptoms predominate. Fewer patients present with hypotension and symptoms of reduced organ perfusion.¹⁻⁵ A few patients who come to the emergency department with AHF have “flash pulmonary edema.”¹ A few patients have onset of symptoms within 4 hours of arrival; most patients have a slow progression of disease, resulting from cardiac ischemia, medication noncompliance, dietary indiscretion, or exacerbation of hypertension. The average patient has had symptoms for almost 5 days before seeking medical attention.¹⁻⁵

AHF is the most common cause of hospital admission in patients older than 65 years, accounting for 1 million admissions annually.⁶ AHF represents a period of high risk for patients, with a 20% to 30% mortality rate within 6 months after admission.⁷⁻⁹ Early care of AHF and time to treatment are linked to outcome. These patients are generally cared for in telemetry units in the United States. Only 10% to 20% of these patients are admitted to intensive care units (ICUs).^{2,3}

Pathophysiologic Considerations

Integral to the understanding of the pathogenesis and treatment of AHF and pulmonary edema is a basic understanding of the forces involved in fluid retention, capillary-interstitial fluid exchange (Starling relationship), the determinants of myocardial pump performance, and the pathophysiology of AHF.

Chronic Progressive Fluid and Water Retention

Renal sodium and water excretion normally parallels sodium and water intake, so that an increase in plasma and blood volume is associated with increased renal sodium and water excretion. In patients with heart failure, sodium and water are retained, despite an increase in intravascular fluid volume. Renal sodium and water retention in these patients may be regulated not by the total blood volume, but by the degree of filling of the arterial compartment—the so-called effective blood volume. The dynamic equilibrium of the arterial circulation, as determined by cardiac output and peripheral vascular resistance or compliance, is the predominant determinant of renal sodium and water excretion.

Arterial underfilling is sensed by mechanoreceptors in the left ventricle, carotid sinus, aortic arch, and renal afferent arterioles.¹⁰ Decreased activation of these receptors because of a decrease in systemic arterial pressure, stroke volume, renal perfusion, or peripheral vascular resistance leads to an increase in sympathetic outflow from the central nervous system, activation of the renin-angiotensin-aldosterone system, and the nonosmotic release of arginine vasopressin, as well as the stimulation of thirst.¹⁰ These factors together with increased release of endothelin and vasopressin and resistance to natriuretic peptides contribute to sodium and water retention leading to decompensation of chronic heart failure.

Pulmonary Edema

The flux of fluid out of any vascular bed results from the sum of forces promoting extravasation of fluid from the capillary lumen versus forces acting to retain intravascular fluid. This concept of a dynamic equilibration between opposing forces in the lung is given mathematical expression in the Starling equation:¹¹

$$Q_f = K_f (P_v - P_{int}) - K_f (P_v - p_{int})$$

Table 24-1. Classification of Acute Pulmonary Edema

Cardiogenic Pulmonary Edema	
A. Acute Increase in Pulmonary Capillary Pressure	b. Volume load imposed on preexisting LV diastolic dysfunction
1. Increased LA pressure with normal LV diastolic pressure	i. Worsening mitral regurgitation
a. Thrombosed prosthetic mitral valve	ii. Vigorous postoperative fluid administration
b. Obstructive left atrial myxoma	iii. Dietary indiscretion
2. Increased LA pressure owing to elevated LV diastolic pressure	c. Pressure load imposed on preexisting LV systolic dysfunction
a. Acute increases in myocardial stiffness or impaired relaxation	i. Accelerated hypertension
i. Myocardial ischemia	
ii. Acute myocardial infarction	Noncardiogenic Pulmonary Edema
iii. Hypertrophic heart disease complicated by tachycardia or ischemia	A. Altered Alveolar Capillary Membrane Permeability (Adult Respiratory Distress Syndrome)
b. Acute volume load	1. Infectious or aspiration pneumonia
i. Acute mitral or aortic regurgitation	2. Septicemia
ii. Ischemic septal rupture	3. Acute radiation or hypersensitivity pneumonitis
c. Acute pressure load	4. Disseminated intravascular coagulopathy
i. Hypertensive crisis	5. Shock lung
ii. Thrombosed prosthetic aortic valve	6. Hemorrhagic pancreatitis
B. Exacerbation of Chronically Elevated Pulmonary Capillary Pressures	7. Inhaled and circulating toxins
1. Increase in elevated LA pressure with normal LV diastolic pressure	8. Massive trauma
a. Mitral stenosis	B. Acute Decrease in Interstitial Pressure of the Lung
b. Left atrial myxoma	1. Rapid removal of unilateral pleural effusion
2. Increase in elevated LA pressure owing to a further increase in LV diastolic pressure	C. Unknown Mechanisms
a. Further increases in myocardial stiffness or impaired relaxation	1. High-altitude pulmonary edema
i. Cardiomyopathy complicated by myocardial ischemia or infarction	2. Neurogenic pulmonary edema
ii. Hypertrophic heart disease complicated by tachycardia or ischemia	3. Narcotic overdose
	4. Pulmonary embolism
	5. After cardioversion
	6. After anesthesia or cardiopulmonary bypass

LA, left atrial; LV, left ventricular.

where Q_f is net transvascular fluid flow across the pulmonary capillary endothelium; K_f is filtration coefficient of the microvascular endothelium (hydraulic conductivity of the capillary wall $\times$ surface area); P_v is hydrostatic pressure in the pulmonary capillaries; P_{int} is hydrostatic pressure in the pulmonary interstitium; p_V is plasma protein oncotic pressure; and p_{int} is protein oncotic pressure within the interstitial space.

Under normal conditions, the sum of the forces is slightly positive, producing a small vascular fluid flux into the precapillary interstitium of the lung that is drained as lymph into the systemic veins. The capillary coefficient (K_f) determines the effectiveness of the endothelial barrier to protein permeability, and so determines the effectiveness of the oncotic gradient. Because the intravascular pressure in the pulmonary capillaries is always higher than plasma osmotic pressure, transcapillary

fluid flux out of the pulmonary capillary is continuous. When the interstitial fluid exceeds the interstitial space capacity, fluid floods into the alveoli.¹² The interstitial space is drained by a rich bed of lymphatics. It is estimated that pulmonary lymph flow may increase threefold before fluid extravasates into the alveolar airspaces. In patients in the ICU, the two most common forms of pulmonary edema are pulmonary edema initiated by an imbalance of Starling forces and pulmonary edema initiated by disruption of one or more components of the alveolar-capillary membrane. Table 24-1 lists the causes of pulmonary edema based on the initiating mechanism.

It has been shown experimentally that pulmonary edema occurs if the pulmonary capillary pressure exceeds the plasma colloid osmotic pressure, which is approximately 28 mm Hg in humans. The normal pulmonary capillary wedge pressure

is approximately 8 mm Hg, which allows a margin of safety of about 20 mm Hg in the development of pulmonary edema.¹³ Although pulmonary capillary pressure must be abnormally high to increase the flow of the interstitial fluid, these pressures may not correlate with the severity of pulmonary edema when edema is clearly present.¹⁴ These pressures may have returned to normal when there is still considerable pulmonary edema because time is required for removal of interstitial and pulmonary edema.

The rate of increase in lung fluid at any given elevation of pulmonary capillary pressure is related to the functional capacity of the lymphatics, which may vary from patient to patient, and to variations in osmotic and hydrostatic pressures. Chronic elevations in left atrial pressures are associated with hypertrophy in the lymphatics.¹⁵ These lymphatics clear greater quantities of capillary filtrate during acute increases in pulmonary capillary pressure. Clinical experience with patients who have chronically elevated atrial pressures suggests that these patients show minimal or no evidence of interstitial lung edema. The mechanisms by which pulmonary capillary pressure increases when the pumping ability of the ventricle is suddenly impaired are discussed later.

When the alveolar-capillary membrane is injured, proteins leak from the capillary into the interstitium, reducing the oncotic counterpressure tendency to oppose capillary filtration. Interstitial edema and the consequent alveolar edema formation can occur in the presence of low hydrostatic pressures.

Determinants of Left Ventricular Pump Performance

Cardiac output equals the heart rate multiplied by the stroke volume. The stroke volume is the volume of blood ejected with each heartbeat; the magnitude of the stroke volume is governed by ventricular loading conditions and the contractile state of the myocardium. The factors involved in regulating cardiac output are discussed in Chapter 6. The following discussion briefly reviews the determinants of left ventricular (LV) pump performance as it pertains to a patient with AHF.

Preload

Preload is the force or load acting to stretch the LV fibers at the end of diastole, determining the resting length of the sarcomeres.¹⁶ Preload expressed in terms of LV end-diastolic pressure or volume (i.e., dimension) is common, but neglects the confounding influence of the complex geometry of the left ventricle.¹⁷ Preload is probably best measured as end-diastolic wall stress because this reflects the interactions between transmural diastolic pressures, ventricular dimensions, and wall thickness. The level of ventricular preload is influenced by multiple variables, including chamber compliance, overall LV performance, intravascular blood volume and venous return, atrial contribution to ventricular filling, intrapericardial and intrathoracic pressures, right ventricular-LV interaction, and pericardial restraint.¹⁸

Because preload determines the end-diastolic fiber length, it is a major determinant of systolic performance. This phenomenon is generally referred to as Starling's law of the heart. The ability of the heart to increase performance using the Starling mechanism (i.e., preload reserve) is limited by the inherent stiffness of the myocardium. In compliant, normal hearts, the preload reserve is an effective mechanism to increase the stroke volume, but in hypertrophied hearts or in hearts that are already

at the limits of their preload reserve (i.e., end-stage heart failure), stroke volume cannot be substantially increased by this mechanism. When the heart operates on the steep portion of the diastolic pressure-volume curve, small increments in LV volumes are associated with large changes in filling pressures. In other words, large increases in filling pressures are required for a small increase in end-diastolic volume.

Myocardial relaxation is also an important determinant of the fiber length at end-diastole. Impaired relaxation shortens the time available for diastolic filling, and may interfere with fiber stretch when relaxation is markedly prolonged or when the heart rate is rapid. As a result, the force acting to stretch the myocardial fiber is opposed by incomplete relaxation at end-diastole.

Afterload

Afterload is the force opposing fiber shortening after the onset of ejection.¹⁶ This force or stress is not constant because arterial and ventricular pressure changes during ejection. Even if the pressure were constant, the systolic force that the ventricle develops would vary in accordance with a complex relationship between the wall force, ventricular pressure, and ventricular dimension.¹⁹ According to the Laplace equation, wall stress (s) is directly proportional to ventricular systolic pressure (P) and radius (R), and is inversely related to wall thickness (h):

$$s = PR / 2h$$

An increase in wall stress because of an increase in ventricular pressure, an increase in ventricular dimension, inadequate hypertrophy, or any combination of these results in decreased myocardial fiber shortening. Because there has been insufficient time for compensatory hypertrophy to develop in patients with AHF, ventricular pump performance is particularly sensitive to changes in afterload.

Preload and afterload are intimately related. When LV preload is increased in a normal heart, systolic LV pressures generally increase, and as a result systolic wall stress (afterload) increases. Likewise, a decrease in afterload promotes LV emptying, which leads to a decrease in preload.

Contractility

Contractility, or inotropic state, is defined as the property of myocardial fibers that determines the extent of shortening independent of loading conditions. Compared with the control state, a positive inotropic intervention (e.g., epinephrine) increases myocardial fiber shortening and stroke volume at any given preload and afterload. A negative inotropic intervention (e.g., β -blocker) has the opposite effect. For any given increment in afterload, shortening and stroke volume decrease to a greater extent when the contractile state is depressed. Conversely, afterload reduction has a small effect on increasing shortening and stroke volume during a positive inotropic intervention.

Heart Rate

Heart rate affects cardiac output under resting conditions and during exercise. When the heart rate increases, the time available for filling during diastole is substantially abbreviated. When LV diastolic compliance is decreased, tachycardia can produce a decrease in ventricular preload that leads to reduced LV stroke volume despite normal systolic function. In hearts with impaired relaxation (i.e., hypertrophied hearts), a significant increase in

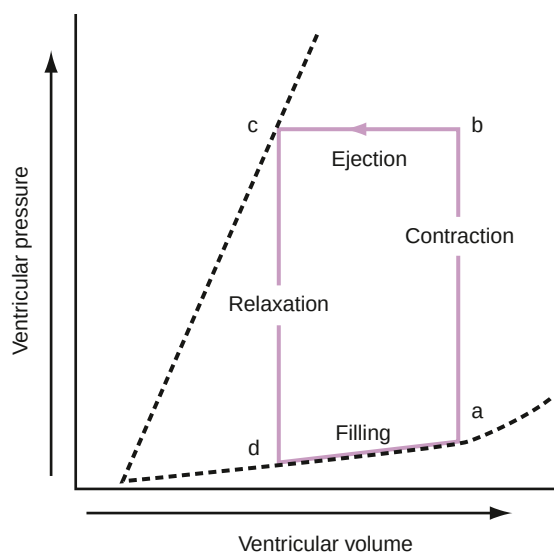


Figure 24-1. Schematic representation of the left ventricular (LV) pressure-volume loop. The aortic valve opens at *b* and closes at *c*. The mitral valve opens at *d* and closes at *a*. The slope of the *broken line* through *c* represents the end-systolic pressure-volume relationship ($E_{\max}$), and the *broken line* through *d* and *a* represents the end-diastolic-volume relationship. As contractile force develops in the left ventricle (LV) in systole, the pressure rapidly increases in the ventricular chamber (*a* → *b*) without changing its volume (i.e., isovolumic phase of systole). When the pressure exceeds the diastolic aortic pressure, the aortic valve opens, and the ventricle ejects its contents into the arterial circulation (*b* → *c*, the ejection phase of systole). At the end of ejection (point *c*), LV pressure decreases, and the aortic valve closes. Pressure rapidly declines at a constant volume (*c* → *d*, isovolumic relaxation) to levels below that of the left atrium. At this point, the mitral valve opens (point *d*), and the relaxing LV fills along the segment *d* → *a*. The trajectory *a* → *b* → *c* represents the contractile or inotropic function of the LV at any given end-diastolic volume, whereas the trajectory *c* → *d* → *a* represents the lusitropic function (relaxation and filling) of the heart at any given end-systolic pressure. The area within the loop graphically depicts the external work (i.e., stroke work) of the ventricle.

heart rate would cause LV filling to occur at the time when the heart is not completely relaxed, which results in increased LV diastolic pressures. In patients with abnormal hearts, tachycardia may cause an exaggerated decrease in stroke volume and an increase in filling pressures.

The normal heart responds to an increase in heart rate by a positive inotropic effect, also known as the *treppe* or *Bowditch phenomenon*.²⁰ In a failing or hypertrophied heart, an increase in heart rate may produce a reduction in, or even a reversal of, the normally positive force-frequency effect.^{21,22} Tachycardia is also likely to increase myocardial oxygen consumption, which may lead to subendocardial ischemia in a heart with a compromised coronary circulation.

Left Ventricular Pressure-Volume Relationships

To appreciate fully the factors that contribute to AHF, it is appropriate to review briefly the pressure-volume relationships of normal and diseased hearts. The relationship between pressure and volume throughout the cardiac cycle can be presented as a pressure-volume loop (Fig. 24-1). The pressure-volume loop encapsulates the systolic and diastolic functions of the heart. Because these loops also circumscribe end-systolic and

end-diastolic volumes, the stroke volume and ejection fraction can be derived. The bottom limb of the loop, called the diastolic pressure-volume curve, describes LV diastolic compliance. The pressure-volume loop can provide a simple but comprehensive description of LV pump function.

Progressive increases in systolic pressure produce a nearly linear increase in end-systolic volume. By matching the end-systolic pressure and volume coordinates from multiple, variably loaded beats, a near-linear relationship is established. The slope of this relationship ($E_{\max}$), determined by altering load, reflects LV contractility (see Fig. 24-1).²³ A positive inotropic intervention is associated with an increased end-systolic pressure and stroke volume and a decreased end-diastolic volume; this results in an increased $E_{\max}$ and a shift of the pressure-volume relationship to the left (Fig. 24-2A). Conversely, a negative inotropic intervention decreases end-systolic pressure and stroke volume and increases end-diastolic volume; this results in a decrease in $E_{\max}$ and a shift of the pressure-volume relationship to the right (Fig. 24-2B).

In the intact human heart, an increase in systolic pressure is associated with an increase in end-systolic volume, and if preload does not increase, stroke volume decreases (Fig. 24-3A). An increase in preload is accompanied by an increase in stroke volume and a modest increase in end-systolic pressure (Fig. 24-3B). Acute and chronic changes in the pressure-volume relationship in the failing heart depend on the underlying myocardial structure and function, the type and extent of injury (e.g., infarction or myocarditis, regional or global myocardial depression), and the severity and nature of the hemodynamic load (pressure versus volume).

Chamber Stiffness

Chamber stiffness is determined by analyzing the curvilinear diastolic pressure-volume relationships (Fig. 24-4). The slope of the tangent (dP/dV) to this curvilinear relationship defines the chamber stiffness at a given filling pressure. An increase in dP/dV because of an increase in volume, shown in Figure 24-4 (A → B), has been called a preload-dependent change in stiffness. When the pressure-volume relationship shifts to the left (A → C), the tangent is steeper at the same diastolic pressure. The latter may be caused by an increase in myocardial mass or intrinsic myocardial stiffness or by changes in several extramycocardial factors. Chamber stiffness of the left ventricle is determined by static factors (e.g., chamber volume, wall mass, stiffness of the wall) and dynamic factors (e.g., pericardium, right ventricle, myocardial relaxation, erectile effects of the coronary vasculature).^{18,24} Most acute alterations in LV chamber stiffness result from a preload-dependent increase in chamber stiffness, a shift to a different pressure-volume curve, or a combination of the two. All can result in elevated left atrial pressures, pulmonary venous hypertension, and the signs and symptoms of acute heart failure.

Compensatory Mechanisms in Acute Heart Failure

Decreases in blood pressure and cardiac output after an acute depression of LV pump performance cause rapid activation of neurohormonal systems, which generate an acute increase in heart rate and arterial resistance and a decrease in capacity of the venous system.^{25,26} The decreased systemic vascular capacity after sympathetic activation is brought on predominantly by changes in the splanchnic vascular bed that result in a leftward

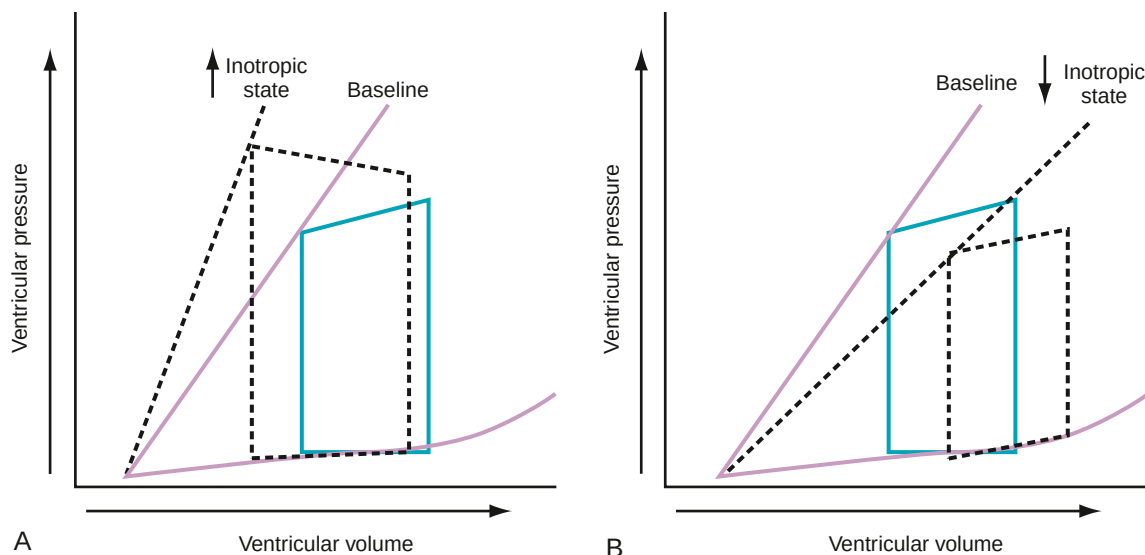


Figure 24-2. Schematic diagrams illustrating the effects of inotropic interventions on the pressure-volume loop. **A**, With a positive inotropic intervention, the pressure-volume loop (*broken line*) is shifted to the left, and the slope of the end-systolic pressure-volume line is increased. **B**, With a negative inotropic intervention, the pressure-volume loop is shifted to the right, and the slope of the end-systolic pressure-volume line is decreased.

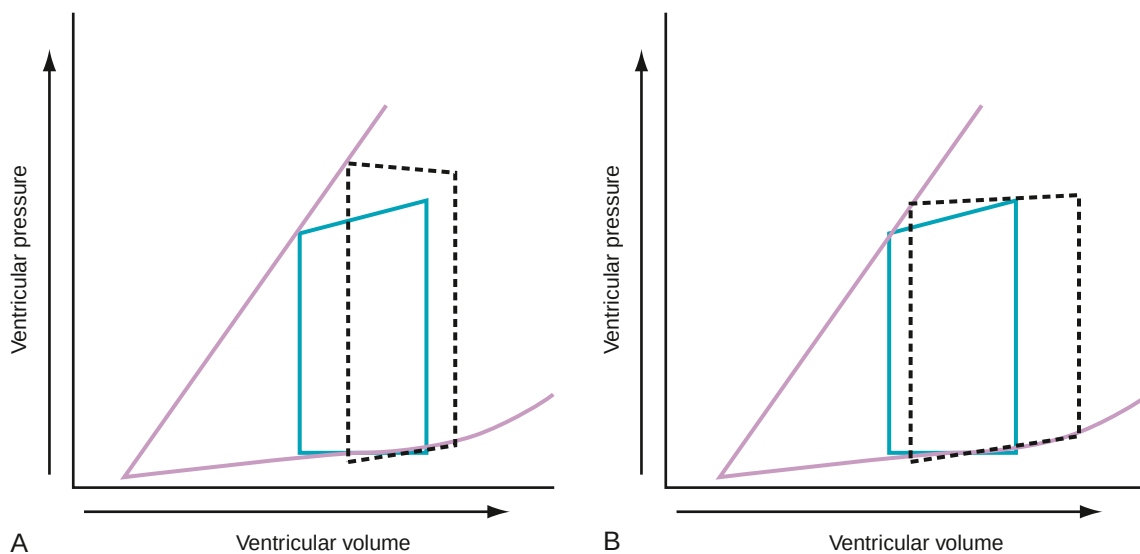


Figure 24-3. Schematic diagrams illustrating the effects of changing loading conditions on the pressure-volume loop in the intact heart. **A**, An increase in afterload shifts the pressure-volume loop (*broken line*) to the right, increasing the end-systolic and end-diastolic volumes and the end-systolic and end-diastolic pressures, while decreasing the stroke volume. The slope of the end-systolic pressure-volume line is usually not affected by a pure change in afterload. **B**, An increase in preload also shifts the pressure-volume loop (*broken line*) to the right, increasing the end-diastolic volume and end-diastolic pressure. The increase in preload may be associated further with a small increase in end-systolic volume and a modest increase in end-systolic pressure, but in contrast to the case with an increase in afterload, the stroke volume increases. Similar to an increase in afterload, the slope of the end-systolic pressure-volume line is not affected by a change in preload.

shift of the venous pressure-volume relationship, causing a redistribution of blood from the unstressed to the stressed circulating pool (i.e., central blood pool).²⁷

Hemodynamic Examples of Acute Heart Failure Syndromes

During the hyperacute phase of myocardial infarction (MI) or with acute ischemia, reduced ventricular ejection increases end-systolic volume (residual volume), and reduced LV compliance

increases the filling pressures. It is thought that the lusitropic dysfunction results from an increase in stiffness in the ischemic myocardial segment (possibly caused by slowing and incompleteness of the relaxation process)²⁸ and dilation of the nonischemic segment, causing a preload-dependent increase in chamber stiffness.²⁹ The increase in LV filling pressure that occurs with acute infarction or ischemia is caused by the combination of a preload-dependent increase in chamber stiffness and a leftward shift of the diastolic pressure-volume curve.

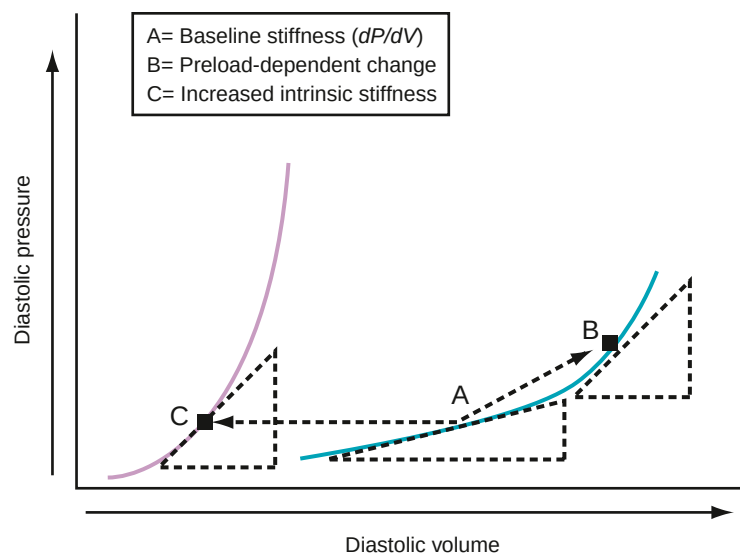


Figure 24-4. Schematic diagram of the diastolic left ventricular pressure-volume curve. The slope of the tangent (dP/dV) to this curvilinear relationship defines chamber stiffness at a given filling pressure. An increase in dP/dV owing to an increase in volume, shown diagrammatically as $A \rightarrow B$, has been termed a preload-dependent change in stiffness. When the pressure-volume relationship shifts to the left, $A \rightarrow C$, the tangent is steeper (increased chamber stiffness) at the same diastolic pressure.

Increased diastolic pressures after an acute ischemic insult may also result from the redistribution of blood from the periphery to the central blood pool. The effects of these changes on the pressure-volume relationship are shown in Figure 24-5A.

With acute volume overload, as seen in patients with acute mitral or aortic regurgitation or after ischemic septal rupture, the left ventricle dilates and operates on a steeper portion of its pressure-volume curve. Consequently, small increments in volume result in a marked increase in filling pressures. The effects of these changes on the pressure-volume relationship are shown in Figure 24-5B.

The lusitropic abnormalities of LV hypertrophy secondary to aortic stenosis, severe hypertension, or hypertrophic cardiomyopathy probably are caused by abnormalities of the static and dynamic determinants of chamber stiffness. Increased passive stiffness of the hypertrophied heart results in part from the increased myocardial mass and the low volume-to-mass ratio; abnormal intrinsic myocardial stiffness also may contribute to increased chamber stiffness. Abnormalities of myocardial relaxation further impair filling in the hypertrophied heart. The effects of these changes on the pressure-volume relationship are shown in Figure 24-5C.

Chronic heart failure is characterized by a compressed pressure-volume loop. This compressed loop, characterized by a decrease in end-systolic pressure and an increase in end-diastolic pressure, means that the work of the failing heart is reduced, while maintaining a near-normal stroke volume. Comparable to the changes with ischemia, the elevated filling pressures in chronic heart failure probably are caused by a combination of a preload-dependent increase in chamber stiffness (i.e., left ventricle operates at higher end-diastolic volumes to optimize the Starling relationship) and a preload-independent increase in chamber stiffness (Fig. 24-5D). It should also be evident from the pressure-volume curve that these hearts operate near the limit of their preload reserve; they are extremely vulnerable to any myocardial insult. Even a minor insult, such as

an arrhythmia, infection, or a small area of infarction, is likely to precipitate acute decompensation in these patients.

Clinical Presentation of Acute Heart Failure

The clinical presentation of AHF is largely related to the degree of fluid overload. The onset and severity of symptoms of AHF vary, and depend importantly on the nature of the underlying cardiac disease and the rate at which the syndrome develops. Patients with AHF have worsening chronic heart failure (70% of all cases), present with heart failure for the first time (25%), or present with advanced or end-stage heart failure—patients who do not respond to treatment (5%). A few patients with AHF present with low blood pressure (<8%) or shock (<3%).³⁰ Most patients are elderly, with an average age of approximately 75 years. The heterogeneity of this patient population is evident when one considers that almost all of these patients have preserved LV ejection fraction, 70% have a history of systemic hypertension, 60% have documented coronary artery disease, 45% have had a prior MI, 30% have a history of atrial fibrillation, 40% have diabetes mellitus, and 30% have underlying chronic obstructive pulmonary disease.³⁰ Secondary mitral regurgitation is common. A patient with AHF may have one of several distinct clinical conditions, as described next.

Decompensation of Chronic Heart Failure

Normotensive Decompensation

Normotensive decompensation occurs in patients with an established diagnosis of heart failure who develop increasing signs or symptoms of decompensation after a period of relative stability. This scenario accounts for greater than 70% of all admissions with heart failure. These patients are usually normotensive. Progressive dyspnea is the most common complaint of patients presenting with decompensated chronic heart failure.

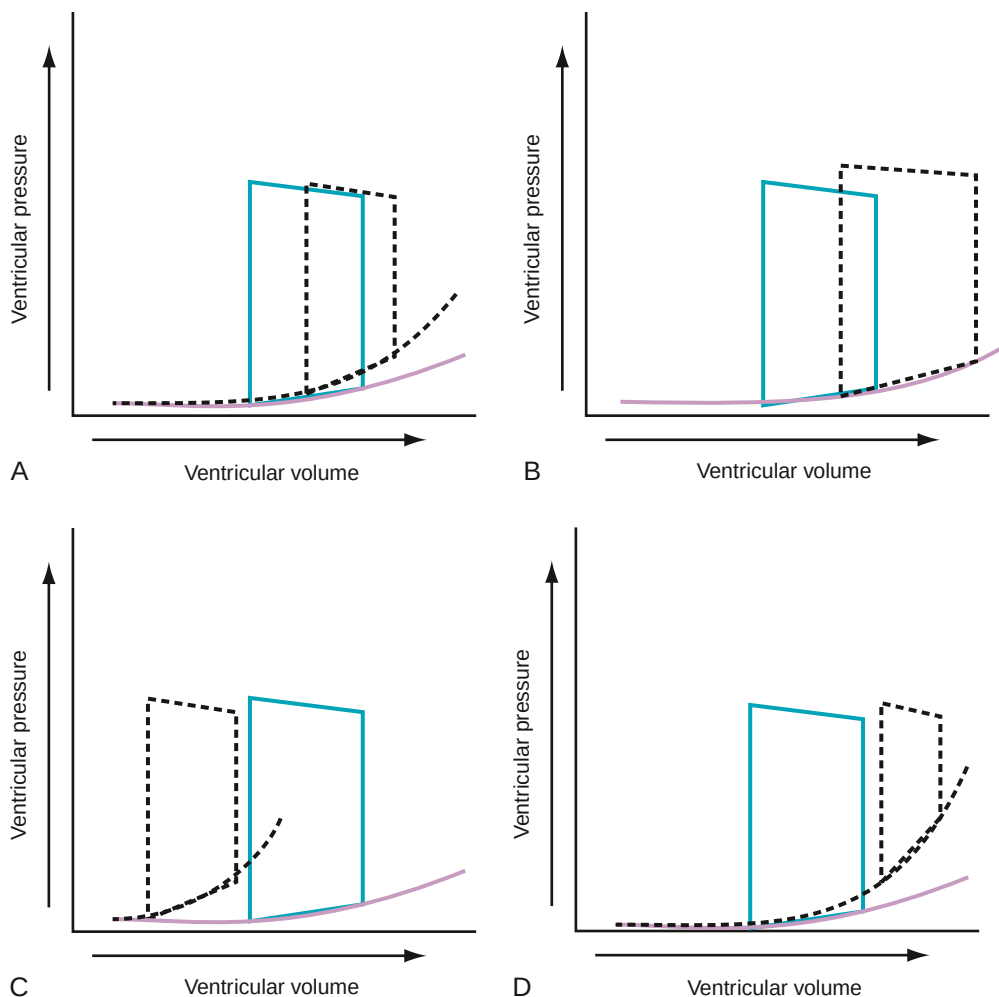


Figure 24-5. Schematic diagrams of four different pathophysiologic states. In each diagram, the control pressure-volume loop and the diastolic pressure-volume relationship (curve) are shown in *solid lines*, and the effects of different pathologic states on the pressure-volume relationship are depicted by the *broken lines*. **A**, With acute ischemia or infarction, the pressure-volume curve is shifted upward and to the right. **B**, In a volume-overloaded heart (i.e., valvular regurgitation), the pressure-volume relationship is shifted to the right along the same diastolic pressure-volume relationship. The increase in diastolic pressure is the result of the left ventricle operating on the steeper portion of the diastolic pressure-volume relationship. **C**, With excessive hypertrophy, the pressure-volume relationship is shifted to the left, so that the heart operates at smaller end-diastolic and end-systolic volumes. The increase in chamber stiffness is reflected by the steep diastolic pressure-volume curve. **D**, In chronic advanced heart failure, the pressure-volume loop is often compressed and shifted to the right. This compressed loop, characterized by a lower end-systolic and increased end-diastolic pressure, implies that the work of the heart is reduced, while maintaining a near-normal stroke volume. Comparable to the situation in **A**, the elevated diastolic pressure is caused by preload-dependent and preload-independent increases in chamber stiffness.

The exaggerated uncomfortable awareness of breathing is usually manifest with mild exertion, or even at rest. These patients are often orthopneic. This orthopnea may become so severe that patients cannot lie down at all and must spend the entire night in a sitting position. In addition, some patients experience episodes of paroxysmal nocturnal dyspnea, which usually begins 2 to 4 hours after the onset of sleep and is associated with marked dyspnea followed by coughing, wheezing, and sweating. Family members occasionally report the presence of periodic respiration or cyclic respiration, characterized by periods of apnea followed by hyperventilation (Cheyne-Stokes respiration). This breathing pattern is often a sign of advanced heart failure.

Patients may report ankle swelling and epigastric tenderness or a sensation of abdominal fullness. Abdominal tenderness is

often due to hepatic congestion and distention of the hepatic capsule. With severe hepatic congestion, the patient may also complain of nausea and anorexia. Other symptoms include nocturia and neurologic symptoms such as confusion, headaches, insomnia, anxiety, disorientation, and impaired memory.

Physical signs vary according to the severity of heart failure and the predominant hemodynamic abnormality. An elevated jugular venous pressure, a positive hepatojugular reflux test, and a tender enlarged liver are frequent findings in these patients. Important physical examination findings include inspiratory, crepitant rales over the lung bases. Rales and wheezing may be heard widely over both lung fields in patients with significant pulmonary congestion. The absence of rales does not imply that the pulmonary venous pressures are not elevated. Diminished

air entry at the lung bases is usually caused by a pleural effusion, which is often more frequent in the right pleural cavity than in the left. Leg edema is frequently evident in both legs, particularly in the pretibial region and ankles in ambulatory patients. Sacral edema can be detected in patients who are bedridden.

The cardiac examination may be entirely normal in patients with heart failure secondary to diastolic dysfunction, whereas most patients with advanced systolic dysfunction exhibit a third heart sound and a laterally displaced apex beat. A murmur of mitral regurgitation is often present when the left ventricle is markedly enlarged, or a tricuspid regurgitation murmur is present when the right ventricle is volume or pressure overloaded. These patients often do not have clinical or radiographic signs of marked pulmonary edema.

Hypotensive Decompensation

Systolic blood pressure is less than 90 mm Hg in 8% of patients with decompensated chronic heart failure. Low output heart failure is characterized by symptoms and signs that are related to decreased end-organ perfusion. A typical patient with this clinical syndrome has severely impaired LV function and usually presents with symptoms of fatigue, altered mental status, or signs of organ hypoperfusion, such as prerenal azotemia or abnormal hepatic enzymes. The patient may present with tachypnea at rest, tachycardia, and a cold and cyanotic periphery. The degree of peripheral hypoperfusion may be so advanced that the skin over the lower extremities is mottled and cool. A diminished pulse pressure, consistent with a reduced stroke volume, is often found in patients with AHF. Occasionally, the clinician may detect pulsus alternans—when a strong or normal pulse alternates with a weak pulse during normal sinus rhythm. This physical finding is rare, but when present is a sign of severe LV dysfunction.

Acute Heart Failure

The syndrome of AHF is characterized by a sudden onset of symptoms or signs of heart failure. AHF occurs when there is an acute change in LV systolic or diastolic function, or in the structural integrity of the valves. It most often is related to hypertension. Other causes are acute MI, ischemic mechanical complications such as papillary muscle rupture, fulminant myocarditis, or severe acute valvular regurgitation in the setting of infective endocarditis.

More than 50% of patients who present with classic signs and symptoms of heart failure have an elevated blood pressure on admission.³⁰ There is usually predominant pulmonary rather than systemic congestion. Many patients have a normal LV ejection fraction. Blood pressure elevation could develop rapidly and is likely related to increased filling pressures and enhanced sympathetic tone. Early and aggressive blood pressure control is an important goal in patients with hypertensive AHF.

Acute Heart Failure with Severe Pulmonary Edema

Severe pulmonary edema is seen in less than 3% of all patients admitted with AHF.³⁰ Patients typically experience a sudden and overwhelming sensation of suffocation and air hunger; this is invariably accompanied by extreme anxiety, cough, expectoration of a pink frothy liquid, and a sensation of drowning. The patient sits bolt upright, is unable to speak in full sentences, and may thrash about. The respiratory rate is increased, the alae nasi are dilated, and there is inspiratory retraction of the intercostal

spaces and supraclavicular fossae. Respiration is often noisy, and there may be audible inspiratory and expiratory gurgling sounds. An ominous sign is obtundation, which may be a sign of severe hypoxemia. Sweating is profuse, and the skin tends to be cool, ashen, and cyanotic, reflecting a low cardiac output and increased sympathetic outflow.

The blood pressure and pulse rate are most often elevated secondary to an increased adrenergic drive. When the blood pressure is found to be markedly elevated, it is more likely to be the cause of, or an important contributing factor to, pulmonary edema, rather than the consequence of the condition. The oxygen saturation is usually less than 90% on room air before treatment. Auscultation of the lung usually reveals coarse airway sounds bilaterally with rhonchi, wheezes, and moist fine crepitant rales that are detected first at the lung bases, but then extend upward to the apices as the lung edema worsens. Cardiac auscultation may be difficult in the acute situation, but third and fourth heart sounds may be present. When valvular abnormalities or mechanical complications after MI result in acute heart failure, the murmurs of mitral and aortic regurgitation and the systolic murmur of ischemic septal rupture are often audible, but detection requires a careful and skillful auscultator.

Diagnosis and Evaluation of Acute Heart Failure

There are three key elements to consider when evaluating a patient with AHF: (1) the rapid diagnosis of AHF is necessary to initiate appropriate treatment, (2) early evaluation and treatment is linked to outcome, and (3) risk stratification may aid the appropriate triage of the patient.

Diagnosis

The diagnosis of decompensated chronic heart failure is generally not problematic, especially when a patient presents with the triad of fluid retention, exertional dyspnea, and history of heart failure. Some observations should be kept in mind, however. Worsening exertional dyspnea could also be due to a range of other conditions, including pulmonary embolism, pneumonia, chronic obstructive pulmonary disease, asthma, pulmonary fibrosis, pleural effusion, anemia, hyperthyroidism, and musculoskeletal disorders.

For patients without a prior cardiac history, the diagnosis of AHF should be based primarily on signs and symptoms according to the Heart Failure Society of America.³¹ When the diagnosis is uncertain, determination of plasma B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration should be considered in patients being evaluated for dyspnea who have signs and symptoms compatible with AHF. The natriuretic peptide concentration should not be interpreted in isolation, but in the context of all available clinical data bearing on the diagnosis of AHF.³¹ The Task Force on Acute Heart Failure of the European Society of Cardiology⁴ emphasizes that the diagnosis of AHF is based on the symptoms and clinical findings, supported by appropriate investigations, such as electrocardiogram (ECG), chest x-ray, biomarkers, and Doppler echocardiography.

There is considerable overlap in BNP and NT-proBNP levels in patients with and without heart failure, which makes the test

Table 24-2. Differentiation of Noncardiogenic from Cardiogenic Pulmonary Edema Based on Clinical Data

	Noncardiogenic	Cardiogenic
History	Underlying disease (e.g., pancreatitis, sepsis)	Acute cardiac event (e.g., myocardial infarction)
Physical examination	Warm periphery Bounding pulses Normal-sized heart Normal JVP No S ₃ No murmurs	Cool, mottled periphery Small-volume pulse Cardiomegaly Elevated JVP S ₃ Systolic and diastolic murmurs
ECG	ECG usually normal	ST segment and QRS abnormalities
Chest x-ray film	Peripheral infiltrates	Perihilar infiltrates
Laboratory test	Normal enzymes BNP <100 mg/mL	Elevated biomarkers
Ventilatory needs	Higher Fio ₂ and PEEP to oxygenate	Lower Fio ₂ and PEEP to oxygenate

BNP, brain natriuretic peptide; Fio₂, inspired oxygen concentration;

JVP, jugular venous pressure; PEEP, positive end-expiratory pressure.

Adapted from Sibbald WJ, Cunningham DR, Chin DN: Non-cardiac or cardiac pulmonary edema? A practical approach to clinical differentiation in critically ill patients. *Chest* 1983;84:452-461.

less robust in an individual patient with intermediate levels of BNP (approximately 200 to 400 pg/mL). Because many conditions increase BNP levels, low values of BNP (<100 pg/mL) are most useful because they make the diagnosis of decompensated heart failure very unlikely as an explanation for dyspnea.³² Decision analysis suggests that BNP testing is generally most useful in patients who have an intermediate probability of heart failure.³¹ AHF remains a clinical syndrome that is characterized by a constellation of symptoms owing to a heterogeneous group of cardiac and vascular disorders, whose diagnosis cannot be based on a single laboratory test. Results of BNP testing must be interpreted in the context of the overall clinical evaluation, and such testing must support rather than override careful clinical judgment.

Differentiating Cardiogenic from Noncardiogenic Pulmonary Edema

It is crucial to establish whether respiratory failure (pulmonary edema) is due to cardiogenic or noncardiogenic causes. This distinction can invariably be made by assessment of the clinical context in which it occurs and through examination of the clinical data available (Table 24-2). The clinical data include tests that are routinely done on all critically ill patients, such as ECG, blood gas analysis, blood count, electrolytes, and chest x-ray.

Noncardiogenic pulmonary edema (NCPE) is invariably associated with an underlying disease, which may or may not be readily apparent. The diagnosis of NCPE often depends on

pretest probabilities: acute respiratory distress in a patient with documented sepsis (i.e., peritonitis) or pancreatitis should raise the strong possibility that the respiratory failure is due to NCPE. In contrast to cardiogenic pulmonary edema (CPE), NCPE is uncommonly associated with a well-defined acute cardiac event (i.e., MI). Subtle physical signs may also aid in differentiating NCPE from CPE. NCPE is usually a hyperdynamic illness, clinically apparent as a warm, vasodilated periphery, whereas CPE is frequently associated with a cold and sweaty periphery. The findings of a third heart sound or murmurs of aortic and mitral regurgitation and aortic stenosis may suggest a cardiogenic cause of pulmonary edema.

ST segment changes on ECG consistent with MI or myocardial ischemia would suggest an acute cardiac event as the cause of the pulmonary edema. Also, ECG evidence of LV strain, left bundle branch block, or other abnormalities of the QRS complex might indicate an underlying cardiac pathology. Unless there are major metabolic disturbances, the ECG is usually normal in patients with pure NCPE.

In NCPE and CPE, arterial hypoxemia is due to changes in the ventilation-perfusion ratio and in extent of intrapulmonary shunting. Patients with NCPE usually have a more pronounced defect in oxygenation than is seen in patients with CPE. This is largely due to the greater shunt fractions found in these patients. In the clinical setting, higher concentrations of inspired oxygen concentrations (Fio₂) and larger positive end-expiratory pressures are required to achieve acceptable oxygenation in NCPE compared with CPE.

Similar to other tests, the chest x-ray may be helpful to differentiate NCPE from CPE. With NCPE, the alveolar and interstitial disease might show a predominant peripheral distribution, whereas in CPE, a perihilar distribution is more evident, often associated with Kerley lines or pleural effusions or both. Heart size is more commonly increased in CPE than NCPE, but the lack of cardiomegaly does not exclude CPE. In most patients, the chest x-ray proves to be of little help; this is due partially to the fact that patients are often too ill to be examined by anything other than a portable unit, and such films are usually of sub-optimal interpretive quality. An example of acute CPE and less severe pulmonary congestion is shown in Figure 24-6.

When the cause of pulmonary edema is clearly evident from the clinical data (i.e., MI), no further diagnostic tests are needed. If there is still uncertainty regarding the etiology of the pulmonary edema, further diagnostic tests are appropriate. BNP level of less than 100 pg/mL or NT-proBNP level of less than 300 mg/mL effectively rules out a cardiac cause for respiratory failure. Elevated BNP levels are found in patients with pulmonary hypertension, cor pulmonale, pulmonary emboli, and compensated heart failure. BNP levels are also higher in women, older patients, and patients with renal failure.³³ More recent data have shown that BNP and NT-proBNP values are similarly elevated in patients with severe sepsis or septic shock and AHF, independently of whether they presented with or without shock.³⁴

Clinical judgment is still required to differentiate CPE from NCPE. An echocardiogram should be obtained in all patients with pulmonary edema in whom the cause of pulmonary edema is unclear. Normal Doppler echocardiography assessments of systolic and diastolic function strongly point toward a noncardiogenic cause of respiratory failure. If uncertainty persists, it is reasonable to obtain hemodynamic information via a pulmonary artery balloon flotation catheter to differentiate CPE from

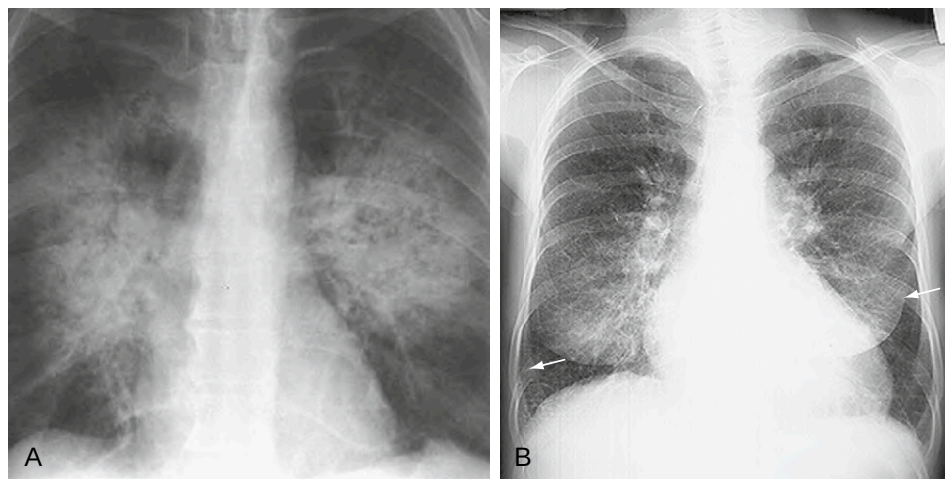


Figure 24-6. Chest x-rays of two patients. **A**, The classic features of acute cardiogenic pulmonary edema. Notice the perihilar alveolar infiltrates. **B**, Marked interstitial changes in the lung bases. Note the Kerley B lines (arrow).

NCPE. With the availability of BNP levels and two-dimensional Doppler echocardiography, however, there seems to be less need to proceed with pulmonary artery balloon flotation catheter placement.

Evaluation and Triage of Patients with Acute Heart Failure

Early Assessment

After the diagnosis of AHF has been established, the initial focus is to ensure optimal oxygenation. Several steps are necessary to evaluate a patient with AHF comprehensively.

Step 1: Define Clinical Severity of Acute Heart Failure

Several grading classifications of the severity of AHF have been in place for many years in coronary care units and ICUs. The Killip classification, based on clinical signs and chest x-ray findings,³⁵ and the Forrester classification, based on clinical signs and hemodynamic characteristics,³⁶ are discussed elsewhere. These classifications have been validated in AHF after acute MI and are most applicable for patients with new-onset AHF. Other authors have proposed a straightforward clinical tool for classifying the severity of chronic decompensated heart failure. This assessment is based on observation of the peripheral circulation (perfusion—warm or cold) and on auscultation of the lungs (congestion—wet or dry). Patients can be classified as warm and dry, warm and wet, cold and dry, and cold and wet.³⁷ Such categorization permits attention to specific therapies. If the patient is wet, diuretics are used.

A pragmatic approach is simply to define the severity of AHF based on oxygen requirements and blood pressure. The sickest patient is the patient with the lowest blood pressure and highest oxygen requirement. A subset of patients with decompensated end-stage heart failure present to the emergency department in occult shock and are clinically indistinguishable from patients with mildly decompensated chronic heart failure and stable heart failure.³⁸ The only parameter differentiating occult shock patients from nonshock patients is a significantly elevated lactic acid level.³⁸

In patients hospitalized with AHF, the risk of in-hospital mortality can be derived from admission clinical and laboratory

variables. A blood urea nitrogen level of 43 mg/dL or greater, serum creatinine level of 2.75 mg/dL or greater, and systolic blood pressure of less than 115 mm Hg are independent predictors of in-hospital mortality.⁸ Several other variables, such as increasing oxygen requirements in the emergency department, a history of multiple hospital admissions, chronic renal insufficiency, ECG evidence of LV hypertrophy, markedly depressed LV function, and a poor response to diuretic therapy, predict in-hospital mortality.

Step 2: Establish Etiology of Acute Heart Failure

The most common causes of AHF are listed in [Table 24-3](#). Echocardiography is an essential tool for the evaluation of the functional and structural changes underlying or associated with AHF.

Step 3: Identify Precipitating Causes of Acute Heart Failure

Precipitating causes are defined as factors that may precipitate acute decompensation in patients with underlying cardiac disease, but are unlikely to cause cardiac decompensation in a patient with a normal heart. Identifying the precipitating causes of acute hemodynamic decompensation has obvious therapeutic implications. [Table 24-4](#) lists common precipitating causes.

Step 4: Decide on Disposition of Patient

Patients with severe respiratory failure and patients in shock or preshock should be admitted to the ICU. Although no validated algorithms exist at this time to guide the clinician for triaging patients with decompensated chronic heart failure to regular floor beds or to the ICU, it seems reasonable that when three or more high-risk variables that predict mortality are present in a patient, serious consideration should be given to admit such a patient to a stepdown unit or ICU. In North America, 14% to 18% of patients with AHF are managed in ICUs.³⁹

Ongoing Evaluation of the Patient

Monitoring of a patient with AHF should be initiated as soon as possible after admission to the emergency department. The type and level of monitoring required for any individual

Table 24-3. Causes of Cardiogenic Pulmonary Edema

Myocardial disease
Coronary artery disease
Acute coronary syndrome
Severe myocardial ischemia
Mechanical complications of myocardial infarction
New infarction or ischemia and pre-existing left ventricular dysfunction
Hypertrophic heart disease
Hypertrophic cardiomyopathy
Hypertrophic heart disease of the elderly
Cardiomyopathy
Idiopathic dilated cardiomyopathy
Myocarditis
Postbypass left ventricular pump dysfunction
Valvular heart disease
Aortic regurgitation
Mitral regurgitation
Mitral stenosis
Aortic stenosis
Atrial myxoma
Hypertensive heart disease
Uncontrolled hypertension

Table 24-4. Precipitants of Heart Failure

Dietary indiscretion
Vigorous fluid administration
Noncompliance to medical regimen
Worsening renal failure
Uncontrolled hypertension
Anemia
Systemic infection
Pulmonary embolism
Myocardial ischemia
Tachyarrhythmias and bradyarrhythmias
Electrolyte disturbances
Hyperthyroidism and hypothyroidism
Cardiodepressant and other drugs
Anti-inflammatory drugs
Antiarrhythmic drugs
Calcium channel blockers
β -adrenergic blocking agents

patient vary widely depending on the severity of the cardiac decompensation and the response to initial therapy. Generally, the following parameters should be measured in all critically ill patients: blood pressure, temperature, respiratory rate, and heart rate. Some laboratory tests should be done repeatedly (i.e., electrolytes, creatinine, and glucose, or markers for infection or

Table 24-5. Monitoring Patients with Acute Heart Failure

Goals	Parameters
Arterial oxygen saturation >95%	Pulse oximetry, arterial blood gas Consider placement of an indwelling radial artery catheter
Blood pressure	Automated blood pressure recordings Frequent assessments (every 5 min) early on to assess BP response to treatment BP via indwelling radial artery catheter
Normal sinus rhythm	Continuous ECG monitoring
Adequate diuretic response	Hourly urine production, daily weight
Adequate organ perfusion	Reversal of metabolic acidosis, lactic acid levels Adequate urine output Mean BP >65 mm Hg Central venous O ₂ saturation >65%
Improved hemodynamics	Mean BP >65 mm Hg Assessment of JVP Central venous pressure line O ₂ saturation Pulmonary artery catheter*
Maintain calorie and nitrogen balance	Blood albumin concentrations Nitrogen balance
Control hyperglycemia	Glucose concentrations

*See text for more detail.

BP, blood pressure; JVP, jugular venous pressure.

other metabolic disorders). After admission to the ICU or a stepdown unit, a patient with AHF should be carefully monitored to ensure that the treatment goals are met, and continued progress is made toward a stable state; Table 24-5 summarizes these goals.

Pulmonary Artery Catheter

Controversy exists about the use of the pulmonary artery catheter in critically ill patients. The concern about pulmonary artery catheter use arose following prior studies that showed higher mortality for patients thought to require a pulmonary artery catheter during hospitalization. More recent data suggest that the routine use of pulmonary artery catheters in patients with AHF is unnecessary and unlikely to lead to a better outcome.⁴⁰ Apart from patients with cardiogenic shock or rapidly decompensating heart failure, and patients who are being considered for heart transplantation with significant pulmonary hypertension, a pulmonary artery catheter is also likely to be helpful in obese patients who may be very difficult to assess and monitor clinically, and in patients with severe LV and right ventricular dysfunction in whom the response to vasodilator and other therapies may be difficult to predict. Some patients with

advanced heart failure are so tenuous that they can be managed optimally only with hemodynamic data feedback.

Treatment of Acute Heart Failure

The management of patients with AHF is primarily aimed at restoring perfusion of vital organs and relieving pulmonary congestion. In hemodynamic terms, the intention is to increase cardiac output and to decrease LV filling pressure, while preserving adequate coronary perfusion.

General Measures

Several general measures are advisable for treating most patients with AHF. Bed rest should be enforced. Patients feel most comfortable in the semi-upright position, with legs dependent.

Oxygenation

Special attention should be paid to maintaining adequate oxygenation. When there is hypoxia ($\text{PaO}_2 < 60$ mm Hg) without hypercapnia, oxygen-enriched inspired gas may suffice; this can be given through nasal prongs, Venturi masks, or reservoir bag masks, depending on the severity of gas exchange abnormality. Noninvasive ventilation by either continuous positive airway pressure breathing or bilevel positive airway pressure may become necessary when oxygenation cannot be maintained, or there is evidence of progressive hypercapnia despite aggressive treatment. The use of noninvasive ventilation is associated with a significant reduction in the need for tracheal intubation and mechanical ventilation. Failing these interventions, intubation and mechanical ventilation may be needed to improve oxygenation and reverse hypercapnia.

Infections

Patients with AHF are prone to infections. The most common are respiratory or urinary tract infections, septicemia, or nosocomial infections. Infections often manifest atypically in patients with AHF. Many patients are sick without a fever. Scrupulous infection control and measures to maintain skin integrity are mandatory in the ICU. Routine cultures are recommended.⁴ Prompt antibiotic therapy should be given when indicated.

Diabetes

Hyperglycemia occurs commonly in patients with AHF owing to impaired metabolic control. Routine hypoglycemic drugs should be discontinued, and glycemic control should be obtained by using short-acting insulin titrated according to repeated blood glucose measurements. Normoglycemia improves survival in diabetic patients who are critically ill.⁴¹

Deep Venous Thrombosis Prophylaxis

Patients with heart failure who are bedridden are at high risk for developing deep venous thrombosis, and prophylactic measures should be strongly considered.

Medications

Morphine

Morphine remains a valuable drug in the treatment of AHF, especially if the syndrome is associated with anxiety, restlessness, and dyspnea. The drug diminishes the patient's distress and reduces the work of breathing. Morphine achieves its

hemodynamic effects by causing arteriolar and venous dilation through its ability to diminish the vasoconstrictive effects of increased sympathetic tone.⁴² Morphine sulfate is usually administered in doses of 3 to 5 mg intravenously over 3 minutes. This dose may be repeated two or three times at 15-minute intervals. The patient should be monitored for respiratory depression, which can be reversed by the narcotic antagonist naloxone. Morphine should be avoided if the pulmonary edema is associated with hypotension, intracranial bleeding, disturbed consciousness, bronchial asthma, chronic pulmonary disease, or reduced ventilation, specifically in patients with an increased arterial PCO_2 . The use of morphine may be associated with an increase in adverse events, including intubation.³⁰

Vasodilators

Reduction of LV preload is highly desirable in patients with AHF and CPE; it is primarily intended to shift central blood volume to the periphery, LV diastolic volume and pressure. When AHF is associated with an expanded circulating volume, as with acute decompensation of chronic heart failure, substantial preload reduction can be achieved without a significant decline in arterial pressure. In the setting of hypertension and normovolemia, aggressive reduction in preload may lead to a substantial decrease in blood pressure. It is important to decide in advance whether a patient who presents with AHF is likely to be at increased risk of developing hypotension with reductions in LV preload.

Ventricular afterload is increased in most patients with heart failure, and the detrimental effects of afterload excess are proportional to the degree of LV systolic dysfunction. Afterload reduction with vasodilator therapy is directed at reducing excessive LV wall stress, with a resultant increase in stroke volume and a decrease in end-diastolic pressure. A reduction in afterload provides the greatest hemodynamic benefit for patients with the most advanced heart failure; a far greater increase in stroke volume and decrease in end-diastolic pressure are achieved with similar reductions in wall stress in patients with severe LV systolic dysfunction compared with patients with milder forms of heart failure (Fig. 24-7). Vasodilators are indicated in most patients with AHF as first-line therapy.

Nitroglycerin

Actions Nitroglycerin causes vasodilation by stimulating guanylate cyclase within the vascular smooth muscle of arterial resistance and venous capacitance vessels.⁴³ The predominant site of action depends on the dose being administered. At lower doses, nitroglycerin acts principally on the peripheral veins and reduces right ventricular and LV filling pressures. At higher doses, nitroglycerin causes modest arterial vasodilation, and consequently it may improve cardiac output.⁴⁴ Nitroglycerin can reduce the degree of mitral regurgitation^{45,46} and decreases the preload-dependent chamber stiffness by redistributing blood from the central blood pool (heart and lungs) to the periphery (mesenteric bed),^{47,48} decreasing LV volumes, which decreases the pericardial constraint.⁴⁹

Nitrates reduce subendocardial ischemia by coronary vasodilation and by reducing myocardial oxygen requirements through unloading effects. One disadvantage of nitrates is the rapid development of tolerance, especially when given intravenously in high doses, limiting their effectiveness to 16 to 24 hours only. Nitrates should be given at doses aimed at

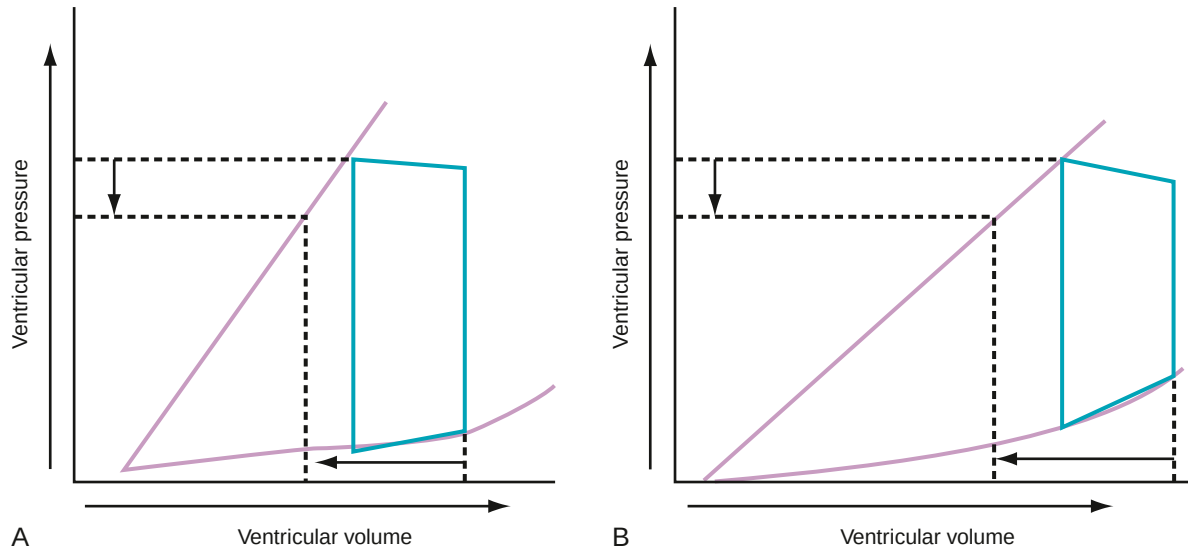


Figure 24-7. Schematic diagram of the left ventricular wall stress-volume relationship. The loop has the same configuration as the pressure-volume relationship. **A**, With mild heart failure, a decrease in wall stress (arrows) results in an increase in stroke volume. **B**, With more advanced heart failure, a similar decrease in wall stress is accompanied by a marked increase in stroke volume. Vasodilator therapy (i.e., afterload reduction) produces a larger increase in stroke volume in advanced heart failure than in mild heart failure.

achieving optimal vasodilation, leading to an increase in cardiac index and decrease in pulmonary wedge pressure.

Use in Acute Heart Failure Randomized trials in AHF have established the efficacy of intravenous nitrates in combination with furosemide, and have shown that titration to the highest hemodynamically tolerable dose of nitrates with low-dose furosemide is superior to high-dose diuretic treatment alone.^{50,51} Nitroglycerin is effective in relieving the symptoms of acute pulmonary edema and is often the vasodilatory agent of choice in patients with underlying ischemic heart disease. Nitroglycerin should be administered in a manner to ensure the fastest onset of action. The intravenous route generally is preferred. The initial infusion rate is 10 µg/min, and the rate may be increased to 300 µg/min to achieve desired effects. The dose of nitroglycerin should not be increased when the systolic arterial pressure is less than 90 mm Hg. From a practical perspective, a reduction of 10 mm Hg in mean arterial pressure should be achieved.

Nitroglycerin can be administered orally or by inhalation (glyceryl trinitrate spray, 400 µg [2 puffs] every 5 to 10 minutes), or buccally (isosorbide dinitrate, 1 or 3 mg), while monitoring blood pressure. Buccal absorption may be erratic. One should be particularly cautious when administering nitrates to a patient with aortic stenosis or hypertrophic obstructive cardiomyopathy.

Nitroprusside

Actions Nitroprusside infusion improves ventricular performance by decreasing all the major components of LV afterload: systemic vascular resistance, arterial stiffness, arterial wave reflectance, and LV size.⁵² Proper dose selection achieves a reduction in afterload and preload with little change in systemic blood pressure. An often overlooked aspect of afterload reduction is the reduction of right ventricular load. Vasodilators that are associated with a decrease in LV filling pressures invariably unload the right heart.⁵³ Within the confined space of the pericardium, interventions that reduce the excessive volume of the right ventricle have a favorable hemodynamic effect on

the septal interaction between the right and left ventricles, and they consequently may improve LV filling and filling pressures. Nitroprusside is likely to achieve some of its favorable effects through this mechanism of ventricular interaction.

The incidence of side effects and toxicity is directly related to the dose and duration of administration. Cyanide may accumulate with prolonged high doses of nitroprusside and contribute to lactic acidosis. Toxicity can be avoided by monitoring blood lactate and thiocyanate levels.

Use in Acute Heart Failure Intravenous nitroglycerin is usually the vasodilator of choice for most patients with AHF, especially if a patient has underlying ischemic heart disease, but nitroprusside is the vasodilator of choice when a substantial reduction in LV afterload is required. Although both vasodilators affect vascular smooth muscle, nitroprusside and nitroglycerin differ in important ways. Because the magnitude of arterial vasodilation achieved with nitroprusside is greater than that with nitroglycerin, nitroprusside has the greater potential to produce hypotension. Such hypotensive action may lead to more neurohormonal activation, and this may be the reason why rebound hemodynamic effects after abrupt withdrawal of the drug occur more frequently with nitroprusside than with nitroglycerin.⁵⁴

Nitroprusside is reserved for clinical situations requiring acute, short-term afterload reduction. Nitroprusside is most beneficial for hypertensive patients or patients with an elevated LV filling pressure (≥ 20 mm Hg) and a systemic arterial pressure of 100 mm Hg or greater. This clinical picture is commonly encountered in patients with a large MI, with decompensated chronic heart failure, with acute valvular regurgitation, or after cardiopulmonary bypass.

Nitroprusside usually represents a stabilizing pharmacologic bridge to more definitive interventions (e.g., valve replacement or coronary revascularization). The end points of acute vasodilator therapy can vary from patient to patient, but reasonable hemodynamic end points include a reduction in LV filling pressure to 15 mm Hg or less and an increase in cardiac output that

would ensure adequate tissue oxygen delivery (usually a cardiac index >2.5 L/min/m²), while maintaining a systemic blood pressure of 90 mm Hg or greater.

The optimally effective and safe administration of nitroprusside often requires hemodynamic monitoring by means of intra-arterial catheters. The initial dose of 0.10 to 0.20 $\mu\text{g/kg/min}$ is gradually increased as needed to attain the desired clinical and hemodynamic effects.

Nesiritide

Actions Nesiritide is a recombinant human BNP that is identical to the endogenous hormone. Nesiritide has venous, arterial, and coronary vasodilatory properties that reduce preload and afterload, and increase cardiac output without direct inotropic effects.⁵⁵

Use in Acute Heart Failure Nesiritide was compared with intravenous nitroglycerin and resulted in improvement in hemodynamics more effectively and with fewer adverse effects, although this did not translate into improvement in clinical outcome.⁵⁶ Nesiritide may cause hypotension, and some patients are nonresponders. The role of this agent is uncertain in the context of AHF. In most hospitals, nesiritide is not given as a first-line agent, but this medication may be considered when a patient does not respond rapidly to conventional treatment. The recommended dose of nesiritide is an intravenous bolus of 2 $\mu\text{g/kg}$ followed by a continuous infusion of 0.01 $\mu\text{g/kg/min}$.

A U.S. Food and Drug Administration expert panel of cardiologists made specific recommendations for nesiritide use, as follows⁵⁷:

- Consider the risks (e.g., worsening renal function, mortality) and benefits to the patient before initiating therapy.
- Use nesiritide only in hospitalized patients with acutely decompensated congestive heart failure with dyspnea at rest.
- Avoid using nesiritide in place of diuretic therapy.
- Avoid regular repetitive use of nesiritide.
- Avoid use for off-label indications, including enhancing renal function or augmenting diuresis.

Other Vasodilators

The intravenous use of direct-acting vasodilators such as hydralazine has a very limited or no role in the management of AHF and CPE. Other vasodilators, such as calcium antagonists or α -adrenergic blockers, cannot be recommended as first-line therapy for patients with AHF. Angiotensin-converting enzyme inhibitors are not indicated in the early stabilization of patients with AHF, and calcium antagonists are not recommended in the treatment of AHF. Diltiazem, verapamil, and dihydropyridines should be considered contraindicated in the setting of AHF.

Diuretics

Actions

Loop diuretics block the sodium-potassium-chloride transporter, resulting in increased urine volume by enhancing the excretion of water, sodium chloride, and other ions, leading to a decrease in plasma and extracellular fluid volume, total body water, and sodium. These effects result in a reduction in right ventricular and LV filling pressures and a decrease in peripheral and pulmonary congestion. Intravenous administration of loop diuretics also exerts a vasodilating effect, manifested by an early (5 to 30 minutes) decrease in right atrial and pulmonary wedge pressure and pulmonary resistances. These hemodynamic

effects result from the direct peripheral arterial and venodilating actions. It is thought that vasodilation rather than diuresis is the principal early mechanism by which diuretics alleviate symptoms of pulmonary edema.⁵⁸ High bolus doses (>1 mg/kg) of diuretics may lead to reflex vasoconstriction. As opposed to long-term use of diuretics, in severe decompensated heart failure, the use of diuretics improves loading conditions and may reduce neurohormonal activation in the short term.⁵⁹

Use in Acute Heart Failure

Intravenous loop diuretics (furosemide, bumetanide) are the most widely used diuretics in the treatment of AHF and CPE. The dose should be titrated according to the diuretic response and relief of congestive symptoms. Administration of a loading dose followed by continued infusion of furosemide or torsemide has been shown to be more effective than bolus alone.^{60,61} Thiazides and spironolactone can be used in association with loop diuretics; the combination in low doses is more effective and has fewer secondary effects than the use of higher doses of a single drug. Combination of loop diuretics with inotropes or nitrates is another therapeutic approach that is more effective and produces fewer secondary effects than increasing the dose of the diuretic. The diuretic doses for patients with mild congestion and new-onset AHF are generally much lower than doses for patients with advanced fluid overload or patients with renal dysfunction. The doses of diuretics as they relate to severity of AHF and the goals of treatment are summarized in Table 24-6.

Diuretic Resistance

Diuretic resistance is defined as the clinical state in which diuretic response is diminished or lost before the goal of treatment has been achieved. Such resistance is associated with a poor prognosis.⁶² There are two forms of diuretic tolerance: (1) Short-term tolerance occurs when the diuretic effect is attenuated after the first dose has been administered; this can be prevented by restoring diuretic-induced loss of volume. (2) Long-term tolerance is observed after prolonged administration of a loop diuretic, which leads to avid sodium reabsorption at more distal sites. This phenomenon argues for the use of sequential nephron blockade with combinations of loop and thiazide diuretics in patients who do not have adequate responses to optimal doses of a loop diuretic. To overcome inadequate response to diuretics, it is important to adhere to the following principles (see Table 24-6):

1. Diuretics should be used in moderation; excessive doses of any single drug should be avoided.
2. A loop diuretic is the diuretic of choice in patients with renal insufficiency and in patients with more than mild fluid retention.
3. The diuretic response of loop diuretics is not increased by giving larger doses, but it may be increased by giving moderate doses more frequently.
4. The clinician can make use of synergism by adding a thiazide when there is apparent tolerance to loop diuretics. This diuretic regimen can be used to achieve euvolemia. Hydrochlorothiazide combined with triamterene should be considered to prevent excessive potassium wasting. Metolazone, a potent thiazide, could be added to a loop diuretic when hydrochlorothiazide seems to be ineffective in promoting sodium excretion. This combination often causes severe electrolyte disturbances.

Table 24-6. Diuretic Dosing and Goals of Treatment

Clinical Scenario	Diuretic	Dose	Goal/Comments
Moderate fluid overload	Furosemide	20-40 mg IV q12h*	Urine output of >200 mL in the first 2 hr after bolus dose
	Bumetanide	0.5-1 mg IV q12h*	
Severe fluid overload	Furosemide	40-80 mg IV q12h [‡] or Bolus of 80 mg IV + continuous infusion at 10-20 mg/hr	Urine output of >400 mL in the first 2 hr after bolus dose and then 150 mL/hr
	Bumetanide	1-2 mg IV q12h [†]	
Severe fluid overload and renal dysfunction (GFR <30 mL/min)	Furosemide	80-200 mg IV q12h or Bolus + continuous infusion at 20-40 mg/hr	Urine output of >200 mL in the first 2 hr after bolus dose and then 100 mL/hr
Diuretic resistance	Add chlorothiazide to furosemide Acetazolamide [§]	250-500 mg IV 30 min before loop diuretic 0.5 mg IV q12h	Urine output of >200 mL in the first 2 hr after bolus dose and then 100 mL/hr

*Double dose if goal not attained.

†If goal not attained, add chlorothiazide (see diuretic resistance).

‡Lower dose if BP <100 mm Hg.

§Consider in the presence of alkalosis.

GFR, glomerular filtration rate.

Adapted from Task Force on Acute Heart Failure of the European Society of Cardiology. Eur Heart J 2005;26:384-416.

5. In patients who have poor responses to intermittent doses of a loop diuretic, a continuous intravenous infusion should be tried.

Positive Inotropic Agents

Positive inotropic agents are indicated in the presence of hypotension and end-organ hypoperfusion (decreased renal function) with or without congestion or pulmonary edema refractory to diuretics and vasodilators at optimal doses. Anecdotal experience suggests that positive inotropic agents may be especially useful in these patients when left and right ventricular systolic function is markedly depressed. Their use is potentially harmful because they increase oxygen demand and calcium loading, and they should be used with caution.⁶³ More recent data do not support the routine intravenous use of these agents as an adjunct to standard therapy in the treatment of patients hospitalized for decompensated chronic heart failure.⁶⁴ The choice of agent depends on the predominant hemodynamic abnormality. The rationales for using certain positive inotropic agents are outlined in Table 24-7.

Dopamine

Actions Physiologically, dopamine is the precursor of norepinephrine and releases norepinephrine from the stores of the nerve endings in the heart. Dopamine has the valuable property in severe heart failure of specifically increasing renal blood flow by activating postjunctional dopaminergic receptors.⁶⁵ This vasodilatory effect is observed at doses of 1 to 2 µg/kg/min and peaks at a dose of 7.5 µg/min, but the vasoconstrictive effect begins at a dose of 10 µg/kg/min. Because the inotropic effects of dopamine result primarily from its indirect effects, its use in advanced heart failure is limited by the neurotransmitter depletion present in the failing heart.⁶⁶ In milder forms of heart

failure, dopamine may have similar effects to dobutamine except for the greater tendency to increase heart rate and a tendency to increase systemic vascular resistance and ventricular filling pressures at medium and higher doses. Dopamine is especially useful in treating acute heart failure when renal blood flow is impaired.

Use in Acute Heart Failure Dopamine should be infused through a long, indwelling catheter because of the risk of extravasation. Extravasation may cause necrosis and sloughing of the surrounding tissue because of the vasoconstrictive effects of the agent. Infusion with dopamine should be started at doses of 2 to 5 µg/kg/min and should not be increased beyond 5 µg/kg/min in patients with blood pressures of 100 mm Hg or greater. This agent may be deleterious in patients with AHF because it may augment the LV afterload, pulmonary artery pressure, and pulmonary resistance. In markedly hypotensive patients with peripheral hypoperfusion, large doses of dopamine can be used to support systemic blood pressure, alone or in combination with norepinephrine.

Dobutamine

Actions Dobutamine is a β-adrenergic agonist that stimulates β₁-adrenergic, β₂-adrenergic, and α₁-adrenergic receptors.⁶⁷ Cardiac contractility is increased by virtue of its β₁ and α₁ effects, but because the α₁-adrenergic effects are generally counterbalanced by the β₂ actions, there is generally little change in blood pressure. Dobutamine markedly increases cardiac output, but produces only modest changes in LV filling pressures and virtually no increase in blood pressure.⁶⁸ Heart rate generally increases only when doses greater than 10 µg/kg/min are used. Compared with dobutamine, dopamine is a better vasoconstrictor,⁶⁸ and milrinone is a better vasodilator.⁶⁹ The elimination of the drug is rapid after cessation of infusion, making it a convenient inotropic agent.

Table 24-7. Treatment for Different Acute Heart Failure Syndromes

Acute Heart Failure Syndrome	Systolic Blood Pressure	First-Line Treatment	Second-Line Treatment	Third-Line Treatment
Hypertensive	>140 mm Hg	Oxygen CPAP if needed Loop diuretic Intravenous nitroglycerin	Increase doses of nitroglycerin or diuretic or both	Intravenous nitroprusside
Normotensive	100-140 mm Hg	Oxygen CPAP if needed Loop diuretic Vasodilators	Increase doses of nitroglycerin or diuretic or both Add thiazide diuretic	Milrinone when there is evidence of prerenal azotemia
Preshock	85-100 mm Hg	Oxygen CPAP Vasodilator and diuretics	Dobutamine or milrinone	Add dopamine
Cardiogenic shock	<85 mm Hg	Oxygen CPAP Volume loading Dopamine >5 µg/kg/min	Norepinephrine	Mechanical support IABP Consider VAD

CPAP, continuous positive airway pressure; IABP, intra-aortic balloon pump; VAD, ventricular assist device.

Adapted from Task Force on Acute Heart Failure of the European Society of Cardiology. *Eur Heart J* 2005;26:384-416.

Use in Acute Heart Failure The usual dose of dobutamine is 2.5 to 15 µg/kg/min. Short-term infusions are often extremely effective in the treatment of unstable AHF, especially when systolic pressures are preserved. Long-term infusion should be avoided because of the development of hemodynamic tolerance.⁷⁰ Dobutamine is likely to increase myocardial oxygen consumption and can cause serious arrhythmias. There are no controlled trials on dobutamine in AHF patients, and some trials show unfavorable effects with increased untoward cardiovascular events.

Milrinone

Actions Milrinone is a type III phosphodiesterase inhibitor that produces dose-dependent increases in cardiac output and decreases in LV filling pressures as a result of the interaction of its positive inotropic, positive lusitropic, and peripheral vasodilator actions.^{71,72} The net result is a hemodynamic profile similar to that of the combination of nitroprusside and dobutamine. Because of its vasodilating effects, milrinone is less likely than dobutamine to increase heart rate and myocardial oxygen consumption. Despite these theoretical advantages, myocardial ischemia has been provoked by these agents, and marked hypotensive episodes have been observed.

Use in Acute Heart Failure Milrinone requires a loading dose of 50 µg/kg over 10 minutes followed by a maintenance infusion of 0.375 to 0.75 µg/kg/min. The dose should be adjusted in patients with decreased renal clearance. This agent may be preferred to dobutamine in patients receiving concomitant β-blocker therapy, or with an inadequate response to dobutamine, or both. The data regarding the effects of milrinone administration on the outcome of patients with AHF are insufficient, but raise concerns about safety.⁶⁴

Digitalis

Digitalis generally has no role in the treatment of AHF, unless the patient has been taking digitalis for chronic heart failure, or if digitalis is given to control a rapid ventricular response in atrial fibrillation.

Vasopressors

Vasopressors are largely used to treat cardiogenic shock and are discussed elsewhere.

Other Treatments

Ultrafiltration

In patients with severe renal dysfunction and refractory fluid retention, continuous venovenous hemofiltration may become necessary. Ultrafiltration has been used in patients with therapy-resistant chronic volume overload. Conventional ultrafiltration requiring central venous access is most often used, particularly if the patient is extremely edematous. Generally, the hemodynamic changes produced by ultrafiltration are modest. The reduction in water with ultrafiltration is accompanied by decreases in right atrial and pulmonary venous pressures. Cardiac output and stroke volume are unchanged or increase slightly. The weight loss is more sustained when contrasted with the weight loss achieved with furosemide treatment.⁷⁴ The typical volume of water removed per ultrafiltration session is 3000 to 4000 mL. This promising therapeutic modality requires further study and refinement before it is more widely used in AHF patients.

Continued Therapy for Chronic Heart Failure

Patients who are admitted with normotensive AHF should be maintained on the usual outpatient doses of β-blockers, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers.

Intra-Aortic Balloon Pump

In patients with refractory heart failure, refractory ischemia, or arrhythmias, an intra-aortic balloon pump placement helps to unload the heart and improve myocardial and systemic perfusion. Absolute contraindications to placement of an intra-aortic balloon pump include aortic insufficiency and aortic dissection.

Surgical Treatment

Surgical therapies for patients with AHF include coronary revascularization, correction of the anatomic lesions, valve replacement or reconstruction, and temporary circulatory support by means of mechanical assist devices.

Choice of Therapeutic Regimen

In choosing the appropriate medical regimen, it is helpful to revisit the different AHF syndromes. These are outlined in Table 24-7. Two special scenarios warrant mention.

Hypertensive Acute Heart Failure

LV systolic function is normal in patients hospitalized with pulmonary edema and hypertension. Vasodilator therapy should aim for an initial rapid (several minutes) reduction of systolic blood pressure of 30 mm Hg, followed by a more measured decrease of blood pressure to the values obtained during stable periods. No attempt should be made to restore normal values of blood pressure because this may cause deterioration in renal function. The initial blood pressure reduction may be achieved by intravenous loop diuretics, particularly if the patient is clearly fluid overloaded with a long history of chronic heart failure, combined with intravenous nitroglycerin or nitroprusside.

Acute Heart Failure with Normal Ejection Fraction

The most effective treatment of patients with AHF with normal ejection fraction is to address the underlying cause. The treatment is similar to hypertensive AHF. In this regard, blood pressure control and the treatment of underlying ischemia are important goals. A major goal of therapy is to reduce the left atrial and pulmonary venous pressures. Diuretics, vasodilators, and other preload-reducing agents are used as discussed previously. The steep or stiff diastolic pressure volume curve (see Fig. 24-4) can be responsible for a substantial decrease in filling pressure with little change in volume; as a result, hypotension often occurs with the usual doses of diuretics. Cautious administration of lower than usual doses of diuretics is advisable. Conversion of an atrial arrhythmia to sinus rhythm is usually beneficial.

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Sudden Cardiac Death

M. Eyman Mortada, Masood Akhtar

CHAPTER 25

Definition
Epidemiology
Pathophysiology
Clinical Presentation

Evaluation Of The SCA Survivor
Therapy
Conclusion

Definition

Sudden cardiac death (SCD) is defined as a natural and unexpected death as a result of cardiac causes that occur within 1 hour of the onset of new symptoms.¹ In some medical circles, the term “sudden cardiac arrest” (SCA) is preferred because the expression “death” conveys finality of the event, which is not necessarily the outcome in all cases. In this communication, both terms will be used as appropriate in the text.

Epidemiology

Cardiovascular disease-related deaths are still the most common cause of mortality in the United States. The two modes of cardiovascular death (i.e., sudden and nonsudden) are equally common. SCD claims 325,000 lives each year in United States,² thus the incidence is 0.1% to 0.2% annually.³ It is usually ascribed to arrhythmic causes and it is the case the vast majority of the time when the initiation of the episode is electrocardiographically documented. However, the victims are seldom under medical observation, thus the exact mechanism leading to cardiovascular collapse is difficult to establish, and the cause is labeled on the basis of presentation and the earliest onsite ECG recordings. Monitored victims and rescue squads encountering individuals with SCA show the following arrhythmias at the time of arrival: ventricular fibrillation (VF) in 80% of the victims, ventricular tachycardia (VT) in 10% who have the best outcome, and bradycardias in 10%.^{4,5} The rhythm disturbance first documented by emergency rescue teams is dependent upon the time elapsed after the cardiovascular collapse. VF is seen early after collapse and progresses to asystole as time passes (Fig. 25-1).

For the most part, patients with bradycardia have little or no response to pacing, suggesting hemodynamic collapse as the underlying problem and bradycardia as the concomitant rhythm (electrical-mechanical dissociation). Occasionally, torsades de pointes may be precipitated by severe bradycardia and cause SCA. The universal futility of cardiac pacing in this setting to improve survival in this population, attests to the possibility that overall, one fourth of SCA victims may have nonarrhythmic etiology. Conduction system abnormalities have been labeled as the cause of SCD in younger population victims without demonstrable heart disease in autopsy studies.⁶

While the possibility of SCA can be literally eliminated for previously identified individuals at high risk, the population at large, for now, must contend with the existing sources of aid (emergency medical services, first responders, rescue squads, etc.) that are available in a given community and their relative effectiveness.

In this communication, more space is provided for lesser known but emerging arrhythmia syndromes and the management approach is mostly geared towards internal or external defibrillation devices. The literature is replete with coronary artery disease (CAD) in SCA and its various presentations; work-up, therefore, will only be briefly discussed.

Pathophysiology

SCA may be best considered as the outcome of an interaction between an abnormal cardiac substrate and a transient functional disturbance, which triggers the arrhythmia at a specific point in time. Increasingly, however, it is being recognized that SCA can occur in the absence of any demonstrable structural heart disease. Furthermore, it is coming to light that for many of these primary arrhythmic etiologies there are identifiable genetic mutations, as will be discussed later in this chapter.

Pathologic Substrates

Over the years, numerous studies have revealed that an overwhelming majority of SCA cases (75% to 80%) are due to acute, chronic, or acute on chronic atherosclerotic CAD.¹ The second most frequent category of disorders is cardiomyopathies, which include both hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy (DCM). These pathologic substrates are:

1. CAD:

It has been demonstrated that there are one or more active coronary lesions in up to 90% of SCD victims⁷ that present as an acute, chronic, or acute on chronic process. This association is described as follows:

- Acute:** There is a close association between the occurrence of SCD and the presence of plaque fissuring and/or erosion, platelet aggregation, and acute thrombosis within the matrix of coronary atherosclerosis. However, only 20% of SCD victims have acute myocardial infarction (MI),⁸ likely because the pathophysiologic mechanism leading to that expression

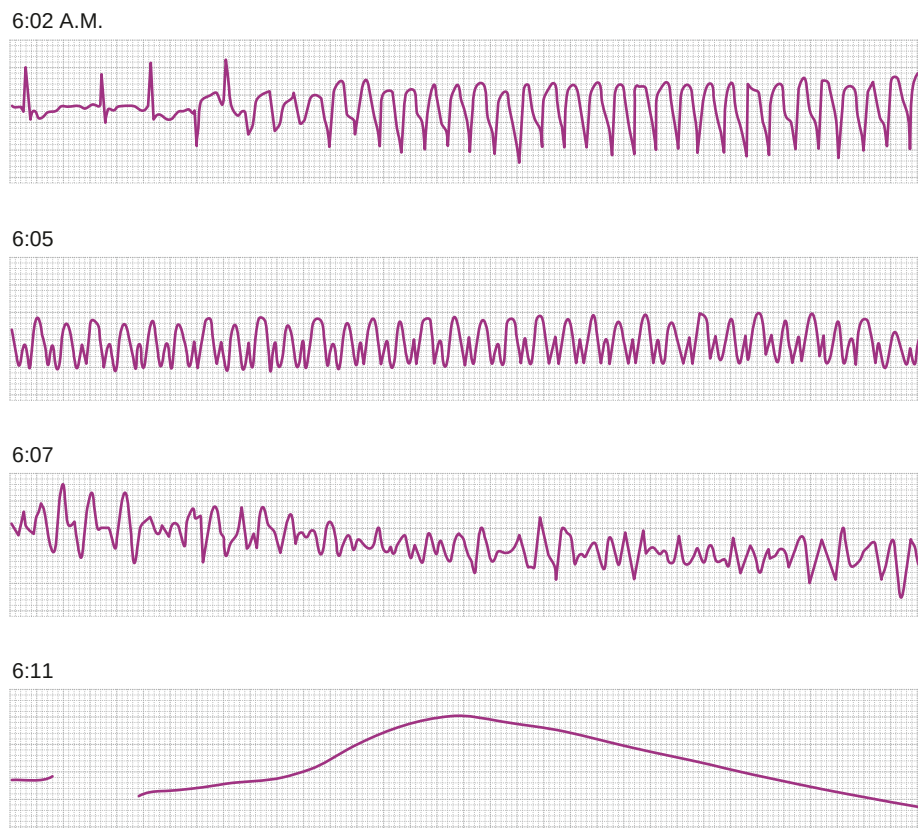


Figure 25-1. Fortuitous Holter recording from a patient who experienced sudden cardiac death outside the hospital documents the usual and typical sequence of events. The initial rapid ventricular tachycardia continues into the second panel with widening of the QRS, probably owing to myocardial metabolic changes. Subsequent transformation to ventricular fibrillation is shown in the third panel, followed by asystole. The initial documented rhythm and, ultimately, the prognosis depend on how soon emergency personnel arrive to treat the individual. (From Akhtar M, Garan H, Lehmann H, et al: *Sudden cardiac death: management of high risk patients*. *Ann Intern Med* 1991;114:499.)

is interrupted by an abrupt cessation of the biologic activity because of lethal arrhythmia.⁹

b. Chronic: Myocardial pathology reflects the presence and extent of chronic coronary atherosclerosis, in that myocardial scars, because of healed MIs, are common.¹⁰

2. Left ventricular hypertrophy (LVH) and HCM:

LVH is now a well-established independent risk factor for SCD,¹¹ both in the presence and absence of concomitant CAD. In fact, the majority of SCA victims with CAD have coexisting LVH, although the mortality associated with LVH does not parallel that of CAD. Hypertrophied ventricular myocytes demonstrate altered membrane electrophysiology, resulting in delayed inactivation of slow inward Ca^{2+} currents and delayed activation of K^{+} rectifier currents accounting for recovery of excitability. Transient ischemia and reperfusion make hypertrophied cells susceptible to afterdepolarizations and triggered arrhythmias.¹² One common feature observed in HCM is myocytes disarray, which is common to most, but not all, genetic forms of the disease. The association between HCM expression and SCA risk is complex because of patterns of inheritance involving not only multiple gene foci but mutation-specific risk.⁹

3. DCM:

The underlying myocardial pathology demonstrated in DCM accounts for approximately 10% to 15% of SCD. The pathologic findings are nonspecific, characterized by dilation

of the ventricles with interstitial patchy fibrosis, myocytes degeneration, and necrosis.

4. Infiltrative, inflammatory, and valvular diseases:

These account for most of the remaining minority of causes of SCA in patients with structural heart disease. Clinically silent myocarditis has been considered among the more common of the causes of SCD in adolescents and young adults.¹³ The pathologic finding in acute viral myocarditis is high-grade inflammatory processes in the myocardium, but some forms of a viral myocarditis may demonstrate diffuse fibrosis, without inflammatory markers.¹⁴

5. Abnormalities of the cardiac conducting tissue:

They are best exemplified by the Wolff-Parkinson-White syndrome (WPW) and diseases of the His-Purkinje system. Patients with WPW who have pathways with short refractory periods are susceptible to VF during atrial fibrillation/flutter.

6. Genetically determined disorders:

They account for a small proportion of SCDs (1% to 2%), occurring predominantly in adolescents and young adults.

a. Inherited: long Q-T syndromes, short QT syndromes, Brugada syndrome, HCM, right ventricular dysplasia, catecholaminergic polymorphic ventricular tachycardia, progressive cardiac conduction defect, sudden infant death syndrome "SIDS," and idiopathic ventricular fibrillation "IVF."^{15,16}

b. Not inherited: congenital cardiac lesions (e.g., anomalous coronary arteries) and myocarditis.¹⁷

Functional Modulators

Functional modulators interact with structural abnormalities, converting them from a stable to an unstable state, promoting the start of fatal arrhythmias. Many of the functional modulators (e.g., transient ischemia and acquired long QT), if sufficiently intense, can initiate a fatal arrhythmia in a victim, in the absence of any structural heart disease. However, this is clinically uncommon.

1. Transient ischemia:

It plays a major role in producing fatal arrhythmias. At the cellular level, acute physiologic changes from ischemia include dispersion of both conduction patterns and refractoriness, providing the environment for reentrant arrhythmias and generating abnormal automatic activity. Ischemia opens up the ATP-sensitive K^+ channels, more in the epicardial than the endocardial cells.¹⁸ This results in heterogeneity in the refractoriness of the two regions, making the myocardium prone to arrhythmias. Reperfusion events may have equally important electrophysiologic consequences. An inward flux of calcium occurs during reperfusion, resulting in overload, and correlates with a burst of spontaneous ventricular ectopy, probably owing to automaticity or triggered activity.

2. Systemic factors:

a. Hemodynamic deterioration:

Acute hemodynamic deterioration may precipitate a secondary cardiac arrest, which unfortunately carries high short-term mortality. The mechanisms could be related to ischemic and metabolic substrates.

b. Electrolyte disturbances:

Hypokalemia has been implicated in an increased risk of sudden and total cardiovascular mortality and plays a particularly important role in the genesis of torsades de pointes and other polymorphic VT.¹⁹

3. Altered systemic autonomic balance:

Structural abnormalities create autonomic disturbances resulting in altered β -adrenergic receptor content, coupling proteins, and adenylate cyclase activity. This causes dispersion of quantitative and qualitative responses to sympathetic stimulation in the abnormal heart, predisposing to arrhythmias. Clinically, altered systemic autonomic balance is manifested as loss of the normal diurnal variation of heart rate variability, which is considered a marker for risk of SCA among MI and SCA survivors.²⁰

4. Drug toxicity:

Drug toxicity, as a cause of SCA, has been documented in connection with a variety of both cardio-active (antiarrhythmic) and noncardiac drugs, such as psychotropic drugs, erythromycin, Seldane, and pentamidine. A variety of electrophysiologic mechanisms are operative in the genesis of lethal ventricular tachyarrhythmias induced by various drugs. However, there may be concurrent structural or functional abnormalities. The latter include transient ischemia, hemodynamic dysfunction, electrolyte abnormalities, and ventricular hypertrophy. Recently, an increased risk of SCA has been reported with the concomitant use of cocaine and alcohol, and is probably because of the generation of a cardiotoxic metabolite, cocaethylene.²¹

5. Acidosis

6. Hypoxemia

Clinical Substrate

To predict SCA, it is important to recognize the conditions leading to abrupt cessation of cardiac output. Figure 25-2 shows data derived from various studies²²⁻²⁶ demonstrating the

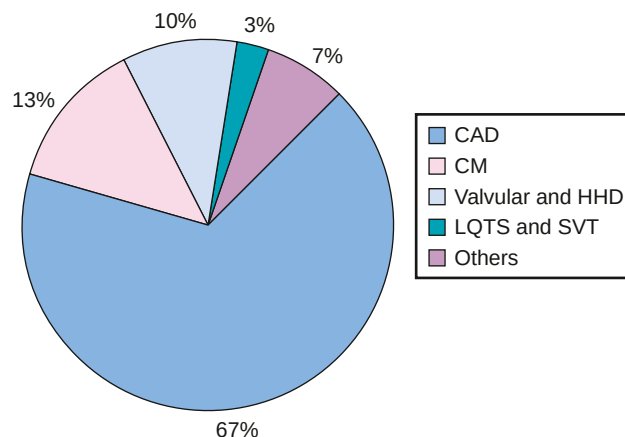


Figure 25-2. Prevalence of underlying heart disease in adult patients who have experienced sudden cardiac death, based on data derived from several studies,²²⁻²⁶ shows coronary artery disease, cardiomyopathies, valvular and hypertensive heart disease, and electrical disturbances as the predominant substrates. CAD, coronary artery disease; CM, cardiomyopathy; HHD, hypertensive heart disease; LQTS, long QT syndrome; SVT, supraventricular tachycardia. (From Deshpande S, Vora A, Axtell K, Akhtar M: Sudden cardiac death. In Brown DL [ed]: *Cardiac Intensive Care*. Philadelphia, Saunders, 1998, pp 391-404.)

predominant substrates of SCD. The relative risk for SCD is dependent upon the underlying substrate and is graphically demonstrated for various populations in Figure 25-3.

Coronary Artery Disease (CAD)

CAD is the most common cause of SCA, where it is the responsible substrate in 65% to 90%²⁷⁻³³ of cases. SCA related to coronary events is more common in younger victims, more common in men than in women, and more common in African Americans than in whites. Approximately 20% of SCA victims show evidence of new ST elevation myocardial infarction at the time of cardiac arrest, but 40% to 75% have evidence of healed MI. Fifty percent of post-MI deaths occur in the first 6 months.⁹ Most of the risk factors for CAD are predictors for SCA (e.g., left bundle branch block on ECG, hyperlipidemia, hypertension, cigarette smoking, obesity, diabetes, and lifestyle).³

Nonatherosclerotic CAD

Nonatherosclerotic CAD is also a significant risk for SCA, especially in the younger population. The common nonatherosclerotic coronary artery abnormalities include:

1. Congenital anomalies:

The most common congenital anomaly is the origin of the left main coronary artery from the right sinus of Valsalva, with passage of this vessel between the aorta and the pulmonary trunk.³⁴ Although death is not universal with this anomaly, virtually all such deaths occur during or shortly following vigorous exercise. It is postulated that the left main coronary may be compressed against the root of the pulmonary trunk during exercise when both of these great vessels dilate, thus compromising coronary blood flow and producing myocardial ischemia. Unfortunately, antemortem diagnosis of this anomaly is rare, despite the fact that a significant number of patients experience prodromal symptoms, such as syncope and angina.

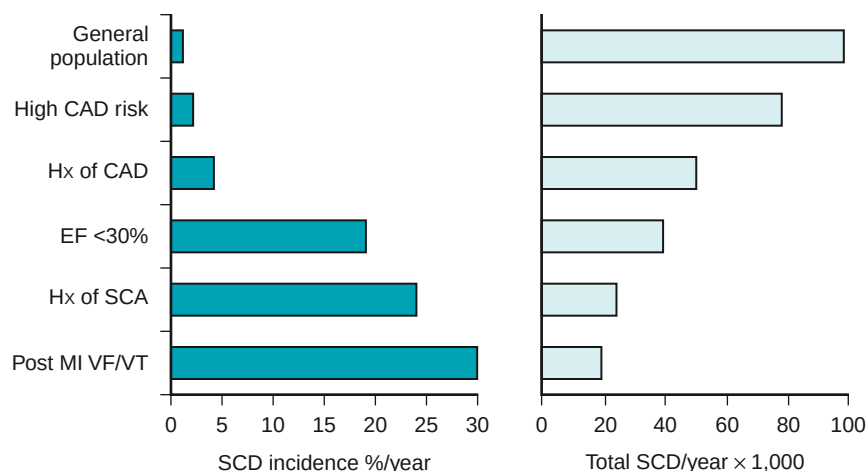


Figure 25-3. The incidence and number of patients with sudden cardiac death (SCD) in various subgroups of patients. *Left*, SCD incidence percent per year in each subgroup. *Right*, Total number of SCDs per year ($n \times 1000$). CAD, coronary artery disease; EF, ejection fraction; Hx, history; MI, myocardial infarction; SCA, sudden cardiac arrest; VF/VT, ventricular fibrillation/ventricular tachycardia. (Modified from Myerburg RJ Kessler KM, Castellanos A: SCD: Structure, function, and time-dependence of risk. *Circulation* 1992;85:I-2-I-10.)

Another coronary anomaly that poses risk for SCA in young individuals is the origin of the right coronary artery from the left sinus of Valsalva, with a consequent course between the aorta and pulmonary trunk.³⁵ Some unusual variants of coronary arterial anatomy, including hypoplasia of the right coronary and left circumflex or the anomalous origin of the left anterior descending or right coronary from the pulmonary trunk,³⁶ may in rare instances be implicated in exercise-related sudden cardiac deaths.

2. Embolism:

Coronary artery embolism usually results from endocarditis of the native or prosthetic aortic and mitral valves,³⁷ although rarely, left ventricular or left atrial thrombi may embolize into the coronaries.

3. Arteritis:

Kawasaki disease,³⁸ polyarteritis nodosa,³⁹ and syphilitic aortitis⁴⁰ can affect the coronary circulation, and SCA may be a rare sequelae.

4. Bridging:

SCA has also been reported to occur, especially during exertion, in patients with severe myocardial bridging, particularly of the left anterior descending artery. In this condition, the artery is completely surrounded by myocardium during a portion of its course, instead of being largely epicardial, and a critical degree of systolic compression resulting in myocardial ischemia may occur, even in the absence of underlying atherosclerotic disease.

5. Dissection:

Spontaneous dissection of the coronary arteries in Marfan syndrome⁴¹ and in the peripartum period of pregnancy,⁴² coronary involvement with any type 1 aortic dissection from other causes, or a rupture of the sinus of Valsalva aneurysm involving the coronary ostia can also cause SCA.⁴³

6. Vasospasm:

Vasospastic angina can have ventricular arrhythmias and culminate in SCA.⁴⁴ This is occasionally an etiology for otherwise unexplained SCA and may also occur as a result of cocaine abuse.

Hypertrophic Cardiomyopathy (HCM)

Despite a relatively low incidence of HCM in the general population, it maintains a high profile risk because 50% to 90% of deaths in patients with HCM are sudden, with an annual mortality rate of 2% to 4%.⁴⁵ Unlike most other heart diseases, the risk of SCA in HCM declines with age.⁴⁶ Patients with this disease characteristically have genetic heterogeneity in the amount of hypertrophy in different regions in the left ventricle. It results from multiple diseased genes, encoding sarcomeric proteins. Microscopically, gross disorganization of muscle bundles and myofibrillar architecture, altered gap junctions, increased basal membrane thickness, and connective tissue accumulation are noted.⁴⁷ These patients, therefore, manifest both electrical instability and consequences of myocardial hypertrophy with altered hemodynamics.

The mortality risk, based on the degree of outflow tract obstruction, has not yet been clearly stratified and, therefore, although hemodynamic considerations may play an important role in SCA, no predictive variables have been identified.⁴⁷ Furthermore, the combination of nonsustained ventricular tachycardia (NSVT) and inducible VT at electrophysiologic testing does confer a higher risk, and, conversely, the absence of NSVT and lack of inducibility indicates a lower risk.

The mechanism for SCA in patients with HCM is most often ventricular arrhythmias.⁴⁸ However, left ventricular outflow obstruction, sinus node dysfunction, atrioventricular (AV) conduction diseases, and supraventricular arrhythmias are alternative mechanisms.⁴⁹ The genesis of these arrhythmias is found in a complex interplay of electrophysiologic and hemodynamic abnormalities, primarily from electrophysiologic derangement of the hypertrophied muscle. Fairly often, SCA is the first manifestation of heart disease in these individuals, and thus is implicated as the substrate explaining the occurrence of these arrhythmias in children or young athletes.⁵⁰ Young age, strong family history, worsening obstructing symptoms,⁵¹ prior episode of SCA, failure to raise blood pressure on exercise, and severe ventricular hypertrophy of more than 3 cm thickness⁵² are incremental risk factors for SCA.

Ventricular hypertrophy secondary to systemic or pulmonary hypertension or owing to valvular or congenital heart disease is also associated with an increased risk for SCA.¹¹ This risk is proportionate to the level of severity of the hypertrophy.⁵³

Idiopathic Dilated Cardiomyopathy (DCM)

Overall survival following a clinical diagnosis of DCM is estimated to be 70% at 1 year and 50% at 2 years.⁵⁴ Most of these deaths are sudden in nature, and the incidence ranges in various series from 28% to 72% of total deaths. Syncope is a poor prognostic indicator in patients with DCM and is associated with a 44% incidence of SCD in 4 years.⁵⁵ Patients with preserved left ventricular function may have a lower short-term mortality from pump failure but are at a greater risk for SCA from arrhythmic events. Ventricular tachyarrhythmias⁵⁶ are the most common mode of death, but bradyarrhythmias⁵⁷ occur also, especially in those patients with advanced pump dysfunction. The arrhythmia most commonly implicated in SCA is primary polymorphic VT or VF. Additionally, rapid sustained monomorphic VT, related to bundle branch reentry,⁵⁸ and monomorphic VT, unrelated to bundle branch re-entry, have been seen. The recognition of this arrhythmia is critical because these patients can be successfully cured by catheter ablation of the right bundle branch.⁵⁸ Catheter ablation, at the present time, cannot be considered a curative option in SCA survivors with ventricular tachycardia related to CAD. Monomorphic VT, unrelated to bundle branch re-entry, is probably the result of the presence of smaller re-entrant circuits within the myocardium. In most instances, the triggering mechanism for the onset of primary polymorphic VT or VF is unclear. In some patients, triggers such as hypokalemia, use of antiarrhythmic medications, and hypomagnesemia may be more easily identifiable.

Long QT (LQT)

Patients with LQT have higher risk of SCA as a result of torsades de pointes and VF. This condition might be as a result of congenital substrate such as in LQT syndrome (LQTS), or may be acquired.

1. Congenital LQTS

The long QT syndromes are phenotypically and genotypically diverse, but have in common the appearance of long Q-T intervals in the electrocardiogram (ECG), an atypical polymorphic VT known as torsades de pointes (TdP), and, in many but not all cases, a relatively high risk for sudden cardiac death.

The prevalence of this disorder is estimated at 1-2:10,000. Congenital LQTS is subdivided into eight genotypes distinguished by more than 400 mutations in at least seven different ion genes and a structural anchoring protein located on seven chromosomes (Table 25-1).^{16,59-63} All of these genotypes have a similar phenotypic presentation (long QT) but different clinical profiles regarding T wave patterns (Fig. 25-4), arrhythmia triggers (Fig. 25-5), prognosis, and response to therapy.⁶³⁻⁶⁶ The phenotype penetration and expression is variable even in the same mutation.⁶⁷ The most common subgroups are LQT1, LQT2, and LQT3; they account for more than 90% of all genotyped LQTS patients.

a. LQT1:

It is the most common (40% to 50%) and least serious life-threatening genotype.^{63,66} The ECG pattern shows a long QT with a broad-based T wave (see Fig. 25-4). The trigger for cardiac arrhythmia is sympathetic hyperactivity associated with

exercise (especially swimming) or emotions (see Fig. 25-5). Catecholamine increases the function of the slowly activating delayed-rectifier potassium channel (IKs) to shorten the Q-T interval during tachycardia. However, due to “loss-of-function” of the IKs channel in LQT1, the Q-T interval is prolonged and causes TdP, leading to SCD. Two patterns of inheritance have been identified:

- (1) Jervell and Lang-Nielsen syndrome.⁶⁸ It is an autosomal recessive disease associated with deafness. Caused by more than 150 mutations in two genes that encode for the IKs channel (KCNQ1 and KCNE1), which affect the cardiac cell membrane and the production of the endolymph in the inner ear.⁶⁹
- (2) Romano-Ward syndrome.^{70,71} It is an autosomal dominant disease, more common, not associated with deafness, and broader (includes all other LQTS).

b. LQT2:

LQT2 is the second most common (35% to 50%) and second least serious life-threatening genotype.^{63,66} The ECG pattern shows long QT with a bifid, notched, low amplitude T wave (see Fig. 25-4). The triggers for cardiac arrhythmia are acute arousal with auditory stimuli or emotions, or during sleep or rest (see Fig. 25-5). It results from mutations in two genes (*KCNH2* “*HERG*,” and *KCNE2* “*MiRP1*”), causing “loss-of-function” of the rapidly activating delayed-rectifier potassium channel (IKr), and leading to Q-T prolongation, then to TdP and SCD.

c. LQT3:

It accounts for 10% of LQTS and manifests with a late-onset peaked or biphasic T wave pattern on the ECG.^{62,63,65} Triggers for cardiac arrhythmia are rest or sleep. There are more than 50 *SCN5A* mutations that cause LQT3. The *SCN5A*-encoded defect causes “gain-of-function,” leading to production of persistent, noninactivating inward sodium current (INa) during the plateau phase of the action potential and prolongation of the Q-T interval.⁶⁹

d. LQT4:

It is a rare subgroup that manifests with moderate Q-T prolongation, severe sinus bradycardia, and episodes of atrial fibrillation.^{72,73} Usually exercise induces polymorphic ventricular arrhythmia, syncope, or SCD. The responsible gene is *Ankrynb2* encoding the ankyrin B protein, which participates in the anchoring of several ion channels (Na⁺/K⁺ ATPase, Na⁺/Ca⁺ exchanger) and proteins (InsP3 receptor) to the cell membrane.^{72,73}

e. LQT5:

It accounts for 2% to 3% of LQTS (rare), and results from the *KCNE1* (*minK*) gene mutation, causing “loss-of-function” in the IKs channel. In homozygous or compound heterozygous form, it manifests as Jervell and Lange-Nielsen type II syndrome.⁷⁴

f. LQT6:

LQT6 is a very rare subgroup resulting from the *KCNE2* (*MiRP1*) gene mutation, causing “loss-of-function” in the IKr channel.

g. LQT7:

It is another rare subgroup of LQTS, results from the *KCNJ2* (*Kir2.1*) gene mutation causing “loss-of-function” in the IK1 channel. It manifests as an Andersen-Tawil syndrome, which is characterized by potassium-sensitive periodic paralysis, neuromuscular manifestations, facial dysmorphic features, variable degree of Q-T interval prolongation with giant U waves, bidirectional, or polymorphic tachycardia, and, rarely, SCD.^{75,76}

Table 25-1. Ion Channelopathy Disorders' Characteristics

Type	Gene Mutation	Locus	Ion Channel	Frequency	Trigger of TdP	Prognosis (cardiac event rate)*	Syndrome
LQT1	<i>KCNQ1</i>	11p15	I _K s	40%-50%	Exercise or emotion	30%	Jervell and Lange-Nielsen type I
LQT2	1. <i>KCNH2</i> "HERG" 2. <i>KCNE2</i>	7q35	I _K r	35%-50%	Auditory, emotion, or rest/sleep	46%	—
LQT3	<i>SCN5A</i>	3p21	I _{Na}	7%-15%	Rest/sleep	42%	—
LQT4	<i>AnkrynB2</i>	4q25	Several	Rare	Exercise	—	Severe SB, and episodes of AF
LQT5	<i>KCNE1</i> "minK"	21q22	I _K s	2%-3%	—	—	Jervell and Lange-Nielsen type II
LQT6	<i>KCNE2</i> "MiRP1"	21q22	I _K r	Very rare	—	—	—
LQT7	<i>KCNJ2</i> "Kir2.1"	17q23	I _K 1	Rare	—	—	Andersen-Tawil
LQT8	<i>CaCNA1C</i> "Cav1.2"	6q8A	I _{Ca}	Rare	—	—	Timothy
LQT9	<i>SCN4B</i>		I _{Na}	Rare	—	—	—
LQT10	<i>CAV3</i>		I _{Na}	Rare	—	—	—

Characteristics include: gene mutation and its chromosomal location, the affected ion channel, the frequency, the triggers of torsades de pointes, prognosis and name of the syndrome if present. LQT = long QT; SB = sinus bradycardia; AF = atrial fibrillation, ↑ = "gain-of-function"; ↓ = "loss-of-function." (The cardiac event rate is from Priori SG, Schwartz PJ, Napolitano C, et al: Risk stratification in the long-QT syndrome. *N Engl J Med* 2003;348:1866-1874. Copyright 2003 Massachusetts Medical Society. All rights reserved. Reproduced with permission.)



Figure 25-4. Three ECGs illustrating the typical Q-T morphology of the three most common long QT syndromes. Left, ECG of LQT1. Center, ECG of LQT2. Right, ECG of LQT3.

h. LQT8:

LQT8 is a rare subgroup type of LQTS called Timothy syndrome.⁷⁷ It is characterized by multiorgan dysfunction and results from a "gain-of-function" mutation in the *CaCNA1C* gene, which encodes the L-type calcium channel (CaV1.2). The manifestations include congenital heart disease, webbing (syndactyly) of the fingers and toes, immune deficiencies, autism, cognitive abnormalities,

and severe Q-T prolongation with childhood sudden death.

i. Other LQT:

There are other LQTS to be discovered. Two new ones were reported recently, LQT9 ("gain-of-function" *SCN4B* gene mutation of I_{Na}) and LQT10 ("gain-of-function" *CAV3* gene mutation of I_{Na}).

The risk of a second event (syncope or SCA) before age 18 is:⁶⁶

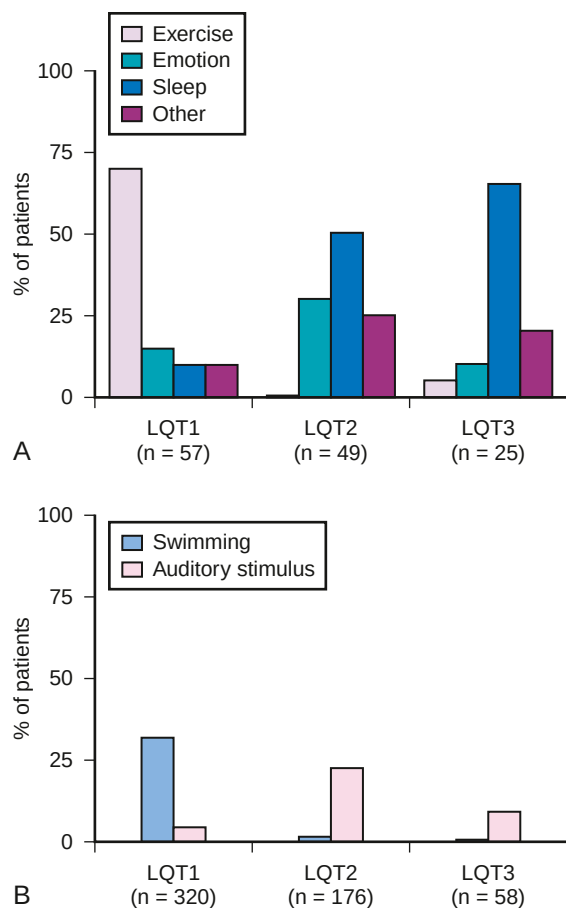


Figure 25-5. Gene-specific triggers for life-threatening arrhythmias in the three most common long QT (LQT) syndromes. *Top*, Exercise, emotion, sleep, or other triggers. *Bottom*, Swimming versus auditory stimulus. (Adapted from Schwartz PJ, Priori SG, Spazzolini C, et al: Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. *Circulation* 2001;103:89-95.)

- High (= 50%) in QTc = 500 ms with LQT1 and LQT2, or male sex in LQT3.
- Intermediate (30% to 49%) in QTc = 500 ms with female sex LQT3, or QTc less than 500 ms in LQT3 or female sex LQT2.
- Low (<30%) in QTc less than 500 ms in LQT1 or male sex LQT2.

Exercise should be restricted in all patients to prevent an event. The mechanism of LQTS is related to the amplification of transmural dispersion of repolarization (TDR) because of preferential prolongation of the action potential duration of M cells. The development of early after depolarization-induced triggered activity underlies the substrate and trigger for the development of life-threatening ventricular arrhythmias.⁵⁹

Recent studies have provided validation for reliance on the estimation of TDR index, measuring Tpeak-Tend interval and for the prediction of risk of SCD in patients with congenital or acquired long QT.^{60,61}

2. Acquired LQT:

Acquired Q-T prolongation is more commonly encountered in clinical practice than congenital long QT and may be associated with bradycardia or caused by hypokalemia, hypomagnesemia, hypothermia, or anorexia nervosa or may be a side

effect from the use of class IA or III antiarrhythmic agents, or liquid protein diets. Bradycardia and delayed ventricular repolarization constitute the substrate for the development of polymorphic ventricular tachycardia that frequently degenerates into VF. SCA, in this group of patients, therefore, is usually iatrogenic, and the propensity to manifest Q-T prolongation after exposure to a trigger such as a drug may be related, in some patients, to an underlying genetic predisposition.

Brugada Syndrome

The Brugada syndrome is a rare condition characterized by a spontaneous or class I antiarrhythmic drug-induced, coved-type ST segment with at least a 2 mm J wave elevation (type I ECG pattern) appearing principally in the right precordial leads (V1-V3) (Fig. 25-6), often followed by negative T wave.⁷⁸ Incomplete or complete right bundle branch block morphology may be present. Unfortunately, this ECG pattern is dynamic, where up to 50% of patients with Brugada syndrome may have a transient normalization of the ECG, or a saddleback-type ST elevation (type II ECG pattern).^{16,59,79}

Symptomatic patients have syncope or SCA due to a rapid polymorphic VT or VF. The predictors of an event include spontaneous type I ECG pattern, inducibility of a sustained ventricular arrhythmia during electrophysiologic study, a previous episode of syncope, and male gender (75% of patients with Brugada syndrome are male).⁸⁰

The disease follows an autosomal dominant pattern of inheritance with variable penetrance in 20% to 50% of the patients. More than 70 mutations of the *SCN5A* gene have been identified as leading to a “loss-of-function” of the INa channel.¹⁶ The arrhythmogenic substrate is the amplification of heterogeneities intrinsic to the early phases (Ito) of the action potential of cells residing in different layers of the RV wall of the heart, leading to loss of the action potential dome at some epicardial sites but not others, creating phase 2 re-entry and coupled extrasystole.⁸¹ A marked TDR develops as a consequence of the heterogeneity, creating a vulnerable window—which when captured by a premature extrasystole can trigger a circus movement re-entry in the form of VT/VF and SCD.⁵⁹

Short QT Syndrome (SQTS)

SQTS is an autosomal-dominant inherited syndrome characterized by a QTc less than 320 ms, tall peaked symmetrical T waves in the ECG (Fig. 25-7), and high incidence of VT/VF and atrial fibrillation secondary to increased TDR.^{59,82} Electrophysiology studies show very short atrial and ventricular refractory periods and easily inducible ventricular fibrillation.⁸³ The mutations have been identified in four different genes to date:^{16,84}

1. SQTS1: *KCNH2* “*HERG*” gene causing “gain-of-function” of the IKr channel.
2. SQTS2: *KCNQ1* (KvLQT1) gene causing “gain-of-function” of IKs channel.
3. SQTS3: *KCNJ2* causing “gain-of-function” of IK1 channel. Uncommon to cause SCD.
4. SQTS4: *CACNA1C* and *CACNB2* causing “loss-of-function” of α_1 - and β_2 -subunits of the L-type calcium channel leading to short QT and Brugada ECG morphology.

Catecholaminergic Polymorphic VT (CPVT)

CPVT is a rare inherited syndrome characterized by physical or emotional stress-induced bidirectional VT, polymorphic VT, and a high risk of SCA in the setting of a structurally normal

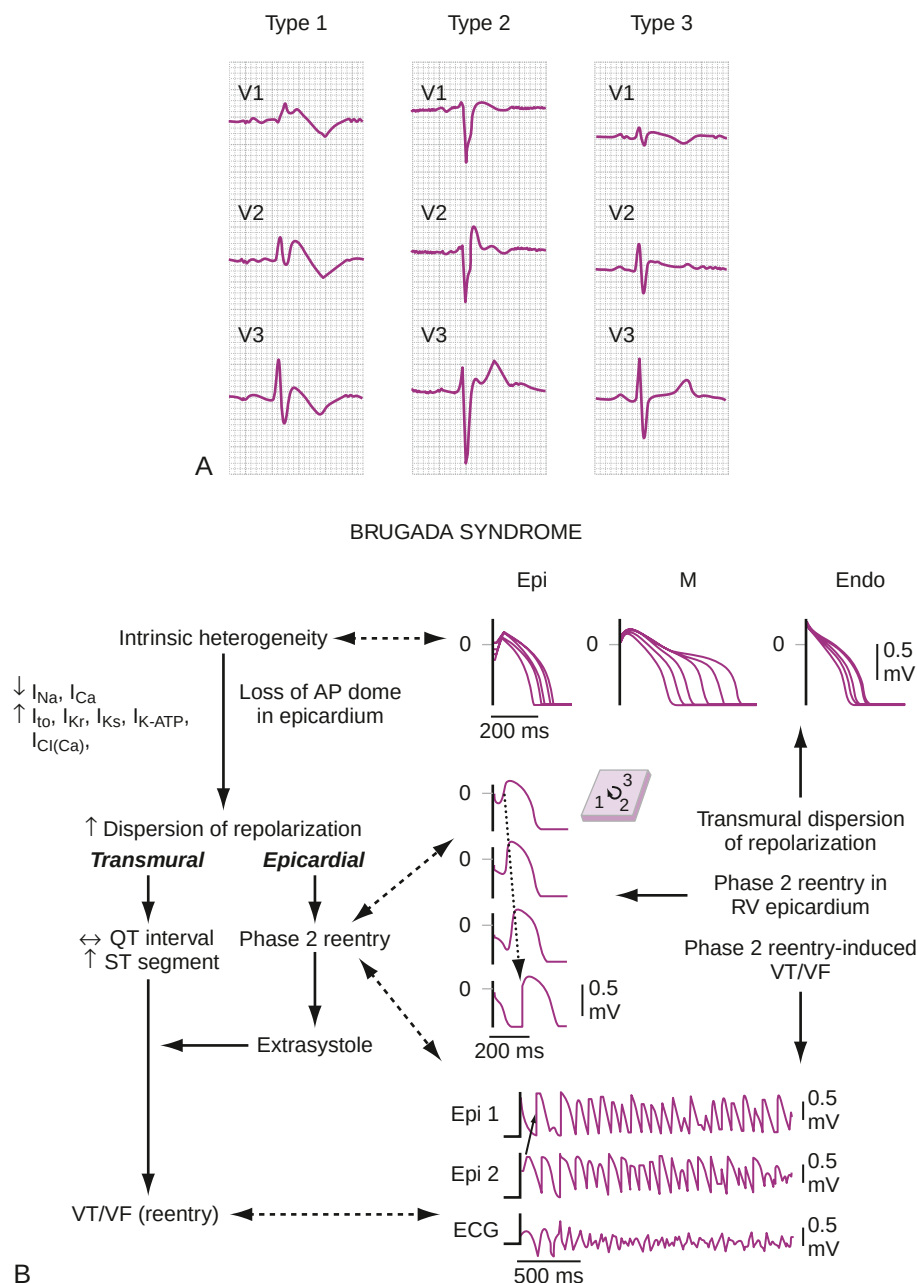


Figure 25-6. A and B. Types of ECG morphology for Brugada syndrome (**A**) and the proposed mechanism for Brugada syndrome (**B**). A shift in the balance of currents amplifies existing heterogeneities by causing loss of action potential (AP) dome at some epicardial, but not endocardial, sites. A vulnerable window develops as a result of the dispersion of repolarization and refractoriness within the epicardium and across the wall. Epicardial dispersion leads to the development of phase 2 re-entry, which provides the extrasystole that captures the vulnerable window and initiates ventricular fibrillation/ventricular tachycardia (VT/VF) via a circus movement re-entry mechanism. RV, right ventricular. (**A**, From Napolitano C, Priori SG: Brugada syndrome. *Orphanet J Rare Dis* 2006;1:35; **B**, from Antzelevitch C: Ion channels and ventricular arrhythmias: cellular and ionic mechanisms underlying the Brugada syndrome. *Curr Opin Cardiol* 1999;14:274-279.)

heart. Thirty to fifty percent of patients with CPVT will have SCA by age 30. Two mutations have been identified: (1) cardiac ryanodine receptor 2 (hRyR2) results in “gain-of-function” of the ryanodine release channel; (2) calsequestrin 2 (CASQ2) results in “loss-of-function” of the calsequestrin calcium reservoir. Both lead to calcium leak and delayed after depolarization arising from the epicardium, endocardium, or M region. Alternation and migration of the source of ectopic activity is responsible for

the bidirectional VT and slow polymorphic VT, leading to amplification of TDR, giving rise to re-entrant VT/VF and SCA.^{85,86}

Arrhythmogenic Right Ventricular Dysplasia (ARVD)

ARVD is a form of cardiomyopathy with fibrofatty infiltration of the right ventricle, characterized by inverted T waves, ϵ waves, notched S wave, and widening of QRS (>110 ms) in the right precordial leads (V1-V3) (Fig. 25-8).⁸⁷ The signaled-averaged

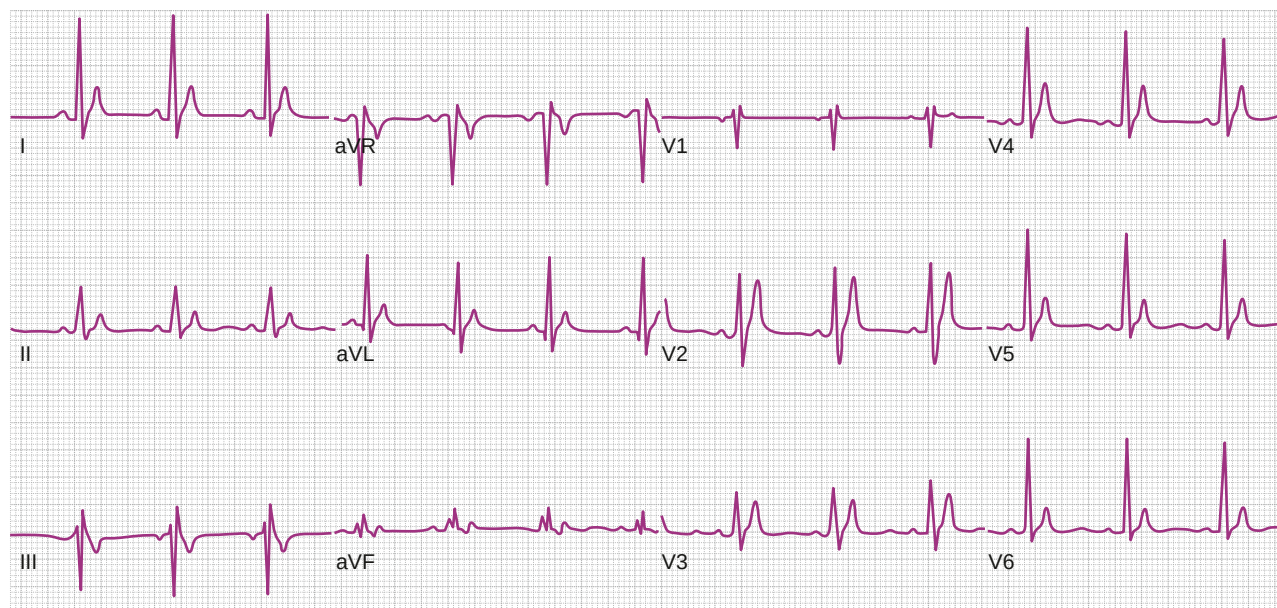


Figure 25-7. A 12-lead ECG from a patient with short QT syndrome. The Q-Tc = 306 ms (<320 ms) with tall, peaked symmetric T wave. (Bjerregaard P, Gussak I: Short QT syndrome: mechanisms, diagnosis and treatment. *Nat Clin Pract Cardiovasc Dis* 2005;2:86. Reprinted by permission from Macmillan Publishers Ltd. Copyright 2005.)

ECG usually is markedly abnormal. Findings of right ventricular dilation/aneurysm on an echocardiogram (or cardiac MRI) may be helpful in diagnosing ARVD. Suspicion for this diagnosis should increase if there is a family history of the disease since it occurs in 30% to 50% of offspring. Multiple genetic mutations were discovered; most of them code for desmosomal proteins, which anchor intermediate filaments to the cytoplasmic membrane in adjoining cells in the gap junction. Inflammation from myocarditis triggers the expression of these genes, leading to an increase in fibrofatty infiltration. The strands of surviving myocardial fibers from the arrhythmogenic substrate are culpable because they establish re-entrant circuits leading to VT/VF and SCA, and are significant in determining how to best manage these patients. These patients would have a normal life span if their arrhythmias were adequately treated with sotalol, an implantable cardioverter defibrillator (ICD), or ablation.⁸⁸

Wolff-Parkinson-White Syndrome (WPW)

The prevalence of WPW is 0.1% to 0.3%⁸⁹ of the general population, and the incidence of sudden death in asymptomatic individuals is, at worst, 1 per 100 patient years of follow-up.⁹⁰ SCA occurs as a result of atrial fibrillation with a very rapid ventricular response over an accessory pathway with short refractory periods, leading to VF.⁹¹ Most patients who experience SCA as a result of WPW have previously manifested symptomatic arrhythmias. Patients with multiple accessory pathways, a family history of WPW with SCD, and, obviously, those with concomitant heart disease are at a higher risk for SCA.

Cardiac Conduction System Abnormalities

Patients with congenital AV block or nonprogressive intraventricular block have a lower risk for SCA. Abnormalities of the specialized cardiac conduction system are a rare cause of SCA and are usually noted in young, otherwise healthy individuals without a prior history of arrhythmia. Unless an exhaustive and

elaborate autopsy analysis is made, the underlying abnormality may never be discovered in the postmortem examination, leading to the belief that no such abnormality existed. Both acquired AV nodal and His-Purkinje disease, owing to CAD and primary fibrosis, can also, uncommonly, cause SCA.

Congenital Heart Disease

1. Congenital aortic stenosis⁹² can predispose to SCA. The risk for SCA correlates with the severity of the stenosis, and aortic valve replacement does not eliminate the risk but has been shown to reduce it.
2. Eisenmenger syndrome⁹³ can also predispose to SCA.
3. Tetralogy of Fallot:⁹⁴ Potentially fatal arrhythmias have been described as late complications in up to 5% of patients undergoing successful surgical repair of tetralogy of Fallot. The presence of premature ventricular contractions may be a marker of increased risk for SCA.
4. Transposition of the great arteries:⁹⁵ The mechanisms of SCA in patients who have undergone surgical procedures for correction of transposition of the great arteries include bradyarrhythmias, sick sinus syndrome, and atrial flutter (the predominant tachyarrhythmia). The incidence of late SCD is approximately 5%. This risk has been reduced with the use of an alternative technique known as the arterial switch operation.
5. AV canal anomalies: SCA has been seen as a late complication after surgical repair of AV canal anomalies.

Valvular Heart Disease

Disease of the heart valves pose an increased risk for future SCA, usually as a result of left ventricular dilation and hypertrophy. Rheumatic valvular heart disease can, uncommonly, result in SCD due to arrhythmias, ball valve thrombus in the left atrium obstructing the mitral orifice, embolization of the coronary arteries, or acute low-output circulatory failure. SCD is one of

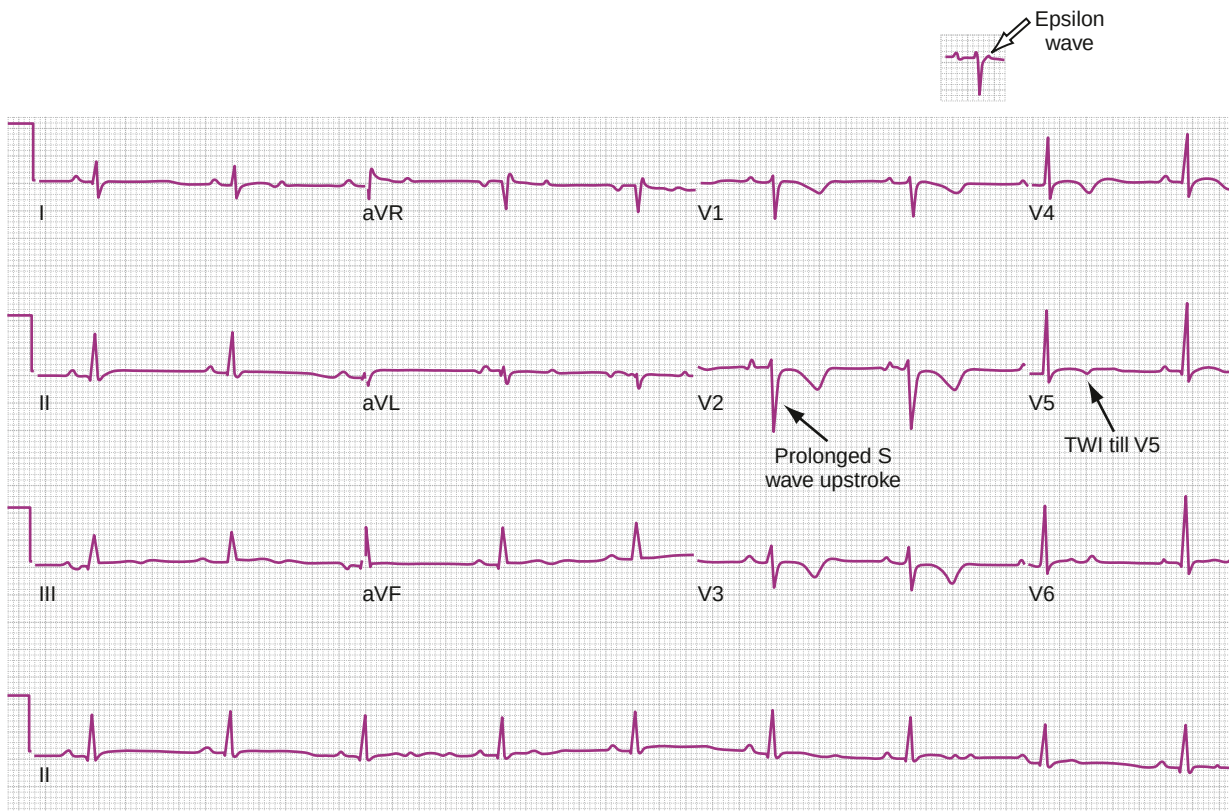


Figure 25-8. ECG morphology of arrhythmogenic right ventricular dysplasia with inverted T waves, ϵ waves, notched S wave, and widening of QRS (>110 ms) in the right precordial leads (V_1 - V_3). (From Nasir K, Bomma C, Tandri H, et al: *Electrocardiographic features of arrhythmogenic right ventricular dysplasia/cardiomyopathy according to disease severity: a need to broaden diagnostic criteria. Circulation* 2004;110:1527-1534.)

the most common modes of death after valve replacement surgery and is attributable to arrhythmias and thromboembolism.

Inflammatory and Infiltrative Diseases

Acute viral myocarditis, with or without left ventricular dysfunction, is an important cause of sudden death in the young. SCA may result from either lethal ventricular arrhythmias or damage to the specialized conduction system during the myocarditis. Collagen vascular diseases (causing myocarditis and vasculitis), progressive systemic sclerosis, granulomatous diseases (such as sarcoidosis), infiltrative diseases (such as amyloidosis and hemochromatosis), intramural tumors, neuromuscular diseases (such as muscular dystrophy, Friedrich ataxia, and myotonic dystrophy), Chagas disease, idiopathic giant cell myocarditis, and cardiac ganglionitis all can cause SCA.¹

Clinical Presentation

It is estimated that only 30% to 40% of SCD victims can be identified as being at risk for SCA before the event. Unfortunately, the majority have only short-lasting symptoms or are completely asymptomatic before experiencing SCD. Some patients report nonspecific symptoms of chest pain, weakness or fatigue, and palpitations weeks to months before the event.⁹⁶ Symptoms occurring a few hours or minutes before the episode are more specific for the underlying heart disease and are usually secondary to arrhythmias, ischemia, or congestive heart failure.

Circulatory deaths are more common with noncardiac terminal events and frequently manifest bradyarrhythmias.

The cardiac arrest itself is characterized by the abrupt loss of consciousness that leads to death without active resuscitation, although, rarely, spontaneous reversions do occur. The maximum survival rates for patients with cardiac arrest outside the hospital are reported to be in the range of 20% to 30%,²⁹ depending upon the availability of bystander and emergency teams. The outcome of resuscitation in the field is strongly influenced by the documented initial rhythm and the time elapsed since the collapse (Fig. 25-9).⁹⁷ Survival is best when the initially documented rhythm is VT. Victims with bradycardia or asystole have a uniformly poor outcome. Only a small subset of patients with bradyarrhythmias, owing to some electrolyte or pharmacologic abnormality, responds well to acute interventions. Young patients with less severe cardiac disease, and without coexisting multisystem disease, have a higher probability of survival. Mortality is higher in patients with associated noncardiac disease, such as renal failure, pneumonia, diabetes, sepsis, and malignancy.

Evaluation Of The Sca Survivor

The initial management of a cardiac arrest survivor, either spontaneously or with advanced cardiac life support (ACLS), is usually performed in an intensive care unit with continuous rhythm monitoring. A significant proportion of these patients

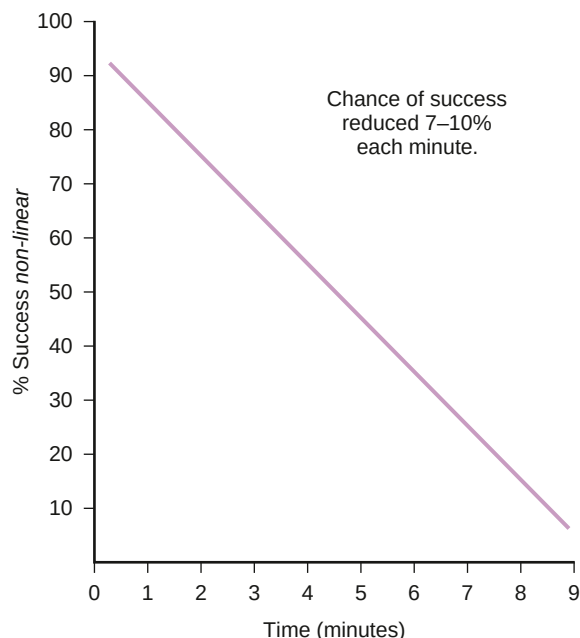


Figure 25-9. Resuscitation success rate versus time. The chance of success reduces 7% to 10% each minute. (From Emergency Medical Technician Department at St. Louis Community College. Available at: <http://users.stlcc.edu/cmittle/emt/aed/sld004.htm>. Accessed February 6, 2008.)

succumb to cardiogenic shock, congestive heart failure, respiratory complications, and sepsis, accounting for an in-hospital mortality of up to 60%.²⁹ Myocardial function in the early phase following resuscitation is usually depressed, and many patients require transient inotropic support for hemodynamic stabilization. Only a small number of patients admitted to the hospital following cardiac arrest are conscious at the time of admission, and, in the first 24 to 48 hours, those that are semiconscious may require heavy sedation or paralysis to facilitate pulmonary toilet and nursing care. The degree of hypoxic brain damage is variable. However, recovery is usually rapid. Coma persisting 3 days beyond the event is usually associated with a poor prognosis.⁹⁸

Following this initial period of stabilization and neurologic improvement, all patients should undergo a complete cardiac evaluation unless it is contraindicated by the presence of terminal illness. The etiology of SCA in these patients can usually be categorized as being associated with either ischemic or nonischemic heart disease, or as occurring in the absence of overt cardiac disease. This approach is helpful in determining the direction to proceed for further evaluation and in determining management strategies. Both noninvasive and invasive laboratory evaluations, including electrophysiologic studies, are performed in these patients and have variable yields and implications depending upon the underlying substrate.

1. History and physical: A detailed history from the patient and witnesses may offer possible clues for triggering mechanisms (such as ischemia and proarrhythmia), and a family history may suggest the underlying heart disease. Knowledge of prodromal symptoms, the nature of activity at the time of the event, and whether there is any history of substance abuse are also important. If antiarrhythmic medications had been prescribed previously, it is useful to draw plasma samples to

determine drug levels. The clinical examination is focused on determining the nature of the underlying heart disease or systemic disease, if any, and the extent of its involvement, particularly with reference to ventricular function. Laboratory evaluation is also aimed at determining the presence of triggering agents (hypokalemia, metabolic disturbances, and toxic substances) and whether the episode of SCA was caused by a reversible circumstance.

- 2. ECG:** An initial resting ECG is useful in determining the presence or absence of underlying structural or functional abnormalities such as acute or prior MI, arrhythmogenic right ventricular dysplasia, long QT syndrome, Brugada syndrome, short QT syndrome, hypertrophic cardiomyopathy, or WPW.
- 3. Holter monitoring:** Ambulatory Holter monitoring and SAECG are commonly used for noninvasive evaluation of cardiac arrest survivors. Although monitoring may or may not document complex ventricular ectopy after cardiac arrest, it has little or no utility in assessing the ability to suppress ventricular ectopy by antiarrhythmic agents or predicting reduction in risk for future SCA. Complex ventricular ectopy therefore appears to be a marker of underlying cardiac disease rather than the cause of increased mortality.
- 4. Signal-averaged electrocardiography (SAECG):** Low-amplitude, high-frequency potentials recorded in the terminal portion of the filtered QRS (SAECG) complex are thought to represent electrical activity from the anatomic arrhythmogenic substrate. Their presence, especially in patients with coronary artery disease, is thought to predict spontaneous future arrhythmic events, mainly when no revascularization was done and particularly when combined with the LV function analysis. SAECG is an excellent negative predictor for SCA in patients with CAD (89% to 99%). It is important to recognize that the prognostic value of the SAECG is less well-defined in patients with nonischemic heart disease, except for in ARVD and hypertrophic cardiomyopathy. The SAECG may be abnormal in 15% to 20% of patients with hypertrophic cardiomyopathy, but its predictive value for SCA remains unproven. Similarly, a recording of asymptomatic nonsustained ventricular tachycardia on Holter monitoring in a patient with HCM does not necessarily predict an adverse prognosis unless the patient experienced prior episodes of syncope or cardiac arrest, or had a history of inducible ventricular tachyarrhythmias.
- 5. Left ventricular (LV) function and echocardiogram:** Evaluation of LV function is critical because LV function is the strongest independent predictor for recurrence and long-term survival following out-of-hospital cardiac arrest.⁹⁹ This may be accomplished using echocardiography or radionuclide ventriculography. The latter may also be employed for imaging the right ventricle to identify ARVD as a cause, but magnetic resonance imaging is probably superior. LV function also predicts successful suppression of inducible ventricular arrhythmias during serial drug testing. In patients with reduced LV function, these arrhythmias are usually not suppressible and are more likely to recur clinically. The two-dimensional (2-D) echocardiography with color Doppler is also used to identify structural abnormalities of wall motion, myocardial contractility, valvular abnormalities, infiltrative myocardial disorders, coronary artery anomalies, and abnormalities of the aortic root.

6. *Exercise stress testing*: Exercise stress testing is used in cardiac arrest survivors primarily to evaluate overt or provokable ischemia. On occasion, the test may be used to provoke the adrenergic form of long QT syndrome or catecholamine-dependent ventricular tachycardias in association with structurally normal hearts. An additional method for evaluating future arrhythmic risk involves measurement of heart rate variability, which is an indirect assessment of the influence of the autonomic nervous system on the cardiovascular system. The loss of the diurnal variation of heart rate variability in patients has been associated with a poor long-term outcome in the post-MI survivor.
7. *T wave alternans*: A noninvasive risk stratifier for SCA is a measurement of beat-to-beat fluctuation in amplitude and/or morphology of the T wave, called T wave alternans. The presence of alternans suggests dispersion of action potential duration and recovery leading to possible risk of re-entry and VT/VF. This test is suitable for all patients who are at risk for SCA, including those with LV dysfunction, post-MI, and heart failure, and has excellent positive and negative predictive value.^{100,101}
8. *Other noninvasive tests*: There are a few other noninvasive assessments to predict risk for SCD, which include measurements of heart rate variability (see above), Q-T dispersion, and baroreceptor sensitivity. There is a lack of strong supportive data for these tests, however, and they are not approved by the U.S. Food and Drug Administration (FDA) at this time for SCA risk stratification.
9. *Cardiac catheterization*: A complete cardiac catheterization, including coronary angiography, left and right heart hemodynamics, and left ventriculography is usually performed initially, even in young patients, to rule out coronary anomalies. In patients suspected of having myocarditis or cardiomyopathy, a right ventricular endomyocardial biopsy may provide additional diagnostic information to guide management, and this may be done during the catheterization procedure.
10. *Electrophysiology study (EPS)*: The practice of assessing antiarrhythmic drug efficacy with an EPS has largely been abandoned. In SCA survivors, there is no indication for an EPS due to strong evidence of ICD benefit in these patients. However, EPS remains the standard tool, especially in high-risk patients who are not candidates for an ICD implantation. The study should be performed in the absence of antiarrhythmic therapy since the results may be influenced by the drug. The likelihood of inducing a sustained ventricular arrhythmia depends upon the underlying heart disease (coronary versus noncoronary), left ventricular function, the presenting clinical arrhythmia (VT or VF), and the aggressiveness of the programmed stimulation protocol. Data suggest that the use of triple versus double extrastimuli yields a higher number of patients who are inducible. Although VF occasionally may be induced, it may be a clinically irrelevant arrhythmia.

EPS is warranted for risk stratification in patients with non-sustained VT, remote MI, and LV dysfunction (ejection fraction of 40%), and in patients with symptoms suggestive of VT/VF (e.g., palpitations, presyncope, or syncope).³ It is a valid diagnostic tool for the investigation of wide-QRS-complex tachycardias of unknown origin, or in conjunction with ablation of ischemic or nonischemic (e.g., right ventricular outflow tract) VT, or

supraventricular tachycardia (e.g., WPW). In addition, it may be helpful in stratifying high-risk patients, who will then need ICD, in Brugada syndrome and HCM. It has not proven useful as a diagnostic tool for other ion channelopathies.

Therapy

Selection of appropriate therapy for SCA survivors should be individualized. Before initiating specific therapy, the patient should undergo electrophysiologic testing and the underlying substrate, ventricular function, and hemodynamic state should be well established.

Pharmacologic Therapy

The selection of pharmacologic therapy as an option for cardiac arrest survivors depends upon the underlying cause.

All post-MI trials and LV dysfunction trials show significant survival benefit associated with the use of a β -blocker agent. In addition, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, and HMG-CoA reductase inhibitors are essential in post-MI patients to reduce risk for acute coronary syndrome and mortality. Nonetheless, antiarrhythmic therapy did not show significant benefit in these patients; instead class IC antiarrhythmic medications were rather harmful and they are contraindicated. Some antiarrhythmic medications such as amiodarone, sotalol, azimilide, or dofetilide may be useful as an adjunct therapy to ICD to reduce the frequency of ventricular arrhythmia and ICD shocks.

In SCA survivors with normal heart structure, pharmacologic therapy may be helpful in reducing the risk of VT/VF and recurrence of SCA. β -blockers, calcium channel blockers, sotalol, or flecainide were used in right ventricular outflow tract tachycardias. Sotalol is the drug of choice in ARVD as a primary therapy or adjunct with ICD therapy to prevent SCD.¹⁰² In low-risk LQTS patients, who are not candidates for ICD implant, β -blockers are the drug of choice to prevent dysarrhythmia. The predictors of failure of β -blockade include Q-T greater than 500 milliseconds, LQT2 or LQT3, and early age episode of SCD (<7 years). Sodium channel blockers (Class IC antiarrhythmic medication) might be helpful in patients with LQT3. On the other hand, sodium channel blockers worsen the Brugada syndrome manifestation, subsequently increasing the risk of arrhythmia and SCA. Quinidine is highly effective in reducing the frequency of VF in Brugada syndrome, especially in ICD shock storm. Quinidine and disopyramide are effective in reducing the frequency of VT/VF in SQTS1 patients. Either disopyramide or β -blockers may be used in patients with HCM. In CPVT, β -blockers, not calcium channel blockers, are used as an adjunct therapy with ICD.

Correcting the secondary causes of SCA may be accomplished with a pharmacologic approach or with oxygen supplementation (e.g., hypoxia). Drug toxicity, leading to dysarrhythmia and SCA, can be managed by stopping the medication or altering its effect. Dysarrhythmia due to electrolyte imbalance (e.g., hypomagnesemia, hypokalemia, hyperkalemia, etc.) can be amended by supplementation or dialysis.

Myocardial Revascularization and Arrhythmia Surgery

Acute myocardial ischemia is considered a contributing factor to SCA based on several clinical observations.⁸ It is therefore likely that prevention or reduction of myocardial ischemia

would consequently decrease the incidence of SCA in those patients with CAD who have either symptomatic or silent myocardial ischemia. In addition, myocardial revascularization has been shown to reduce the incidence of SCA when used as a secondary prevention of cardiac arrest in patients who have been successfully resuscitated from a previous episode related to acute MI.¹⁰³ It is important to note that the induction of VF in the preoperative EPS may be suppressed in over half of these patients by myocardial revascularization.

Revascularization includes using a medical approach (anti-thrombins/antiplatelets), cardiac catheterization and angioplasty, or myocardial bypass graft surgery. Any one of these techniques is associated with reduction of the risk for SCD.³

Revascularization alone is unlikely to eliminate clinical or inducible monomorphic VT, especially in patients with a fixed anatomic substrate (myocardial scar/ventricular aneurysm). Thus ICD will be indicated with a possible need for an electrophysiologic-guided excision or ablation of this tissue, but the technique is fairly complicated and should be performed by a team with experience in this procedure.¹⁰⁴

Catheter Ablation

Catheter ablation is considered a state-of-the-art approach to curative management of VT, and as a primary or adjunct therapy to an ICD. In a minority of patients, the underlying etiology for SCA may be demonstrated to be supraventricular in origin (e.g., WPW). Ablating the source of the supraventricular tachycardia will prevent further VT/VF and risk of SCA. Patients with bundle branch re-entry VT, those with idiopathic VT originating in the right ventricular outflow tract or left ventricle, and patients with fascicular VT may have SCA. The importance of performing a detailed electrophysiologic study in a SCA survivor is highlighted by the fact that all of these arrhythmias can be cured by radiofrequency catheter ablation, thus obviating the need for further therapy and possibly eliminating future risk. In addition, postinfarction refractory VT with multiple ICD shocks can be treated with a meticulous complex electrophysiology study and mapping, and the highly complicated technique of ablating the protected isthmus inside the scar tissue and the exit sites across the scar borders.¹⁰⁵ Most of these sites can be approached endocardially using transvascular catheters; or, if that fails, a percutaneous epicardial approach may be used.¹⁰⁶

Automated External Defibrillator (AED)

Ninety-three percent of SCA victims die before they reach a hospital or other source of emergency help because of the brief window for resuscitation available from the initial onset of VT/VF to the point of death. The chance of successful resuscitation reduces by 7% to 10% each minute. Therefore increased availability of instant defibrillation via AEDs in public areas is essential to improve the out-of-hospital SCA survivor rate.^{107,108} Response time should be less than 4 to 6 minutes for the patient to benefit from the use of AEDs.¹⁰⁹

AEDs were developed in the early 1970s, and trials were conducted during the 1980s. Most of these trials showed AEDs were equivalent if not better than manual defibrillators. The overall sensitivity in detecting VF by AEDs has been reported as 76% to 96%. Specificity (correctly identifying non-VF rhythms) is reported to be nearly 100%.¹¹⁰

Most of the current AEDs are biphasic devices, not due to their superiority over monophasic shock devices, but because

they use less energy, the batteries reach full charge more quickly and have a longer battery life.¹¹¹

Public access defibrillation has been shown to be an important part of a successful chain of survival programs. Placement of AEDs has been most cost-effective in select locations with significant public traffic or density, including casinos, airports, sports stadiums, corporate offices, shopping malls, schools, community centers, high-risk homes, and senior centers. The U.S. Food and Drug Administration (FDA) has approved the use of AEDs in public areas. American Airlines was the first to carry AEDs on aircraft during long overwater flights in 1997, and recent FAA regulations mandate that aircraft carry AEDs and that flight personnel be trained in their use (amendment to part 121 of the Aviation Medical Assistance Act of 1998).

Audible and/or visual prompts guide the user through the process, making them easy to use. Most AEDs require that an operator initiate the delivery of the shock in some way, such as pushing a button. Some AEDs can be purchased over-the-counter; however, most need a physician's prescription. The average price for a single AED unit is between \$1,200 and \$2,300.

In August 2002, the FDA gave approval to the first home-use AED. Since then, most states have passed liability immunity legislation for use of an AED in a nongrossly negligent manner. Today, more than 50,000 AEDs are in use.

Implantable Cardioverter Defibrillator (ICD)

The ICD has emerged as one of the most revolutionary therapies developed to treat patients with life-threatening ventricular arrhythmias. In the past 3 decades, it has evolved from its more primitive form to a sophisticated device capable of tiered therapy and data storage. The basic premise behind the effectiveness of this device is that the majority of SCDs result from malignant ventricular tachyarrhythmias. The ICD system consists of sensing and defibrillation electrodes connected to a generator that houses the battery and integrated circuitry (Fig. 25-10). Ventricular tachyarrhythmias are detected by rate, duration, and morphology criteria, and programmed therapies are automatically delivered based on the detection criteria of the arrhythmia sensed. In addition, all ICD generators now provide backup ventricular bradycardia pacing, providing a safety net for primary or secondary bradyarrhythmic events. The device may be implanted using a thoracotomy approach, but currently the preferred method is the outpatient nonthoracotomy approach. This simplification of implantation and the tremendous benefit of the ICD make it the most effective form of VT/VF treatment.

The therapy choices to treat ventricular tachyarrhythmia include antitachycardia pacing, low-energy synchronized cardioversion, and high-energy cardioversion/defibrillation. A detection algorithm allows differentiation of sinus tachycardia or supraventricular arrhythmias from ventricular tachyarrhythmias to obviate unnecessary delivery of therapy. Noninvasive interrogation of the device using an external wand allows the review of ventricular electrograms stored from detected episodes, affording confirmation of device effectiveness.

Although SCA is the result of a complex interaction of functional disturbances with an underlying structural abnormality, the ICD effectively terminates VT/VF regardless of its mechanism (Fig. 25-11). In this regard, it provides unsurpassed protection against arrhythmic SCD because it does not attempt to modulate structural or functional abnormalities as antiarrhythmic drugs do. The beneficial effect of these drugs, even when

chosen after they have been demonstrated to effectively suppress VT/VF, may be negated by alterations in the functional state of the individual (acute ischemia, hypokalemia, catecholamine surge, etc.).

Perioperative mortality associated with ICD implantation has now been reduced to less than 1%. ICD therapy, compared



Figure 25-10. Schematic representation of a current implantable cardioverter defibrillator and lead system. A right ventricular endocardial rate-sensing/defibrillation lead is shown inserted via the left subclavian vein with its tip in the right ventricular apex. This lead is connected to a pulse generator overlying the left pectoralis major muscle. (From *Implantable/Treatments/Cardioverter Defibrillators (ICDs)*. Available at: www.HRSpatients.org. Accessed January 28, 2008.)

with conventional or traditional antiarrhythmic drug therapy, has been associated with mortality reductions from 23% to 55% depending on the risk group participating in the trial, with the improvement in survival due almost exclusively to a reduction in SCD.³

Secondary prevention of SCD trials solidly support the implantation of an ICD in all patients surviving SCA that was not due to transient causes, regardless of the structural status of their heart.^{3,112-116} ICD is superior to any antiarrhythmic therapy, although, if antiarrhythmic therapy is warranted, amiodarone is the most effective choice to reduce the recurrence of VT/VF. In patients with spontaneous or electrophysiology study-induced sustained VT, ICD implant is strongly recommended for SCD prevention.

Furthermore, recent studies and updated guidelines consider an ICD essential in the primary prevention of SCD in high-risk patients.^{3,115,116} All patients with ischemic or nonischemic LV dysfunction (ejection fraction of 35%) and congestive heart failure who are on optimized medical therapy are considered at high risk for SCD.¹¹⁷ If such a patient has ischemic cardiomyopathy and has undergone revascularization therapy, LV dysfunction may improve, resulting in a decrease in risk for SCD. LV function must be re-evaluated in 90 days; if it remains 35%, the risk for SCD still exists and an ICD is required.¹¹⁸ In medically treated acute myocardial infarction (AMI) patients with LV dysfunction, an ICD implant must be deferred for at least 40 days after AMI since studies show no difference in outcome between patients with or without ICD during this period. If the patient's ejection fraction remains 35% after 40 days, an ICD is warranted.¹¹⁹ An exception to the 90- or 40-day waiting period rule would be if the patient develops nonsustained VT and has inducible sustained VT on an electrophysiology study. In this instance, an ICD would be indicated.¹²⁰ Some patients with LV dysfunction are candidates for cardiac transplantation; the ICD

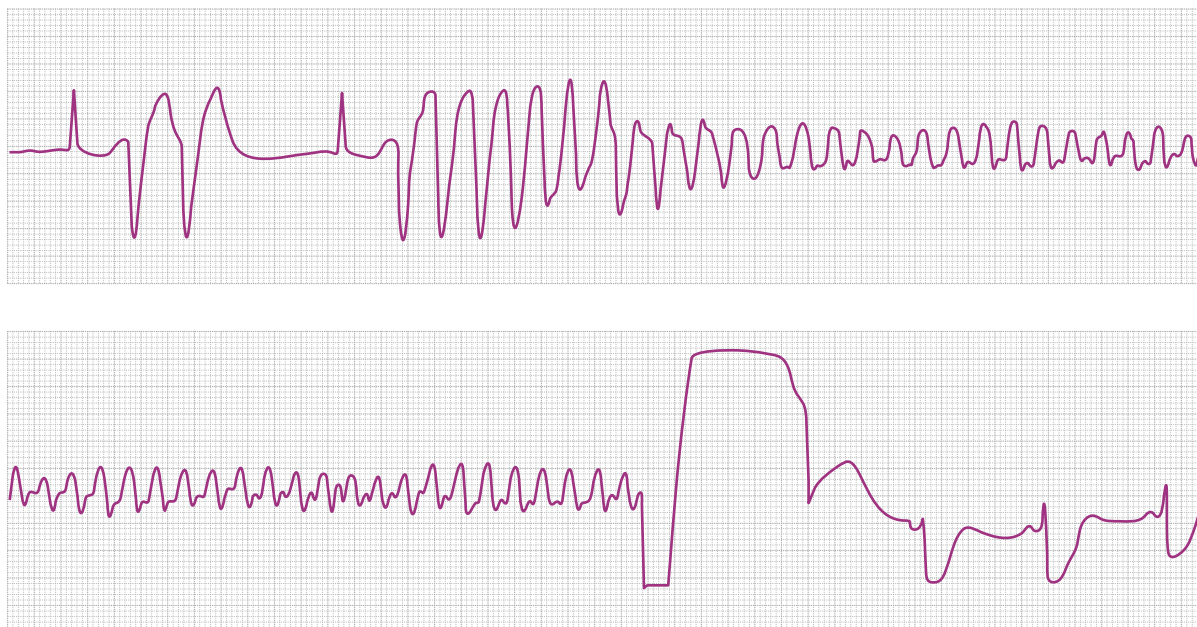


Figure 25-11. A clinically documented implantable cardioverter defibrillator shock. The rapid ventricular tachycardia is promptly detected and effectively terminated by a single shock with restoration of sinus rhythm (lower panel). (From Tchou PJ, Kadri N, Anderson J, et al: *Automatic implantable cardioverter defibrillators and survival of patients with left ventricular dysfunction and malignant ventricular arrhythmias*. *Ann Intern Med* 1988;109:529.)

may also be used as a “bridge to cardiac transplantation” for SCD prevention in selected individuals.¹²¹

Patients with normal LV function could still be at high risk for SCD, requiring an ICD for primary prevention of SCD. Patients with HCM are an example, where the indications for an ICD include history of prior resuscitation from VT/VF, presence of very thick intraventricular septum (>3 cm), history of failure to raise blood pressure on exercise, nonsustained VT with inducible sustained VT on an electrophysiology study, and a strong family history of SCD.

Patients with normal heart structure can be at high risk for SCA if they have inherited certain ion channelopathy syndromes, although these cases are rare. ICD is necessary in the following high-risk subgroups:

1. **LQTS**: resuscitated from cardiac arrest, syncope at young age (<5 years old), very long QT (>500 ms), Jervell and Lange-Nielsen syndrome, and males with LQT3.
2. **Brugada**: resuscitated from cardiac arrest, Brugada type I ECG morphology, inducible sustained VT on an electrophysiology study.
3. **Idiopathic ventricular fibrillation**.
4. **ARVD**: especially in patients who were resuscitated from cardiac arrest and who had rapid sustained VT, depressed LV function, or inducible sustained VT on an electrophysiology study.
5. **SQTS**.
6. **CPVT**.

There are a few conditions for which ICD implantation is contraindicated; they include the following:^{4,115,116}

1. VT/VF resulting from arrhythmias amenable to surgical or catheter ablation (e.g., WPW, right ventricular outflow tract VT, fascicular VT).
2. VT/VF due to a transient and reversible disorder (e.g., AMI, electrolyte imbalance, drugs, or trauma).
3. Terminal illnesses with projected life expectancy of less than 6 months (e.g., metastatic cancer, drug-refractory advanced heart failure in a patient who is not a candidate for cardiac transplantation).
4. Noninducible VT on an electrophysiology study in cases for which a complex electrophysiology study is indicated.
5. Significant psychiatric illnesses that may be aggravated by device implantation or may preclude systematic follow-up.
6. Incessant VT or VF.

In summary, the results of electrophysiologic study, the degree and type of underlying heart disease, and level of LV function are critical determinants in guiding management.

Wearable Automatic Defibrillator

This vestlike device (Fig. 25-12) has been approved by the FDA for patients with a transient high risk for VF, such as those awaiting cardiac transplantation, as a bridge until the ICD is implanted (during the 40-day waiting period after a recent MI or 90 days after a revascularization), or in patients who are candidates for ICD but who are at high risk for infection during the antibiotic therapy.

Conclusion

SCA is a major public health concern worldwide. CAD is by far the most common underlying pathology, and a substantial proportion of SCAs occur outside the hospital. Noncoronary



Figure 25-12. A LifeVest is a vestlike external defibrillator manufactured by Zoll Lifecor Corporation (Pittsburgh, PA). (Courtesy of Zoll Lifecor Corporation, Pittsburgh, PA. Available at: www.lifecor.com.)

cardiac diseases, although comprising the minority of victims, may occur in otherwise healthy individuals in whom an ante-mortem diagnosis is often difficult. A substantial risk of recurrence persists in these patients and mandates secondary prevention measures. Any significant reduction in the incidence of SCD in the community will require accurate identification of potential victims, training and implementation of bystander cardiopulmonary resuscitation (CPR) (e.g., external cardioverter defibrillators), and effective primary and secondary preventive interventions.

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Pacemaker and Implantable Cardioverter-Defibrillator Emergencies

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CHAPTER 26

Pacemaker Emergencies NASPE/BPEG Generic (NBG) Pacemaker Code Complications of Cardiac Pacing System Implantation Pacing and Sensing Problems Rapid Paced Ventricular Rates Biventricular Pacing Systems	Cardiac Pacing Under Specific Clinical Circumstances Implantable Cardioverter-Defibrillator Emergencies Inappropriate ICD Shock Electrical Storm Drug Effects on ICD Function ICD-Pacemaker Interactions Ineffective ICD Therapy

SECTION I Pacemaker Emergencies

Since the first cardiac pacemaker was implanted in 1958, the field of cardiac pacing has grown rapidly. The number of pacemakers implanted annually increased from 94,755 in 1990 to 267,278 in 2002. From 1990 to 2002, there were 2.25 million pacemakers and 415,780 implantable cardioverter-defibrillators (ICDs) implanted in the United States.¹ Thus it is likely that most physicians will have an opportunity to manage patients with these devices, and it is therefore important for physicians to be familiar with the various modes of pacing and with certain aspects of normal and abnormal pacemaker and ICD function. In this section, we discuss the evaluation and management strategies of the more commonly encountered clinical problems in patients with permanent and temporary antibradycardia pacing systems.

Indications for permanent cardiac pacemaker implantation have been published by a joint task force of the American College of Cardiology and the American Heart Association.^{2,3} The indications have been classified as follows:

- Class I: Conditions for which there is general agreement that permanent pacemakers should be implanted.
- Class II: Conditions for which permanent pacemakers are frequently used but there is divergence of opinion with respect to the necessity of their insertion.
- Class III: Conditions for which there is general agreement that pacemakers are unnecessary.

Table 26-1 summarizes the indications for permanent cardiac pacing in adults according to the task force guidelines. However, it is recognized that these indications continue to expand, and that clinical situations exist that indicate the need for pacing therapy, yet fall outside the guidelines, in which case documentation of the need is of great importance.

The indications for temporary cardiac pacing are listed in Table 26-2. These indications are relatively broad, both because of the temporary nature of the clinical problem and the relative ease of implantation and removal of the pacing system. Temporary pacing is indicated in patients awaiting a permanent pacemaker who are symptomatic or who require rate support all or most of the time. Additional indications are symptomatic transient bradyarrhythmias, prophylaxis against bradyarrhythmias, or bradycardia-dependent tachyarrhythmias and hemodynamic dysfunction due to slow rate or atrioventricular (AV) dyssynchrony.

NASPE/BPEG Generic (NBG) Pacemaker Code

In 1974, the Inter-Society Commission on Heart Disease Resources introduced a three-letter pacing-mode code for anti-bradycardia pacing systems to convey their functions by simple conversational means.⁴ This mode-code system was expanded to a five-letter one in 1981 to include programmability and anti-tachycardia functions.⁵ This code has been adopted and modified by the North American Society of Pacing and Electrophysiology (NASPE) (now the Heart Rhythm Society) Mode Code Committee and the British Pacing and Electrophysiology Group (BPEG), and is designated the NASPE/BPEG generic (NBG) code. Since its inception, the code has undergone multiple revisions; the last in 2002.⁶ Use of this code by medical and nursing intensive care personnel is recommended, both to facilitate communication and also to accurately describe pacemaker function.

The pacemaker mode code is shown in Table 26-3. The first three letters are always designated. The fourth and fifth letters are omitted if they are "O." With advances in pacing technology, further revision of the code will almost certainly be necessary. A description of the most commonly used pacing modes is shown in Table 26-4.

Table 26–1. Guidelines for Implantation of Cardiac Pacemakers in Adults: Class I and II Indications**Class I**

- A. Atrioventricular block
 - 1. Third-degree and advanced second-degree AV block at any anatomic level, associated with any one of the following:
 - a. Bradycardia with symptoms (including heart failure)
 - b. Documented periods of asystole greater than 3.0 seconds, or escape rate less than 40 beats/min in awake asymptomatic patients
 - c. Arrhythmias and other medical conditions that require drugs that result in symptomatic bradycardia
 - d. Post–AV junction ablation
 - e. Postoperative AV block that is not expected to resolve after cardiac surgery
 - f. Neuromuscular diseases with AV block, with or without symptoms
 - 2. Second degree AV block with symptomatic bradycardia
- B. Chronic bifascicular and trifascicular block
 - 1. Intermittent third-degree AV block
 - 2. Type II second-degree AV block
 - 3. Alternating bundle-branch block
- C. Sinus node dysfunction
 - 1. Sinus node dysfunction with documented symptomatic bradycardia, including frequent sinus pauses that produce symptoms. In some patients, bradycardia is iatrogenic and will occur as a consequence of essential long-term drug therapy of a type and dose for which there are no acceptable alternatives
 - 2. Symptomatic chronotropic incompetence
- D. Carotid sinus hypersensitivity
 - 1. Recurrent syncope caused by carotid sinus stimulation; minimal carotid sinus pressure induces ventricular asystole of more than 3 seconds; duration in the absence of any medication that depresses the sinus node or AV conduction
- E. After the acute phase of myocardial infarction
 - 1. Persistent second-degree AV block in the His-Purkinje system with bilateral bundle branch block or third degree AV block within or before the His-Purkinje system after AMI
 - 2. Transient advanced (second- or third-degree) infranodal AV block and associated bundle-branch block. If the site of block is uncertain, an electrophysiologic study may be necessary.
 - 3. Persistent and symptomatic second- or third-degree AV block
- F. To prevent tachycardia
 - 1. Sustained pause-dependent VT, with or without prolonged QT, in which the efficacy of pacing is thoroughly documented
- G. Children, adolescents, and patients with congenital heart disease
 - 1. Advanced second- or third-degree AV block associated with symptomatic bradycardia, ventricular dysfunction, or low cardiac output
 - 2. Sinus node dysfunction with correlation of symptoms during age-inappropriate bradycardia
 - 3. Postoperative advanced second- or third-degree AV block that is not expected to resolve or persists at least 7 days after cardiac surgery
 - 4. Congenital third-degree AV block with a wide QRS escape rhythm, complex ventricular ectopy, or ventricular dysfunction
 - 5. Congenital third-degree AV block in the infant with a ventricular rate less than 50 to 55 bpm or with congenital heart disease and a ventricular rate less than 70 bpm
 - 6. Sustained pause-dependent VT, with or without prolonged QT, in which the efficacy of pacing is thoroughly documented
- H. Hypertrophic cardiomyopathy
 - 1. Class I indications for sinus node dysfunction or AV block as described previously
- I. Dilated cardiomyopathy
 - 1. Class I indications for sinus node dysfunction or AV block as described previously
- J. After cardiac transplantation
 - 1. Symptomatic bradyarrhythmias/chronotropic incompetence not expected to resolve and other Class I indications for permanent pacing

Class IIa and b

- A. Atrioventricular block
 - 1. Asymptomatic complete AV block with ventricular rates of greater than 40 beats/min
 - 2. Asymptomatic Type II second-degree AV block with a narrow QRS
 - 3. Asymptomatic Type I second-degree AV block at intra-His or infra-His levels
 - 4. First- or second-degree AV block with symptoms similar to pacemaker syndrome
 - 5. Marked first-degree AV block (more than 0.30 second) in patients with LV dysfunction and symptoms of congestive heart failure in whom a shorter AV interval results in hemodynamic improvement
 - 6. Neuromuscular diseases such as myotonic muscular dystrophy, Kearns-Sayre syndrome, Erb dystrophy (limb-girdle), and peroneal muscular atrophy with any degree of AV block (including first-degree AV block), with or without symptoms

Table 26–1. Guidelines for Implantation of Cardiac Pacemakers in Adults: Class I and II Indications—cont'd**Class IIa and b—cont'd**

- B. Chronic bifascicular and trifascicular block
 1. Syncope not demonstrated to be due to AV block when other likely causes have been excluded, specifically ventricular tachycardia (VT)
 2. Incidental finding at electrophysiologic study of markedly prolonged HV interval (greater than or equal to 100 milliseconds) in asymptomatic patients
 3. Incidental finding at electrophysiologic study of pacing-induced infra-His block that is not physiologic
 4. Neuromuscular diseases such as myotonic muscular dystrophy, Kearns-Sayre syndrome, Erb dystrophy (limb-girdle) and peroneal muscular atrophy with any degree of fascicular block, with or without symptoms
- C. Sinus node dysfunction
 1. Sinus node dysfunction, occurring spontaneously or as a result of necessary drug therapy, with rate less than 40 beats/min when a clear association between symptoms and documented bradycardia has not been shown
 2. Syncope of unexplained origin when major abnormalities of sinus node function are discovered or provoked in electrophysiologic studies
 3. In minimally symptomatic patients, chronic heart rate less than 40 bpm while awake
- D. Carotid sinus hypersensitivity
 1. Recurrent syncope without clear, provocative events and with a hypersensitive cardioinhibitory response
 2. Significantly symptomatic and recurrent neurocardiogenic syncope associated with bradycardia documented spontaneously or at the time of tilt-table testing
- E. After the acute phase of myocardial infarction
 1. Persistent second- or third-degree AV block at the AV node level
- F. To automatically detect and pace to terminate tachycardias
 1. Symptomatic recurrent supraventricular tachycardia that is reproducibly terminated by pacing in the unlikely event that catheter ablation and/or drugs fail to control the arrhythmia or product intolerable side effects
 2. Recurrent supraventricular tachycardia or atrial flutter that is reproducibly terminated by pacing as an alternative to drug therapy or ablation
- G. To prevent tachycardia
 1. High-risk patients with congenital long Q-T syndrome
- AV re-entrant or AV node re-entrant supraventricular tachycardia not responsive to medical or ablative therapy
 2. Prevention of symptomatic, drug-refractory, recurrent atrial fibrillation in patients with coexisting sinus node dysfunction
- H. Children, adolescents, and patients with congenital heart disease
 1. Bradycardia-tachycardia syndrome with the need for long-term antiarrhythmic treatment other than digitalis
 2. Congenital third-degree AV block beyond the first year of life with an average heart rate less than 50 bpm, abrupt pauses in ventricular rate that are two or three times the basic cycle length, or associated with symptoms due to chronotropic incompetence
 3. Long Q-T syndrome with 2:1 AV or third-degree AV block
 4. Asymptomatic sinus bradycardia in the child with complex congenital heart disease with resting heart rate less than 40 bpm or pauses in ventricular rate of more than 3 seconds
 5. Patients with congenital heart disease and impaired hemodynamics due to sinus bradycardia or loss of AV synchrony
 6. Transient postoperative third-degree AV block that reverts to sinus rhythm with residual bifascicular block
 7. Congenital third-degree AV block in the asymptomatic infant, child, adolescent, or young adult with an acceptable heart rate, narrow QRS complex, and normal ventricular function
 8. Neuromuscular diseases with any degree of AV block (including first-degree AV block), with or without symptoms, because there may be unpredictable progression of AV conduction disease
- I. Hypertrophic cardiomyopathy
 1. Medically refractory, symptomatic hypertrophic cardiomyopathy with significant resting or provoked LV outflow obstruction
- J. Dilated cardiomyopathy
 1. Biventricular pacing in medically refractory, symptomatic NYHA Class II or IV patients with idiopathic dilated or ischemic cardiomyopathy, prolonged QRS interval (greater than or equal to 120 milliseconds), LV end-diastolic diameter greater than or equal to 55 mm, and ejection fraction less than or equal to 35%
- K. After cardiac transplantation
 1. Symptomatic bradyarrhythmias/chronotropic incompetence that, although transient, may persist for months and require intervention

Abbreviations: AV, atrioventricular; MI, myocardial infarction

Adapted from Gregoratos G, Abrams J, Epstein AE, et al: ACC/AHA/NASPE 2002 guideline for implantation of cardiac pacemakers and antiarrhythmia devices: summary article: report of the American College of Cardiology/American Heart Association task force on practice guidelines (ACC/AHA/NASPE committee to update the 1998 pacemaker guidelines). *Circulation* 2002;106:2145-2161.

Complications of Cardiac Pacing System Implantation

The complications of cardiac pacing can be classified as those related to the presence of the pacing system as a foreign body (mechanical complications) and those related to apparent or real pacing system malfunction. Acute complications related to the temporary or permanent pacing system implantation procedure itself, such as hemothorax, pneumothorax, subclavian artery puncture, and myocardial perforation, are outside the scope of this chapter.

Table 26–2. Indications for Temporary Cardiac Pacing

Class I

1. Asystole
2. Symptomatic bradycardia (includes sinus bradycardia with hypotension and Type I second-degree AV block with hypotension not responsive to atropine)
3. Bilateral BBB (alternating BBB or RBBB with alternating LAFB/LPFB) (any age)
4. New or indeterminate age bifascicular block (RBBB with LAFB or LPFB, or LBBB)
5. Mobitz Type II second-degree AV block

Class IIa

1. RBBB and LAFB or LPFB (new or indeterminate)
2. RBBB with first-degree AV block
3. LBBB, new or indeterminate
4. Incessant VT, for atrial or ventricular overdrive pacing
5. Recurrent sinus pauses (greater than 3 seconds) not responsive to atropine

Class IIb

1. Bifascicular block of indeterminate age
2. New or age-indeterminate isolated RBBB

Abbreviations: AV, atrioventricular; BBB, bundle branch block; R, right; L, left; LAFB, left anterior fascicle block; LPFB, left posterior fascicle block; VT, ventricular tachycardia.

Adapted from Ryan TJ, Anderson JL, Antman EM, et al: J Am Coll Cardiol 1996;28:1367-1368

Infection

Infection is an uncommon complication of pacemaker implantation, with the incidence ranging from 0.8% to 5.7%, reported in a review of 21 studies of pacemaker and ICD implantations.⁷ Routine use of antistaphylococcal antibiotic prophylaxis at the time of implantation or generator change has been shown to have consistent benefit in a meta-analysis of seven randomized controlled trials, representing 2023 patients, in decreasing the rates of short-term pocket infection, skin erosion, or septicemia.⁸ We recommend routine prophylaxis with antistaphylococcal antibiotics.

Pacemaker pocket infection can occur as early as hours to days after the implantation procedure or as late as several years. *Staphylococcus aureus* and *S. epidermidis* are the most common organisms involved; episodes arising within 2 weeks of implantation are more likely to be due to *S. aureus*, whereas *S. epidermidis* is the principal organism causing late infections.^{10,11} Despite the established trend of performing permanent pacemaker implantation in the cardiac catheterization laboratory rather than in the operating room, the incidence of pocket infection has remained the same.¹² Clinical manifestations of pocket infection are usually obvious and include fever, chills, purulent drainage, and signs of inflammation at the pocket site. Initial therapy is usually with intravenous antibiotics that provide antistaphylococcal coverage. Management frequently requires removal of the entire pacemaker system.¹³⁻¹⁵

Endocarditis can occur after pacemaker implantation and has a mortality rate as high as 27%.¹⁵ The most frequent pathogens are *S. aureus* and *S. epidermidis*.^{10,11} The diagnosis of device-related endocarditis is suggested by modified Duke criteria; it has been suggested that in the case of devices, pulmonary emboli and generator pocket abnormalities should be used as additional major criteria.^{15,16}

Fever and chills are the most common symptoms. Other signs of endocarditis, such as new murmurs of tricuspid or pulmonary insufficiency or signs of pulmonary hypertension due to septic emboli, should be carefully sought. Vegetations can be best demonstrated by transesophageal echocardiography (TEE), although they are sometimes visualized by transthoracic echocardiography (TTE). TEE has been repeatedly shown to be superior to TTE in the diagnosis of device-related endocarditis, with vegetations on the tricuspid valve or pacing lead visualized

Table 26–3. The NASPE/BPEG Generic (NPG) Pacemaker Code

Position	I	II	III	IV	V
Category	Chamber(S) Paced	Chamber(S) Sensed	Response to Sensing	Rate Modulation	Multisite Pacing
	O = None	O = None	O = None	O = None	O = None
	A = Atrium	A = Atrium	T = Triggered	R = Rate modulation	A = Atrium
	V = Ventricle	V = Ventricle	I = Inhibited		V = Ventricle
	D = Dual (A + V)	D = Dual (A + V)	D = Dual (T + I)		D = Dual (A + V)
Manufacturers' designation only	S = Single (A or V)	S = Single (A or V)			

Note: Positions I through III are used exclusively for antibradyarrhythmia function.

Abbreviations: NASPE, North American Society of Pacing and Electrophysiology; BPEG, British Pacing and Electrophysiology Group

Adapted from Bernstein AD, Daubert JC, Fletcher RD, et al: The revised NASPE/BPEG generic code for antibradyarrhythmia, adaptive-rate, and multisite pacing. North American Society of Pacing and Electrophysiology/British Pacing and Electrophysiology Group. Pacing Clin Electrophysiol 2002;25:260.

Table 26–4. Commonly Used Pacing Modes

Position of Letter				Description
I	II	III	IV Rate	
<i>Chamber Paced</i>	<i>Chamber Sensed</i>	<i>Mode of Response</i>	<i>Adaptation</i>	
A	O	O		Asynchronous (fixed rate) atrial pacing
A	A	T		Triggered atrial pacing. Output pulse is delivered (and sensed by the atrial electrode) at the time of sensing, or at the programmed escape interval (rarely used)
A	A	I		Demand atrial pacing; output inhibited by sensed atrial activity
A	A	I	R	Demand atrial pacing; output inhibited by sensed atrial activity; paced rates increase and decrease in response to sensor input
V	O	O		Asynchronous (fixed rate) ventricular pacing
V	V	T		Triggered ventricular pacing. Output is delivered (and sensed by the ventricular electrode) at the time of sensing or at the programmed escape interval (rarely used)
V	V	I		Demand ventricular pacing; output inhibited by sensed ventricular activity
V	V	I	R	Demand ventricular pacing; output inhibited by sensed ventricular activity; paced rates decrease and increase in response to sensor input.
V	D	D		Paces ventricle; senses in both atrium and ventricle and paces ventricle after the programmed atrioventricular interval.
D	D	I		Demand atrial and ventricular pacing; tracking of atrial rhythm does not occur
D	D	I	R	Demand atrial and ventricular pacing; paced rates increase and decrease in response to sensor input; tracking of atrial rhythm does not occur
D	D	D		Paces and senses in both atrium and ventricle; paced activity up to programmed upper rate limit
D	D	D	R	Paces and senses in both atrium and ventricle; paces up to the programmed upper rate limit; paced rates increase and decrease in response to sensor input

by TEE in 90% to 96% of patients, compared with 22% to 43% by TTE.^{15–20} Complete eradication of the infection usually involves removal of the entire pacing system.^{13,15,21}

Thrombosis and Thromboembolism

Venous thrombosis due to the presence of the pacing lead(s) in the subclavian vein and superior vena cava occurs quite commonly, as assessed by venographic techniques.²² One prospective trial found that six months after pacemaker or defibrillator implantation, 14% of patients developed a new obstructive venous lesion, none of whom were symptomatic.²³ Most thromboses are subclinical, and fortunately, major thrombosis causing symptoms and signs of significant venous obstruction (such as the superior vena cava obstruction syndrome) is rare.²⁴ The propagation of thrombus and dislodgement with embolism can cause or contribute to acute or chronic right ventricular inflow or outflow obstruction and can cause acute or recurrent pulmonary embolism.²⁵ Patients with an implanted permanent pacing system having unexplained right-sided heart failure, tachycardia, chest pain, dyspnea, and nonspecific systemic symptoms such as weakness and malaise should be promptly evaluated for these complications, and appropriate studies such as echocardiography and venography should be performed to document their presence. Major and symptomatic venous

thrombosis can cause arm and facial edema, pain, absence or diminution of ipsilateral venous pulsations, prominent subcutaneous venous pattern due to collateral circulation, and even exophthalmos. Treatment usually requires intravenous heparinization followed by oral anticoagulation; other treatment modalities include local thrombolysis and balloon angioplasty.^{26,27}

Intracardiac (generally right atrial) thrombosis around the intracardiac portion of the electrode catheter is more dangerous and more difficult to manage. The size of a right atrial thrombus can range from one to several centimeters in diameter.²⁸ The hemodynamic significance of the intracardiac clot depends on its size and location; atrial arrhythmias can occur if the sinoatrial area is involved. Functional tricuspid stenosis or insufficiency can be manifestations of thrombus, similar to those of an atrial myxoma. Intracardiac thrombosis should be considered when refractory right ventricular failure is present; the diagnosis can be confirmed by transthoracic or preferably transesophageal echocardiography.^{29–31}

The true incidence of pulmonary embolism due to transvenous pacing leads is higher when assessed by ventilation perfusion scans than is clinically apparent,³² the latter reported to range from 0.6% to 3.5%.^{33,34} This discrepancy indicates that most emboli are not of sufficient size to be clinically significant, at least acutely, although chronic pulmonary hypertension in



Figure 26-1. Intermittent failure to capture in the ventricle. All P waves are paced in this patient with a DDD pacing system. Alternate ventricular pacing pulses do not capture, leading to spontaneous conduction to the ventricle from the paced P waves. The problem was corrected by output programming. The changing atrioventricular intervals may be hemodynamically detrimental in critically ill patients.

patients with pacemakers should prompt consideration of this diagnosis. The treatment is anticoagulation with intravenous heparin and subsequent oral warfarin. The use of streptokinase, urokinase, or alteplase should be considered when an active clot is considered to be recurring. When pulmonary emboli are recurrent, thoracotomy with cardiopulmonary bypass may be necessary to remove the clot and pacing lead.³⁵

Systemic embolization can occur in patients with permanent pacemakers in two ways. A paradoxical embolus can result from a venous thrombosis in the presence of an established or transient intracardiac right-to-left shunt (i.e., patent foramen ovale); a careful search both for venous thrombosis and a patent foramen ovale by echocardiography with bubble contrast study may be warranted.³⁶⁻³⁸ In addition, patients implanted with a VVI(R) pacing system (see Table 26-4) have a higher incidence of paroxysmal and chronic atrial fibrillation,³⁹⁻⁴² which predisposes to embolic events.⁴³⁻⁴⁶ A meta-analysis evaluating over 35,000 years of patient follow-up showed that patients with a VVI pacemaker had a 22% rate of atrial fibrillation compared with a 17% rate with atrial and dual-chamber-based systems; a possible increase in the rate of stroke was also suggested.⁴² It has not been established if anticoagulation can reduce the incidence of thromboembolic events or prolong life in these patients.

Pacing and Sensing Problems

Pacing and sensing problems in patients with permanent pacemakers can originate in the pulse generator, the pacing leads, or the interface between myocardial tissue and the lead electrodes. Pacing problems can be classified as failure to capture and failure of pacing output. Sensing problems are due to oversensing (sensing of unwanted signals) or undersensing (failure to sense) of the intracardiac signal.

Pacing Problems

Failure to capture and failure to output are serious complications that can be life-threatening. The severity of their consequences depends on the duration of the problem (intermittent versus persistent) and whether the patient is pacemaker-dependent (asystolic or symptomatic without adequate rate support). Symptoms that should alert one to the possibility of pacing failure include symptoms of cerebral hypoperfusion (dizziness, presyncope, syncope) and those due to pulmonary venous hypertension, such as breathlessness. These symptoms occur because the patient's native escape cardiac rhythms are too slow to maintain adequate cardiac output and systemic perfusion.

A complete pacing sequence involves delivery of the pacing stimulus and subsequent depolarization of cardiac tissue. Temporal opportunity to capture must be present; that is, the

atrial or ventricular tissue must be in a nonrefractory state. The minimal amount of electrical energy required to cause a depolarization is called the stimulation or capture threshold. The energy delivered by the pulse generator is the product of pulse duration (in milliseconds) and the voltage amplitude (in volts). The stimulation threshold should ideally be less than or equal to 1.0 V (at pulse width of 0.4 to 0.5 ms) at the time of initial implantation. At implant, this stimulation threshold is highly dependent on the electrode-tissue interface, which is determined in large part by lead position. The stimulation threshold increases to variable degrees during a maturation process and reaches a stable value 6 to 8 weeks after implant. Thus, at the time of implantation, the voltage output is programmed to a higher level than the measured threshold, with individualized optimal reprogramming undertaken 2 to 3 months later. Currently used leads have reduced both acute and chronic stimulation thresholds by up to 50%.^{47,48}

Failure to Capture

The electrocardiographic diagnosis of failure to capture is made by demonstrating the occurrence of the stimulus output, which, when delivered outside the refractory period of atrial or ventricular tissue, is not followed by a P wave or QRS complex (Figs. 26-1, 26-2, 26-3, and 26-4). The causes of failure to capture fall into one of three major categories: (1) increase in stimulation threshold from various causes; (2) defective pacing leads; and (3) pulse generator battery depletion. It is important to note that stimulus delivery during tissue refractoriness is not true failure to capture, and is designated "functional noncapture."

Failure to capture is usually due to an increase in atrial or ventricular stimulation threshold. An increase in myocardial stimulation threshold can occur under several circumstances (Table 26-5). Increase in stimulation threshold is the most common cause of failure to capture that occurs in the first 8 weeks after pacemaker implantation and is due to the maturation process at the interface of the electrodes and myocardial tissue. This problem can be managed by noninvasively reprogramming the energy output of the pulse generator to a higher value (by increasing the pulse duration or the voltage amplitude or both). The stimulation threshold decreases to a stable level after 2 months, at which time the energy output can be reprogrammed to a lower value to prolong the battery life. The use of corticosteroid-eluting pacing leads has decreased the local tissue reaction and the thickness of the fibrous capsule surrounding the tip electrode,⁵⁴ reducing both acute and chronic stimulation thresholds.^{47,48} Although now quite rare, continued increases in capture threshold over months can occur, reaching voltage outputs that could potentially exceed the capacity of the pulse generator.



Figure 26-2. Continuously recorded lead II in a patient with a VVI pacing system with lead wire fracture. Failure to sense and intermittent failure to capture are present. The pacing artifact amplitudes vary, with the smaller artifacts not followed by paced QRS complexes. The long intervals between pacing artifacts are a multiple of the basic pacing rate of about 68 beats/min. The problem was corrected by lead replacement. The *closed circles* indicate pacing stimuli, many of which are barely visible.



Figure 26-3. “Functional noncapture” in the atrium in a patient with a DDD pacing system, owing to lack of temporal opportunity. The QRS complexes are paced. Following each QRS complex are retrogradely conducted P waves that are not sensed because they fall in the postventricular atrial refractory period; they do not inhibit the subsequent atrial output. The atrial stimulus does not capture atrial tissue, however, because the atria have just been depolarized retrogradely. Failure to capture cannot be correctly diagnosed unless it is established that temporal opportunity to capture is present.

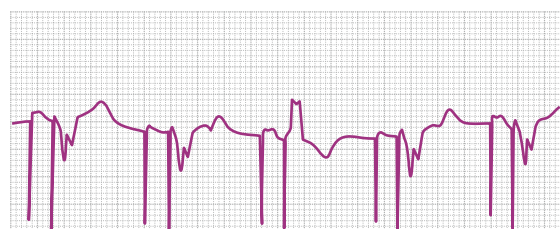


Figure 26-4. The intermittent failure to capture in the atrium results in a retrogradely conducted atrial depolarization from the paced QRS complexes. If the retrograde P wave is sensed, ventricular pacing is triggered, potentially resulting in a pacemaker-mediated tachycardia. In this case, the retrograde P wave falls within the programmed postventricular atrial refractory period and was not sensed. Atrial noncapture with resulting ventriculoatrial conduction can be hemodynamically detrimental, especially in critically ill patients. The problem was solved by atrial output reprogramming.

Various metabolic disturbances are known to increase the myocardial stimulation threshold. Although hypoglycemia does not cause important changes in stimulation threshold, severe hyperglycemia (serum glucose level above 600 mg/dL) has been reported to cause a more than 50% increase.⁵⁵ Hyperkalemia can also increase the stimulation threshold significantly, generally when the serum potassium level exceeds 7 mEq/L (Fig. 26-5).⁵⁶⁻⁵⁹ Although determination of the serum potassium level can take time, there is usually electrocardiographic evidence of hyperkalemia that should suggest this diagnosis: this evidence includes a prolonged P wave duration, loss of visible P waves, markedly prolonged QRS complex duration (spontaneous or paced), and merging of the QRS complex with the ST-T wave (“sine wave” morphology, see Fig. 26-5). Management includes

Table 26-5. Causes of Pacemaker Noncapture

1. Elevation of stimulation threshold
• Metabolic disturbances (hyperkalemia, hyperglycemia, alkalemia or acidosis, hypoxemia or hypercapnia, hypothyroidism) • Drugs (quinidine, procainamide, lidocaine, mexiletine, encainide, flecainide) • Acute myocardial infarction • Exit block due to lead fibrosis
2. Pacing lead defects (fractures, insulation break)
3. Lead maturation, dislodgement, or perforation
4. Inappropriately low programmed output
5. Battery end of life

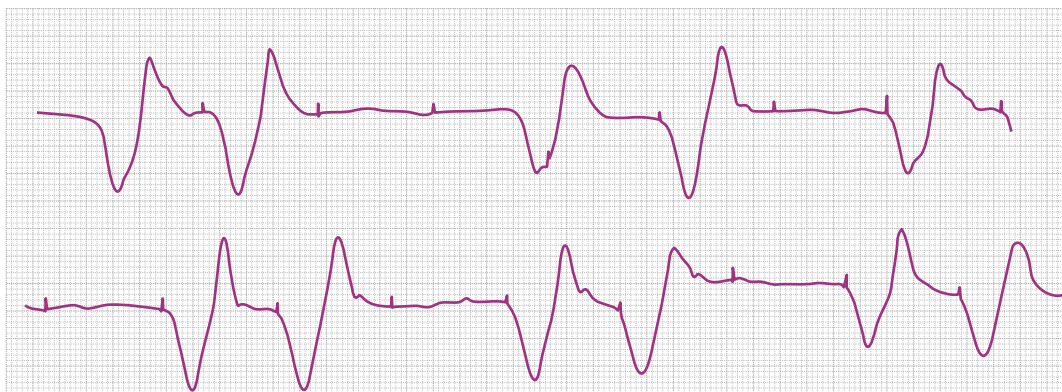


Figure 26-5. Lead MCL₁ rhythm strip recorded in a hyperkalemic patient ($K^+ = 7.9$ mEq/dL) during cardiopulmonary resuscitation after an asystolic arrest. A VVI pacing system is present. Type II pacemaker exit block is present, in which every third pacing stimulus is not followed by a QRS complex. The patient had no pulse with this rhythm. Resuscitation was unsuccessful despite correction of the hyperkalemia. This type of failure to capture is more common with hyperkalemia than with acidosis secondary to cardiac arrest. That these QRS complexes represent paced ventricular depolarizations is diagnosed from their presence only after a pacing stimulus and the irregular periodicity of the rhythm.

correction of the hyperkalemia and/or temporarily increasing the energy output of the pulse generator by noninvasive programming or both. This latter maneuver is not always successful, however, and simply increasing pulse generator voltage output will not reverse electromechanical dissociation. Both metabolic acidosis and alkalosis can increase the stimulation threshold by as much as 70% to 80%.⁵⁹ Hypoxemia and hypercarbia can also cause elevation of the capture threshold, which can be reversed by supplemental oxygen and hyperventilation⁵⁵; although uncommon today, this may be especially relevant during induction of general anesthesia in patients with cardiac pacemakers. Many of these metabolic disturbances occur during cardiopulmonary resuscitation. In patients with cardiac pacing systems who are pacemaker-dependent, correction of these metabolic disturbances is crucial to a successful resuscitation. Despite the foregoing, failure to capture using today's pacing systems is not common because of both a high safety margin provided by the programmed energy output and improved lead design.

Drugs that affect the excitability of the myocardium can increase the stimulation threshold, especially when high doses are required to achieve a therapeutic effect. All classes of antiarrhythmic agents are used in intensive care units, and many of them have been shown to affect the myocardial stimulation threshold. Sodium channel blockers, including quinidine and procainamide (Vaughn Williams Class IA antiarrhythmic agents), lidocaine and mexiletine (Class IB), and encainide and flecainide (Class IC), have all been reported to increase cardiac stimulation thresholds.⁶⁰⁻⁶⁶ Digitalis, β -adrenergic antagonists (class II antiarrhythmic agents), and angiotensin-converting enzyme inhibitors have no important effect on the pacing threshold.^{61,64-66a} The effect of amiodarone (a Class III antiarrhythmic agent), whether given intravenously or orally, on the pacing threshold is not well defined, although evidence suggests no significant effect.⁶⁷ Verapamil, a calcium channel antagonist (Class IV antiarrhythmic agents), has been reported to increase capture threshold,⁶¹ but this is unusual. Atropine, isoproterenol, corticosteroids, and epinephrine have been shown to decrease the myocardial capture threshold.^{66a} Successful management of failure to capture because of the effects of antiarrhythmic agents includes rapid detection and correction of any accompanying metabolic disturbance or electrolyte imbalance. Hyperkalemia

potentiates the effect of some Class IA antiarrhythmic agents, particularly quinidine.⁶⁸ Sodium lactate and sodium bicarbonate have been reported to reverse the effects of the sodium channel antagonists quinidine and procainamide.^{69,70} Removal of quinidine or procainamide by hemodialysis or hemoperfusion is not effective because of their extensive tissue distribution. Noninvasive programming of the pulse generator to a higher energy output may temporarily allow consistent capture until the offending drugs are excreted. As indicated earlier, current pacing systems are only rarely associated with these clinical problems.

Acute myocardial infarction can result in an increase in stimulation threshold and failure to capture. This is usually, but not always, accompanied by sensing problems (usually undersensing). The mechanisms responsible for the elevation of pacing threshold include local hyperkalemia from tissue necrosis, shock, and high levels of certain antiarrhythmic agents. The failure to capture can be intermittent or complete and can present as type I (Wenckebach) or type II exit block (see Fig. 26-5).^{71,72} The management of failure to capture in the setting of acute myocardial infarction, in addition to correcting any coexisting metabolic or electrolyte disturbances, is to increase energy output by noninvasive programming of the generator. With current early and aggressive treatment strategies in acute myocardial infarction, failure to capture in this clinical setting is uncommon.

Failure to capture can also result from insufficient energy reaching myocardial tissue because of too high a resistance along the lead wire or to leakage or short-circuiting of current before its reaching the electrode-tissue interface. This can be due to lead fracture or lead insulation failure, respectively. Because permanent pacing leads bend with each systole, the cumulative stress on the lead over years can be substantial. Stresses on leads introduced into the subclavian vein are also imposed when they are compressed by soft tissues during movement of the clavicle. In one large, albeit older, study of 2226 patients, the incidence of lead fracture was reported to be 3.9% (1.2% per patient year).⁷³ Common sites of lead fracture are between the connector and the venous entry, with only 7% occurring within the vascular system itself.⁷³ Although complete lead fracture is manifested on the electrocardiogram by the absence of pacing stimulus artifacts (no energy reaching body tissues), a partial fracture, in which the circuit is sometimes "made" or "broken," is more common, normal



Figure 26-6. Inappropriate pauses (closed circles) in paced rhythm and failure to sense (arrowhead) are shown in this tracing recorded from a patient with a VVI pacing system. The interstimulus interval is about 840 ms (base rate about 71 beats/min), and is measured as the shortest pacing artifact-to-pacing artifact interval. The pauses in stimulus output delivery are not explained by any event registered on the rhythm strip. The absence of pacing stimuli could indicate either “far field” oversensing with normal inhibition or conductor wire fracture. Because of the accompanying failure to sense a native R wave that would be well outside the refractory period of the pacemaker, lead fracture is more likely and was documented in this patient.



Figure 26-7. Oversensing resulting in a pause in paced rhythm (top) in this VVI pacing system is corrected by applying the magnet over the pulse generator, stimulating the sensing function, and achieving stable ventricular pacing (bottom). The arrowhead indicates the expected time of delivery of the pacing stimulus. In the case of complete lead fracture, because current is not reaching body tissues owing to the fracture, pacing artifacts would not be seen on the surface ECG. In this instance, the differential diagnosis of no visible output includes battery end of life. Interrogation of the pulse generator is required for definitive diagnosis. In the case of lead fracture, lead resistance would be extremely high, but battery voltage would be normal.

sensing and pacing during the “making” of the circuit will be seen, along with intermittent abnormal sensing and pacing function (Fig. 26-6, and see Fig. 26-2). Potential differences between the two ends of a broken electrode can cause electrical signals (“false” signals) that can be sensed, resulting in pauses in pacing stimulus intervals in single chamber devices and either pauses or earlier-than-expected ventricular stimulation in dual chamber systems, the cause of which is not readily apparent. Applying the magnet over the pulse generator, which disables the sensing function, can secure the diagnosis of oversensing due to lead fracture if the visible interstimulus intervals are a multiple of the basic pacing rate (Fig. 26-7). Highly penetrated chest radiographs in both posteroanterior and lateral views should be performed and evidence of a lead fracture should be carefully sought. Interrogation of the pacing system will reveal high lead impedance along the fractured lead, reflecting discontinuity within the lead. Lead wire fracture with failure to capture can be an emergency if the patient is pacemaker dependent.

Lead insulation failure can cause current to leak into body tissues and insufficient current to be delivered at the myocardium to cause depolarization, with resultant failure to capture. An insulation break can be caused by needle nick damage at the time of pacemaker pocket closure or, much less commonly

today, by degradation due to design-related failure.^{74,75} Inappropriate sensing of unwanted signals generated by the current leak (oversensing) may coexist. On the electrocardiogram, a bipolar lead with an insulation break may manifest a larger than usual pacing stimulus artifact; the pacing artifact polarity may also change. Comparison should be made with a baseline 12-lead analog electrocardiogram for magnitude and polarity of the pacing artifacts. The definitive diagnosis of lead insulation failure can be made by interrogation of the pacing system, which demonstrates lead resistance below the normal range for the particular lead in question.

Lead displacement, including myocardial penetration and perforation, is a common cause of failure to capture early after implantation. Undersensing usually coexists. When suspected, highly penetrated radiographs of the chest in both posteroanterior and lateral views should be obtained and compared with those taken immediately after pacing system implantation. A 12-lead electrocardiogram should also be obtained so that the morphology of the paced QRS complexes can be compared. Once lead dislodgement is confirmed, repositioning is usually required, although occasionally output and sensing threshold programming can restore normal pacing system function. The use of active and passive fixation leads in the atrium and

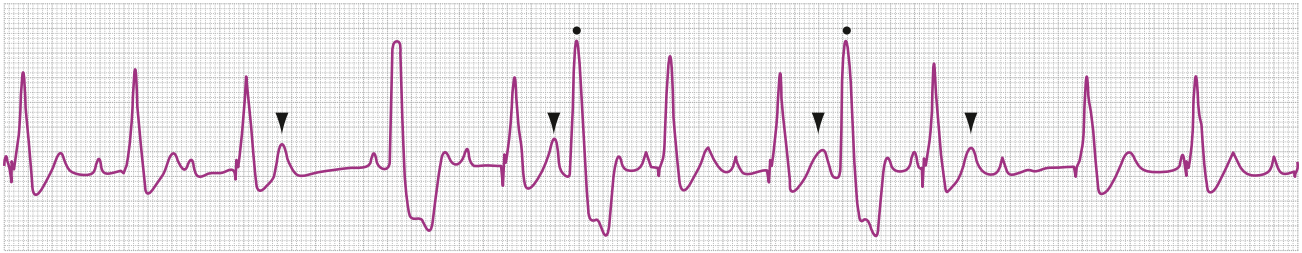


Figure 26-8. T wave oversensing (arrowheads) in a 45-year-old woman with a VVI pacing system. The base rate is 65 beats/min (interstimulus interval about 920 ms), shown by the first three consecutive paced QRS complexes. The T waves of the third and seventh paced QRS complexes are sensed, inhibiting the ventricular output so that a pacing stimulus is not delivered at the expected time. A spontaneous QRS complex follows the first oversensed T wave. The refractory period set up by the oversensed T wave causes functional undersensing of some spontaneous QRS complexes (closed circles). The problem was resolved by sensitivity programming.

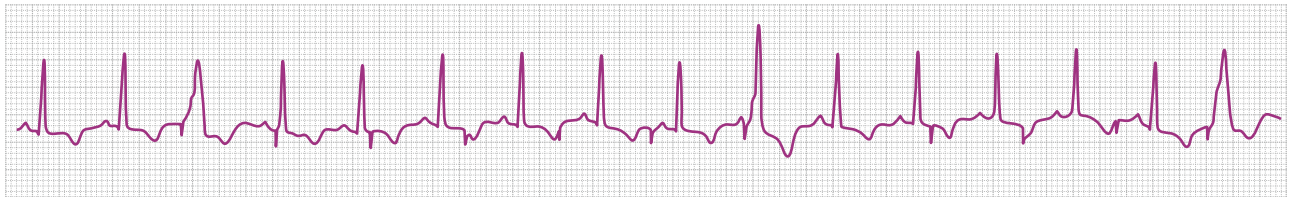


Figure 26-9. Failure to sense in a 59-year-old hypertensive patient with renal insufficiency, who had a VVI pacing system implanted for episodic atrioventricular block. Failure to sense is diagnosed from the inappropriate appearance of pacing artifacts despite a normal QRS rhythm. Capture function is intact (3rd, 10th, and 16th QRS complexes); the second captured complex is a fusion complex in which ventricular depolarization is caused in part by the sinus P wave preceding the QRS complex and the pacing stimulus. The refractory period of ventricular tissue is about 400 ms; output stimuli occurring before this interval has elapsed do not produce ventricular depolarizations (functional noncapture).



Figure 26-10. Intermittent failure to sense in the atrium leading to dissociation between sinus P waves and the ventricular paced QRS rhythm (all QRS complexes are paced). The failure to sense results in the delivery of the atrial stimulus output, which does not capture, owing to atrial refractoriness (functional noncapture). The sinus P waves can be seen to be deforming the T waves of the paced QRS complexes. The 2nd, 8th, and 13th paced QRS complexes result from normal triggered response to the intermittently sensed P waves.

ventricle has largely obviated the problem of lead dislodgement in permanent pacing systems, although the problem still exists in the temporary pacing setting.

Failure of Output

Failure of output is manifested on the surface electrocardiogram as an absence of pacing artifacts. Absence of pacing stimuli due to failure of output should not be confused with absence of visible pacing stimuli due to lead fracture, loose connections between the pulse generator and the leads, oversensing, and low programmed voltage generating low amplitude artifacts (see Figs. 26-6 and 26-7); in these circumstances, pacing pulses are emitted by the pulse generator in the normally expected manner.

True output failure indicates battery depletion or component failure. To confirm the diagnosis of failure of output, a magnet can be placed over the pulse generator to demonstrate absence of pacing artifacts on the electrocardiogram. The differential

diagnosis of lead fracture can sometimes be detected on an overpenetrated chest radiograph; the lead impedance measured during pacemaker interrogation (the diagnostic maneuver of choice) will be high or infinite. In contrast, true output failure due to battery end-of-life will yield the expected battery voltage depletion on pacemaker interrogation.

Sensing Problems

Problems related to sensing the intracardiac electrical signal can be conveniently divided into those caused by oversensing of unwanted signals or undersensing of the intrinsic intracardiac signal (Figs. 26-8, 26-9, 26-10, and 26-11; Tables 26-6 and 26-7). In asynchronous or magnet mode of pacing (AOO, VOO, DOO), the sensing function is disabled and fixed-rate pacing at the manufacturer-specific magnet rate and other intervals, such as the AV interval, result. Appropriate sensing in the atrium and ventricle is an indispensable part of pacemaker function. Several

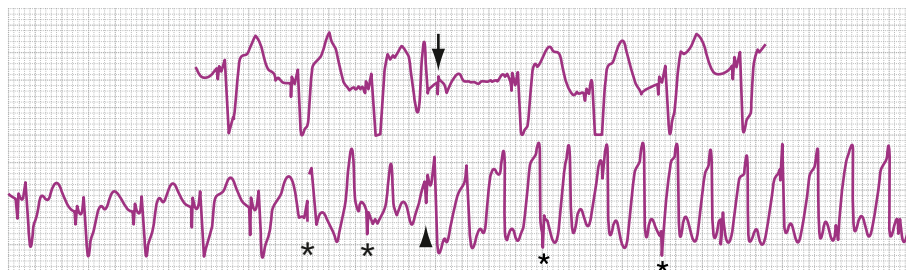


Figure 26-11. Failure to sense resulting in ventricular tachycardia. The patient was admitted to the hospital with an acute anterior wall myocardial infarction and developed high-degree atrioventricular block. Temporary cardiac pacing was instituted. Despite setting the highest sensitivity value to allow for sensing of signals of small magnitude, undersensing resulted in delivery of a pacing stimulus on the T wave of ventricular extrasystoles (arrow and arrowhead). In the *top strip*, no tachycardia resulted, but sustained ventricular tachycardia requiring cardioversion is seen in the *bottom strip*. The patient did not survive.

Table 26-6. Causes of Oversensing

1. Intracardiac events

- P wave sensing by ventricular lead
- R wave sensing by atrial lead
- T wave sensing by ventricular lead
- “False” signals generated by the two ends of a fractured lead or by current leaks due to insulation failure

2. Skeletal myopotentials

3. Medical sources of environmental (electromagnetic) interference

- Diathermy (obsolete)
- Ionizing radiation
- Magnetic resonance imaging
- Cardioversion, defibrillation
- Transcutaneous pacing
- Electrotherapy (transcutaneous nerve stimulation, implanted neuromuscular stimulators, electroconvulsive shock therapy)
- Lithotripsy

4. Ambient sources of environmental (electromagnetic) interference

- Radiofrequency emissions (short wave, mobile radio transmitters, garage door openers)
- High tension lines
- Arc welding
- Rotating radio detectors
- Induction furnaces
- Electronic article surveillance devices
- Tasers
- Portable music players

factors influence sensing functions, including the lead configuration (bipolar versus unipolar), the amplitude and the slew (rate of change of voltage [dV/dt]) of the intracardiac signals, and the sensitivity setting (sensing threshold) of the pacemaker generator. The pacemaker “senses” the voltage difference between the two electrodes (anode and cathode) of the pacing system. In unipolar systems, one electrode (the cathode) is the tip of the pacing wire and the other electrode (the anode) is the pacemaker generator itself. The large antenna thus created enlarges the intracardiac signal (and extracardiac signals), allowing for

Table 26-7. Causes of Undersensing

1. Low amplitude or slew of intracardiac signals

- Acute myocardial infarction
- Congestive heart failure
- Ventricular origin
- Hyperkalemia
- Some antiarrhythmic agents (especially Class IA agents)

2. Pacing system

- Lead fracture
- Lead insulation break
- Lead maturation or dislodgement
- Inappropriately programmed sensitivity
- Magnet application
- Battery depletion

easier sensing. In bipolar pacing systems, the electrodes are in proximity to each other on the lead; the sensed signal is between the closely spaced electrodes. Although studies indicate little difference in the sensed signal between unipolar and bipolar lead configurations, on occasion, in the acute setting unipolarization of a temporary pacing system can be useful.⁷⁶ Unipolarization can also be used in permanent pacing systems in some cases of lead insulation break to re-establish normal pacing and sensing function, at least temporarily.

The intracardiac ventricular signal is generally between 6 and 15 mV and the atrial signal is generally 1 to 4 mV. A signal with a lower slew such as one originating in ventricular tissue is more likely not to be sensed than one with a high slew rate. After each pacing output pulse and after every sensed spontaneous cardiac signal, atrial and ventricular refractory periods are initiated during which the pacemaker will not respond to incoming signals (Table 26-8). The refractory period in the ventricular channel is usually programmed between 250 and 400 milliseconds to prevent sensing of the late part of the QRS complex and T wave. T wave oversensing can occur if the refractory period is programmed too short or if the sensitivity is too low (see Fig. 26-8).

Oversensing

Oversensing is present when the polar generator sensing circuit identifies an electrical event sensed in the ventricular channel as an R wave or an electrical event sensed in the atrial channel as a P wave (see Figs. 26-7 and 26-8). These electrical events

Table 26–8. Parameters of Cardiac Pacing System Relevant to the Critical Care Unit

Rates:
• Low (base) rate: the rate that the patient's spontaneous rate must fall below to initiate pacing • Upper rate limit: the highest rate at which the pacemaker will output; either in response to the atrial rate ("atrial driven") or to sensor input ("sensor driven") • Magnet: the rate during application of the magnet. This rate will differ depending on the manufacturer and the model of the pacemaker • Elective replacement indicator (ERI): the (usually magnet) rate that indicates the elective replacement time for a particular pulse generator • End of life indicator (EOL): the (usually magnet) rate that indicates that the pulse generator should be replaced urgently
AV interval: The interval between the atrial and ventricular stimulus delivery, or between the time of sensing the atrial depolarization and the delivery of the ventricular stimulus (this can be a dynamic value, changing with rate and other factors)
Refractory period: The interval during which the pulse generator will not respond to electrical signals, independently programmable for atrial and ventricular channels
Pacemaker energy output: The factors in the output are voltage, current, and pulse duration contemporary pacemaker generators allow programming of the voltage and pulse duration; to control energy output; independently programmable for atrial and ventricular channels
Sensitivity: The amplitude of the electrical signal that the pulse generator is programmed to sense, independently programmable for atrial and ventricular channels
Mode of function: See Table 31-4. The mode programming operation in the critical care setting is to program from dual-chamber to single-chamber (almost always ventricular) mode of operation to prevent rapid paced ventricular rates due to tracking of atrial tachyarrhythmias.

may be generated in the pacing system itself, in the heart, in the body musculature, or in the environment (see Table 26-6). The consequence of oversensing is a pause in paced rhythm (AAI or VVI modes) or, if the oversensed atrial event causes triggered pacing in the ventricle, an earlier than expected paced ventricular event (DDD modes may have either response, depending on where the impulse was oversensed). Appropriate pacing function can be demonstrated by placing the magnet over the pulse generator, temporarily disabling sensing function (AOO, VOO, DOO modes). This maneuver serves to exclude failure of output as a cause of absent pacing artifacts and can also clarify a diagnosis of lead fracture.

The sensing circuits of the pacemaker generator are able to differentiate P, R, and T waves by their amplitudes, slew rates, and durations. It is not uncommon for the atrial sensing circuit to detect a remote ("far field") R wave because of its large amplitude, a phenomenon termed *far-field oversensing*. Oversensing can cause inhibition of output, resulting in a pause in delivery of the atrial output stimulus. "Crosstalk" can occur in the ventricular channel upon sensing an atrial pacing stimulus of high

output, especially if the ventricular sensitivity is programmed to a low value. Inhibition of ventricular output due to crosstalk can result in long pauses in rhythm. Management of far-field oversensing and crosstalk consists of (1) decreasing the sensitivity of the atrial or ventricular channel by noninvasive programming; (2) programming a sufficiently long postventricular atrial refractory period (PVARP), a period of time after paced or spontaneous ventricular depolarization during which the atrial channel does not respond to sensed input; and (3) in the case of ventricular crosstalk, decreasing the atrial output. Rarely, crosstalk can occur when the atrial lead is positioned, or has dislodged, near the tricuspid valve or into the ventricle.⁷² It is extremely unusual to sense sinus P waves in the ventricular channel if the ventricular pacing lead is positioned in the right ventricular apex. An ectopic P wave originating close to the AV node, on the other hand, has been reported to be sensed in the ventricular sensing circuit.⁷⁸

T wave oversensing is rare in today's permanent pacing systems but is still observed in temporary pacing. It is often the paced T wave with its larger intracardiac amplitude that is oversensed, although oversensing of ventricular fusion complex T waves has been reported.⁷⁹ T wave oversensing in a VVI paced system is usually not hazardous because the pause in paced rhythm due to inhibition by the oversensed signal is only slightly larger than the programmed escape interval. The requirements for T wave oversensing are a short programmed refractory period and a high programmed sensitivity, and management is by noninvasive programming to more appropriate settings; the pulse generator can be programmed to a decreased sensitivity or to a longer refractory period so that the T wave falls within it, thus avoiding inhibition of output. Oversensing of concealed ventricular extrasystoles (depolarization confined to the His-Purkinje system and invisible on a surface electrocardiogram) was first reported in 1972⁸⁰⁻⁸¹; its prevalence is unclear but is considered to be low.

Skeletal myopotentials, particularly pectoralis major myopotentials, can achieve an amplitude as high as 3 mV. Myopotential oversensing is not uncommon in unipolar pacing systems, and the incidence of inappropriately long pauses can be as high as 30%.⁸² The high incidence is due to the amplitude of the signal being augmented by the distance between the cathode (intracardiac electrode) and anode (pulse generator). In contrast, bipolar pacing systems are relatively immune to skeletal muscle interference even when programmed sensitivity is increased, which is one of the reasons that the majority of current systems implanted use bipolar leads. Diaphragmatic myopotential oversensing by bipolar electrodes⁸³ has been reported, however, and has been accompanied by a high programmed sensitivity and provoked by cough, hiccoughs, or a Valsalva maneuver.⁸³ Patients having symptoms of light-headedness, syncope, presyncope, or dyspnea during certain arm or torso movements should have these same movements repeated with electrocardiographic monitoring to identify pauses due to skeletal myopotential oversensing. It is not unusual that only particular types of movement cause oversensing whereas others do not. In a unipolar system, if myopotential oversensing cannot be corrected by noninvasive programming to a lower sensitivity, or if undersensing results from the programming change, change to a bipolar lead may be required. If absolutely necessary, mode change to an asynchronous one (AOO, VOO, DOO) by placing the magnet over the pulse generator or by noninvasive programming will eliminate

the oversensing; however, the possibility of competitive atrial and ventricular rhythms is real.

External electromagnetic interference (EMI) from the environment, particularly from electrical appliances emitting energy at frequencies of 50 to 60 Hz, can also cause oversensing with resulting inhibition of output or triggered pacing. The sources of interference include radiofrequency transmitting devices,^{84,85} arc welding,⁸⁶ automobile ignition systems,⁸⁶ radar,⁸⁷ and portable music players.⁸⁸ Several other exogenous sources of EMI encountered in a medical setting can affect pacing system function (see Table 26-6) and are discussed later in this chapter in response to interference, some pulse generators revert from their programmed mode to an “interference mode,” which is usually a fixed-rate (asynchronous) mode of function at a specific “interference rate.” Some bipolar pacing systems revert to unipolar pacing, a design feature that should be appreciated so that an erroneous diagnosis of pacemaker malfunction is avoided. Reversion to an interference mode is designed to prevent the occurrence of asystole in the presence of EMI. EMI oversensing is more common in unipolar pacing systems. Newer pacemaker generators have special shielding and filters that have eliminated or significantly reduced the incidence of EMI oversensing.

Undersensing

When native R waves and P waves are not detected by the sensing circuits of the pacemaker system, inappropriate delivery of pacing stimuli ensues (see Figs. 26-9, 26-10, and 26-11). The consequences of undersensing depend on the response of the pacing system to sensed events. In single-chamber demand pacing systems (AAI, VVI), undersensing causes asynchronous fixed-rate pacing. In VVI systems, R wave undersensing could cause a stimulus output to be delivered in the T wave, the vulnerable period, potentially causing a transient or sustained ventricular arrhythmia (see Fig. 26-11). Similarly, an atrial stimulus delivered in the vulnerable period of atrial tissue can cause atrial arrhythmias such as atrial fibrillation. The common causes of undersensing are listed in Table 26-7 and generally reflect poor quality of the intracardiac signals or an inappropriately low programmed sensitivity.

Native intracardiac signals can become smaller in magnitude and longer in duration with a slower rate of change of voltage during conditions such as congestive heart failure and acute myocardial infarction.⁸⁹ Hyperkalemia or drug toxicity, especially from Class IA antiarrhythmic agents, can decrease the slope and amplitude of phase 0 of the cardiac action potential, thereby generating a suboptimal intracardiac signal. Undersensing during these conditions is often transient and can be managed by watchful waiting, providing there is no accompanying failure of capture and the patient is not pacemaker-dependent. Because of the altered and nonuniform membrane excitability under these conditions, however, the risk of pacemaker-induced arrhythmias is high.^{59,90-96} In addition to treating the underlying clinical problems, the pulse generator can be programmed to a higher sensitivity or programmed to unipolar configuration (in specific devices) to enhance the magnitude of the native depolarization.

Undersensing of ectopic ventricular complexes can be due to suboptimal signal quality (true undersensing) or to their occurrence within the ventricular channel's refractory period, which follows all ventricular sensed events and stimulus outputs. The

former condition can be managed by noninvasively programming the pacemaker to a higher sensitivity. The latter condition can be managed by decreasing the refractory period of the ventricular channel at the potential expense of oversensing T waves. Yet another approach is to suppress the ventricular extrasystoles with antiarrhythmic medications; the decision should depend on the clinical condition of the patient and the risk-benefit ratio of the various approaches.

Local fracture or dislodgement should always be considered when undersensing occurs. These conditions are serious and are often accompanied by a failure to capture. Chest radiographs should be obtained to evaluate lead position and integrity, although lead fracture is often not visible on standard radiographs. Interrogation of the pulse generator reveals high lead impedance with lead fracture, and lead replacement will be required.

The preceding discussion has been predominantly focused on issues with permanent pacemakers, although many of the same principles apply to temporary transvenous pacing. A guide to troubleshooting temporary pacemaker problems is given in Table 26-9.

Rapid Paced Ventricular Rates

Tracking the sensed sinus rate is an important function of a dual-chamber pacing system that senses in the atrium (DDD, VDD, see Table 26-4). During tracking, a sensed atrial event triggers a ventricular output at the end of the programmed AV interval (similar to a PR interval) unless a spontaneous ventricular event is sensed (Figs. 26-12 and 26-13). One potential problem during normal tracking function is oversensing in the atrial channel, which inhibits atrial output but triggers ventricular pacing at an inappropriate time. The consequence is an undesirable paced ventricular arrhythmia or even pacemaker-mediated tachycardia (PMT). Decreasing the atrial sensitivity risks atrial undersensing; programming to a nonsensing mode such as DDI or VVI may be necessary in the acute clinical situation. Removal of the patient from the source of environmental interference will eliminate the problem of electromagnetic interference oversensing. If a unipolar atrial lead has been used and noninvasive programming cannot solve the problem, change to a bipolar lead may be required as it will be less prone to oversensing.

If atrial tachyarrhythmias occur in patients with DDD pacing systems, tracking up to the programmed upper rate limit can occur (see Table 26-8). This upper rate is programmed based on the patient's activity, age, and presence of coronary artery or other cardiac disease. When the atrial rate exceeds the programmed upper rate limit (sinus tachycardia, atrial tachycardia, atrial flutter), ventricular pacing can resemble an “electronic AV block,” either as a second-degree fixed-ratio block or Wenckebach response (Fig. 26-14). With these rapid paced ventricular responses to rapid atrial rates, cardiac output can suddenly decrease, particularly with fixed ratio block. If the atrial rhythm is fibrillation, the paced ventricular rhythm is usually irregular (see Fig. 26-14). It must be remembered that sensor-based pacing systems have a programmable upper rate that may be independently programmed and different from the atrial-driven upper tracking rate.

Pacemaker-mediated tachycardia (PMT) is a well-known complication of DDD pacing.⁸⁹⁻⁹⁴ The PMT usually begins with a premature ventricular complex with retrograde ventriculoatrial

Table 26–9. Troubleshooting in Temporary Cardiac Pacing

Problem	Possible Causes	Corrective Measures
Failure to capture (pacing output pulses visible)	Output programmed inappropriately low High stimulation threshold due to ischemia, antiarrhythmic drugs, electrolyte imbalance, metabolic disorders Lead malposition	Increase output Increase output, treat ischemia, alter medications, correct electrolyte and metabolic abnormalities Chest radiograph, paced electrocardiogram; reposition lead
No visible output (pacing output pulses not seen)	Loose connections Oversensing (inhibition of pacer output by inappropriately sensed signals) Crosstalk inhibition (sensing of atrial output by the ventricular channel leading to inhibition of ventricular output)	Check all connections Decrease sensitivity Reduce atrial output; decrease ventricular sensitivity
Failure to sense (inappropriate delivery of pacing stimulus outputs)	Sensitivity programmed inappropriately low Lead malposition Poor intracardiac signal	Increase sensitivity Reposition lead Treat correctable causes of poor signal (such as acidosis, hyperkalemia, congestive heart failure)



Figure 26-12. Normal tracking function of sinus tachycardia in a patient with a DDD pacing system. In the beginning of the lead II rhythm strip, there is group beating owing to the third sinus P wave of the group occurring in the postventricular atrial refractory period and not triggering an output in the ventricle. At the end of the strip, 1:1 tracking of the sinus rate is present. The diagnosis of the cause of a rapid paced ventricular rate in non–rate-adaptive pacing systems can be established by programming to VVI mode of function (in which tracking of atrial activity does not occur) at slow rate; this clarifies the atrial rhythm and rate.

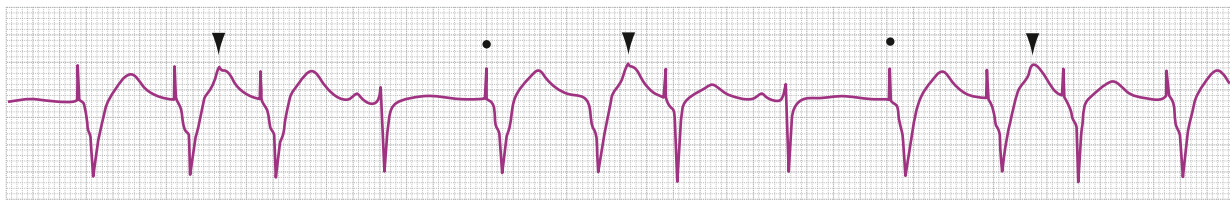


Figure 26-13. VDD mode of function. This pacing system senses atrial and ventricular electrical activity, but paces only the ventricle. Atrial sensing is followed by triggered ventricular pacing at the programmed atrioventricular interval, unless a spontaneous QRS complex has occurred, in which case the device is inhibited. The pacing stimulus terminating a pause is delivered in the ventricle (*closed circles*) because atrial pacing does not occur, a finding that allows the diagnosis of VDD function. In this example, the upper rate limit has been programmed to 100 beats/min. Because the upper rate cannot be violated, the sensed P waves (*arrowheads*) initiate a longer than programmed atrioventricular interval so that the timing of the ventricular pacing stimulus does not exceed this upper rate limit. The automatic extension of the atrioventricular interval is a form of “electronic AV block” that can also resemble type I and type II atrioventricular block.

conduction; the retrograde P wave is sensed in the atrial channel, triggering a ventricular output that once again causes retrograde ventriculoatrial conduction, thus creating an “endless loop” (Fig. 26-15). The initiating mechanism of PMT is almost always AV dissociation, created by a ventricular extrasystole,

loss of atrial capture, or oversensing in the atrial channel. The easiest way to terminate PMT is by application of a magnet over the pulse generator. The elimination of atrial sensing will abolish the triggered ventricular output. Other more definitive ways to prevent sensing of retrograde P waves include programming

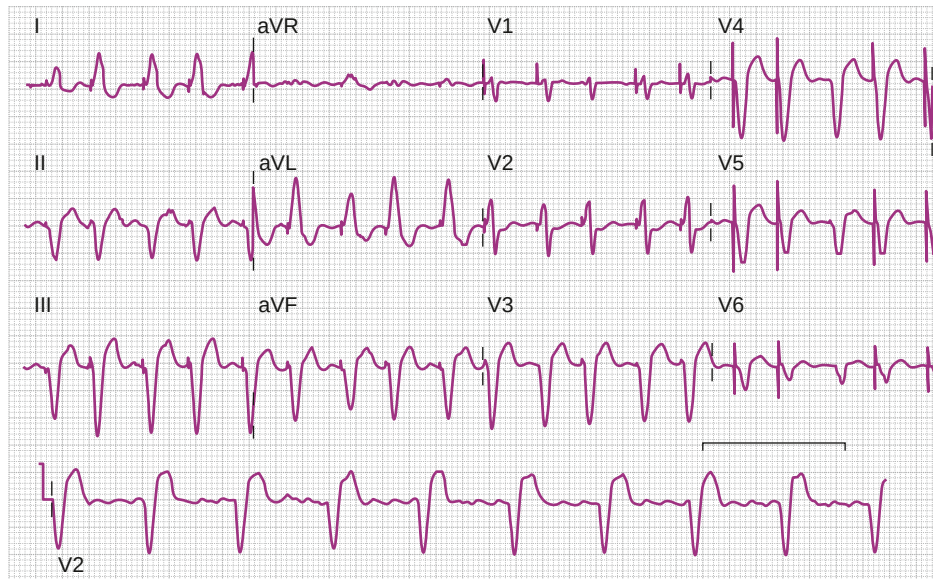


Figure 26-14. A 12-lead ECG in a 68-year-old patient with a DDD pacing system placed for complete atrioventricular block recorded during the complaint of palpitations. The pacemaker had been programmed to a base rate of 60 beats/min and an upper rate of 150 beats/min. The atrial rhythm is not discerned. The paced ventricular rhythm (all QRS complexes are paced) is irregular. The pacing system is not a rate-adaptive one. The irregularity of the paced ventricular rate suggests the presence of an atrial tachyarrhythmia with normal tracking of sensed atrial depolarizations. The V_2 rhythm strip (*bottom*), recorded after programming to VVI mode of function, shows atrial fibrillation. The rapid paced ventricular rate could represent normal tracking function in response to atrial flutter, fibrillation, or tachycardia; the irregularity of the rate suggests that flutter or fibrillation is most likely. Atrial flutter and fibrillatory waves can often have an amplitude of greater than 2 mV, allowing them to be sensed.

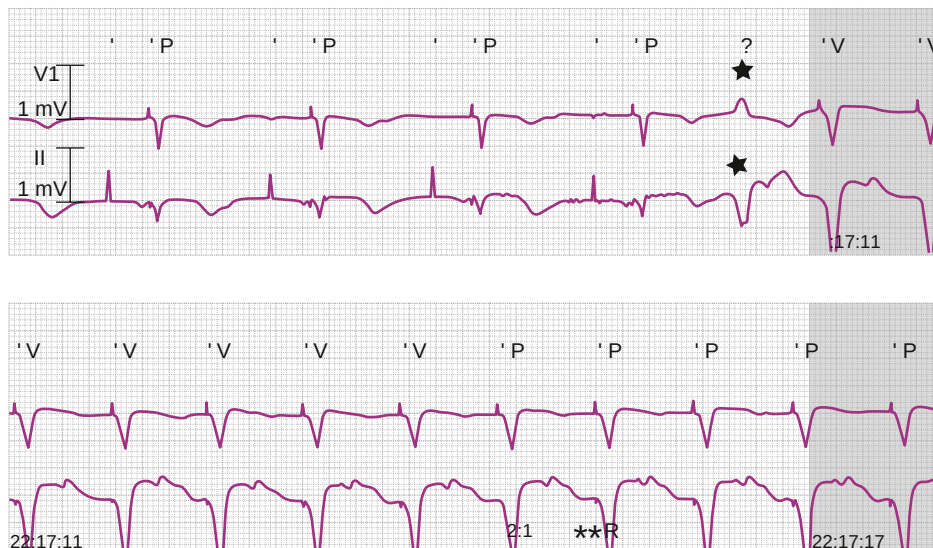


Figure 26-15. Continuous telemetry strip (leads V_1 and II) in a 54-year-old patient with a DDD pacing system placed for sick sinus syndrome. The pacemaker had been programmed to a base rate of 50 beats/min and an atrioventricular interval programmed to 280 ms. The top rhythm shows atrial pacing with narrow QRS complexes preceded by pacing stimulus suggestive of pseudofusion. A premature ventricular complex (denoted by the stars) is followed by retrograde P wave that is sensed, and it initiates a pacemaker-mediated tachycardia (sensing in the atrium followed by pacing in the ventricle). The tachycardia was terminated by placing a magnet over the pacemaker (that caused lack of sensing of the P waves). A final programming change was made to increase the postventricular atrial refractory period (PVARP) to prevent this tachycardia in the future.

a longer postventricular atrial refractory period (PVARP) and programming the specific pulse generator response to detection of premature ventricular depolarizations. Similarly, PMT can be terminated by programming “on” specific algorithms designed for this purpose.

Biventricular Pacing Systems

The implantation of biventricular pacing systems has become more common with evolving indications for their use in patients with systolic dysfunction. The basis for this newer therapy is the

observation that existing left bundle branch block or intraventricular conduction delay can worsen heart failure by creating ventricular dyssynchrony. Randomized controlled trials have demonstrated benefit in these patients, including a decrease in mortality, reduction in heart failure hospitalizations, and improvement in New York Heart Association (NYHA) heart failure class.^{95a-l} Current recommendations for implantation of these devices include NYHA Class III to IV heart failure, symptomatic heart failure despite appropriate medical therapy, left ventricular ejection fraction less than 35%, and QRS duration greater than 120 msec.^{95a-l}

Implantation of the left ventricular lead via the coronary sinus carries with it unique procedure-related complications. These include coronary vein trauma or dissection with the possibility of cardiac tamponade, and diaphragmatic or phrenic nerve pacing. The management of these immediate complications is beyond the scope of this chapter.

Biventricular pacemakers carry their own set of capture, sensing, and lead-related problems that are unique to the presence of the left ventricular lead, in addition to the problems delineated above for all pacing devices. Malfunction of the left ventricular lead may itself lead to ventricular dyssynchrony and a clinical presentation of worsening heart failure, or lack of improvement in symptoms and functional class.

Because of the location of the left ventricular lead in the coronary sinus, pacing impulses must penetrate the venous wall and any surrounding fat to reach the myocardium. For this reason, higher capture thresholds are often seen, and any migration of the lead within the coronary sinus may cause elevated thresholds and consequent loss of capture. Although loss of pacing through the left ventricular lead may, in comparison to prior tracings, lead to a widened QRS or different QRS morphology, these findings are not reliable and intracardiac electrograms seen on pacemaker interrogation may be necessary to confirm the diagnosis. If the right and left ventricular leads are programmed to stimulate in an “offset” fashion (one ventricle stimulated slightly in advance of the other to optimize interventricular synchrony), there will be two stimulus artifacts visible on the electrocardiogram if the biventricular leads are

functioning appropriately; these should not be confused with artifacts or false signals (Fig. 26-16, A and B).

Cardiac Pacing under Specific Clinical Circumstances

Myocardial Infarction

Myocardial infarction occurring in the patient with a pacemaker presents a variety of challenges, including those discussed earlier. The initial challenge is presented by the abnormal depolarization and repolarization patterns caused by pacing, obscuring the classic electrocardiographic diagnostic clues to the presence of myocardial infarction. An effort to discern spontaneous QRS complexes, including temporary programming to a low pacing rate or a long AV interval to facilitate spontaneous QRS activity, may reveal the diagnostic findings. In the presence of right ventricular pacing, the most useful findings are (1) primary ST segment and T wave changes (displacement of the ST segment and T wave vectors toward the major QRS vector), especially in comparison to prior paced electrocardiograms; (2) abnormal q or Q waves in leads V₃ or V₆; and (3) late notching of the S wave in the precordial leads (Cabrera sign).⁹⁵ These criteria and others are similar to those used in patients with left bundle branch block and are described in detail elsewhere⁹⁶⁻⁹⁸; despite good specificity for the diagnosis of myocardial infarction, the sensitivity is less than 20%⁹⁵⁻⁹⁸. Use of QRST isointegral maps has been reported to be helpful in detecting myocardial infarction in patients with paced rhythms.⁹⁹

Another potential complication in the diagnosis of acute myocardial infarction in a paced patient is the effect of a recently implanted pacemaker on serum creatine kinase isoenzyme and troponin patterns. Although minor transient increases in creatine kinase and troponin do occur, small prospective studies suggest that cardiac pacemaker implantation causes no significant confounding of the enzymatic diagnosis of myocardial infarction.^{100-100b} A pericardial friction rub, a not uncommon finding after pacemaker lead implantation that has been well documented in case reports, may mimic the mechanical

Figure 26-16. A, A 12-lead ECG in a 72-year-old patient with a biventricular pacemaker implanted for advanced heart failure. There is simultaneous delivery of pacing stimuli in the right and left ventricles as denoted by the star in lead I. **B,** A 12-lead ECG in the same patient with sequential delivery of pacing stimuli in the left and right ventricles (denoted by star in lead I) that leads to narrower QRS complexes and more effective biventricular pacemaker therapy (improved heart failure symptoms). In this patient, the left ventricle was paced earlier than the right ventricle.



complications of a myocardial infarction.^{101a-101d} In one case report, the finding of a loud systolic sound and apical thrill suggestive of mitral regurgitation or ventricular septal defect in a patient with a myocardial infarction was, in fact, due to a temporary pacing wire.¹⁰¹

Several aspects of the pathophysiology of myocardial infarction can cause failure to capture, including hyperkalemia (both systemic or local, from myocardial necrosis), metabolic acidosis, hypoxemia, and hypercarbia in patients with cardiogenic shock or pulmonary edema, and antiarrhythmic agents, most frequently those in Vaughn Williams Class I. All of these conditions can increase the myocardial stimulation threshold, and treatment of failure to capture in these settings is directed at correcting the underlying abnormality; if failure to capture persists, the pacemaker energy output should be increased.

Undersensing in the setting of myocardial infarction most often reflects a decrease in the integrity of the intracardiac signal.^{83,102} The deterioration of the signal can be caused by local myocardial ischemia, acidosis, electrolyte abnormalities, edema, and necrosis. The local effects are exacerbated by regional abnormalities in signal propagation owing to necrosis and changes in ventricular geometry and by systemic hyperkalemia and Class I antiarrhythmic agents. These alterations in the intracardiac signal are usually transient, requiring only careful observation. However, if life-threatening pacemaker-induced arrhythmias occur as a result of undersensing causing a stimulus to be delivered at a critical time (see Fig. 26-11), the sensitivity can be increased. If the appropriate programming equipment or personnel are not immediately available, complete inhibition of the pacemaker output can be achieved with continuous chest wall stimulation, although this technique is rarely necessary in current practice.^{88,103} It is important to note that in the presence of myocardial infarction, the exact nature of the intracardiac signal abnormality is not evident on the surface electrocardiogram and thus neither undersensing or oversensing can be predicted from the surface ECG.¹⁰⁴ Pulse generator interrogation with intracardiac electrography, acquired through the generator via the programmer, is required in many cases to confirm these diagnoses.

Cardiopulmonary Resuscitation

The paced patient requiring cardiopulmonary resuscitation often has or develops specific clinical problems that can contribute to pacing system malfunction, including myocardial ischemia, acidosis, hyperkalemia, and many other metabolic abnormalities. The standard resuscitation protocols should be followed in patients with permanent pacemakers; although attention must also be directed to establishing normal pacemaker function after the resuscitation procedure is completed. Not only can the myocardial stimulation threshold be markedly increased during cardiopulmonary resuscitation, necessitating either reprogramming of the pacemaker or additional pacing through transcutaneous or temporary transvenous routes, but also significant problems with sensing can occur during chest compressions. Although one might anticipate that chest compressions could cause lead dislodgement with complications ranging from failure to capture to myocardial perforation, these rarely occur. In one report there was no evidence of damage to permanent leads in four patients who had prolonged chest compressions.¹⁰⁵ In another report the function of VVI pacing systems in four patients with witnessed well-documented out-of-hospital cardiac arrest was analyzed; sensing malfunction,

presumably due to the severely damaged state of the myocardium, was demonstrated in all patients, with more pronounced pacemaker dysfunction in those patients receiving defibrillation.¹⁰⁶ In no case did the pacemaker malfunction have an adverse effect on outcome. Most sensing and pacing problems are transient, but thorough evaluation of the pacing system, including interrogation and programming functions, should be made after the resuscitation procedure.

Direct Current Cardioversion and Defibrillation

Transthoracic direct current (DC) shock is used as both an emergent and nonemergent treatment for atrial and ventricular tachyarrhythmias. Modern pacemakers are equipped with protection mechanisms against damage from DC shock. The most common of these mechanisms is the Zener diode,¹⁰⁷ which directs a surge in current toward the electrode, protecting the pacemaker circuitry but delivering this energy to the endocardium. In addition, the cardioverter-defibrillator can cause capacitive coupling with the endocardial lead, causing direct discharge at the electrode-endocardium interface.¹⁰⁸ This large focal discharge is thought to be responsible for the ensuing transient or permanent failure to sense and capture that is observed after DC shock in the absence of apparent damage to the pulse generator itself.^{108a} Failure to capture by an implanted pacing system can also occur after discharge of an automatic implanted cardioverter-defibrillator.^{109,110} Other electrostatic discharges caused merely by placement of the defibrillator paddles can also generate noise that is interpreted as signals by the pacemaker.¹¹¹ The protective mechanisms of the pacemaker are not always sufficient to safeguard the electronic components, and there are multiple reports, albeit from the older literature, of damaged circuitry,^{112,113} changes in programmed mode of function^{111,114,115} and even model number,¹¹⁶ complete pacemaker failure,¹¹⁷ and microdislodgement of the lead.¹¹⁸ In a recent study of 36 patients with unipolar pacing systems,¹¹⁹ DC shock resulted in failure to capture in 50% of the patients, lasting from 5 seconds to 30 minutes. Predictors of pacemaker dysfunction included higher peak and cumulative shock energies and lower pacemaker pulse amplitude. In patients in whom the pacing threshold was measured before and after the DC shock, there was a sixfold increase in pacing threshold 3 minutes after cardioversion, returning to baseline at 24 hours; failure to sense was noted in 7 of the 17 patients (41%) in whom this could be assessed. Although not studied, it is believed that bipolar electrodes are less susceptible to some of those complications owing to the decreased distance between cathode and anode.

The general precautions for DC cardioversion and defibrillation in patients with pacemakers attempt to minimize the current delivered to the pacemaker system. These precautions include placing the defibrillator paddles at least 10 cm away from the pulse generator, ensuring that the paddles are placed perpendicular to the dipole of the pacing system (usually an anteroposterior position of the defibrillator paddles is optimal) and using the minimal effective energy setting. More specific precautions will depend on the individual patient. For example, in a patient whose pacemaker has been programmed to VOO mode, the "synchronized" defibrillator may track the asynchronous outputs of the generator and discharge in the myocardial relative refractory period, inducing ventricular fibrillation.¹²⁰ Regardless of the precautions taken before cardioversion or defibrillation, a thorough evaluation of the pacing system should

be performed as soon as practically possible, including sensing and capture functions, measurements of base and magnet rates, integrity of programming commands, and telemetry function.

Electrotherapy

Electrical stimulating techniques such as transcutaneous electrical nerve stimulation are often indicated to treat pain related to muscular or neurologic problems. Studies have indicated a low incidence of adverse effects of transcutaneous electrical nerve stimulation on older pacemaker models that were more susceptible to electromagnetic interference than contemporary devices.¹²¹

Electroconvulsive therapy represents another application of electric current to reset excitable tissue, in this case, that of the brain. However, because of the localized application of the electrical stimulus to the head, there is a low probability for the occurrence of problems, although monitoring and standard resuscitation equipment, and a trained programmer, should be available.¹²²⁻¹²⁵

Electrocautery and Anesthesia

Electrocautery is the most common exogenous source of electromagnetic interference that can interact with pacemakers. Electrocautery uses radiofrequency current to transect tissue and achieve hemostasis. Coagulation and cutting circuits of electrocautery devices differ in their effects on permanent pacemakers. Bipolar coagulation cautery, in which the current flow is localized between the two poles of the instrument, is not expected to cause problems if kept more than 6 inches from the pulse generator. However, in unipolar electrocautery devices, the electrical current flow is not restricted to the tissue interposed between two electrodes and spreads throughout the body. This conductive electromagnetic interference, and the myopotentials resulting from the procedure itself, can result in pulse generator inhibition, electrical burns at the myocardial-electrode interface, atrial or ventricular tachycardia and fibrillation,¹²⁶ pulse generator component failure,^{115,127,128} loss of or change in output, reprogramming of rate or mode of function,^{115,129,130} runaway pacing,^{131-132a} and other malfunctions.^{133,134} Occasionally, electrocautery signals, perceived as “noise” by the pulse generator, can result in reversion mode pacing at a specific rate. Despite these reports, electrocautery is, in general, very safe in patients with pacemakers, although special precautions are helpful.^{135,136}

As with DC shock, these precautions attempt to limit the electromagnetic interference delivered to the pacemaker. The vector of the dipole for the electrocautery device with respect to that of the pacemaker is important.¹³⁷ These should not intersect with each other if at all possible. Bipolar electrocautery can minimize this interference, if only unipolar electrocautery is available, then the indifferent electrode should be placed as far from the pacemaker leads as possible. In addition, the use of low energy and short electrocautery bursts spaced far apart can minimize the hemodynamic effects of pacemaker inhibition. A magnet should not be applied prophylactically in all patients because there is no uniform pulse generator response to this maneuver and magnet rates and AV intervals are often different from programmed values. Magnet application may result in initiation of a programming procedure and inappropriate random reprogramming by the electrocautery device. In addition, an ICD will behave differently in response to a magnet than will a pacemaker without defibrillation functionality. Electrocautery can cause electromagnetic noise on the ICD sensing lead that is detected as ventricular fibrillation (VF) and can lead to inappropriate shock. Magnet placement over

the ICD (taped in place) will suspend detection of ventricular tachycardia (VT) or VF without interrupting back-up bradycardia pacing. Removal of the magnet will cause the ICD to resume detection and therapy (within 10 seconds) if VT or VF occur intraoperatively unless permanent magnet inactivation is programmed in the ICD. An alternative approach is to program the detection and therapy “off” during surgery and turn it “on” postoperatively; external defibrillators are used for intraoperative VT/VF. As in any procedure in pacemaker-dependent patients, the availability of programming equipment and trained personnel is essential. We have advocated using a pacemaker specialist to evaluate and clear the paced patient for procedures involving electrocautery.¹⁸⁰

General anesthesia can present a range of problems for the paced patients, although it rarely does so due to contemporary anesthesia techniques. Many metabolic and electrolyte abnormalities can affect pacemaker function, including hypoxemia, hypercarbia, and hyperkalemia, but except in emergent cases, these conditions rarely develop during anesthesia. However, vigilance and an understanding of the specific pacemaker's programmed parameters is crucial in the event of an emergency. For example, anesthetic induction with depolarizing agents that cause significant muscle fasciculations can cause complete inhibition of pacemakers because of oversensing, resulting in cardiac arrest in pacemaker-dependent patients.¹³⁸ This complication can be prevented by temporary reprogramming of the pacemaker to an asynchronous mode.

Other Minor Surgical Procedures (Lithotripsy, Endoscopic Electrocautery)

Advances in technology have produced a variety of new special procedures and techniques that can interact with implanted pacemakers. Extracorporeal shock wave lithotripsy is associated with electromagnetic and mechanical forces that may influence pacing system function.¹³⁹⁻¹⁴² Published studies of in vitro testing have indicated that about 4% of 15 pacemaker generators of various manufacturers tested failed when exposed to lithotripsy. Pulse generators employing a piezoelectric crystal sensor seem to be the most susceptible to failure,¹⁴⁰ and rate-adaptive generators that use this type of sensor should have the sensor mode programmed “off” during lithotripsy; this will prevent an unwanted increase in paced heart rate and shatter injury to the piezoelectric element. Patients in whom rate-adaptive pacing devices are implanted in the abdomen should probably not undergo lithotripsy because of the possibility of injury to the sensor. Despite these concerns, lithotripsy has been used successfully for the treatment of nephrolithiasis in patients with pacemakers,^{143-143b} including some with abdominal pulse generator sites,¹⁴⁴ although complications have been reported.¹⁴⁵ In a survey of 131 patients treated in 98 sites,¹⁴⁶ there were four pacemaker-related complications, none of which were fatal or required replacement of the pacemaker. All pacemakers should be thoroughly checked for proper function immediately after treatment.

Endoscopic electrocautery is also a frequently performed procedure that is generally safe in patients with pacemakers, although complications have been rarely reported.¹⁴⁷ Intra-aortic balloon counterpulsation can be triggered from the pacemaker output stimuli on the electrocardiogram, and care must be taken to ensure that proper timing is achieved. Consultation with a cardiologist or the pacemaker manufacturer is advisable before these procedures, and the availability of a trained programmer and continuous cardiac monitoring is essential.

Radiation Therapy

Epidemiologic data suggest that as the population ages, more patients with both cancer and pacemakers will be presenting for medical care. In some patients, the cancer itself may cause damage to the conducting tissue, necessitating pacemaker placement,¹⁶¹ whereas in other patients, the radiating therapy can cause complete heart block^{162,163} or sinus node dysfunction.¹⁶⁴ The high-energy ionizing radiation used in radiation therapy can cause significant damage to the semiconductors of pacemakers, even at very small doses.¹⁶⁵ This damage can be divided into three types: (1) temporary change in “interference mode” pacing lasting for the duration of the irradiation only; (2) change to interference mode pacing that necessitates reprogramming the pulse generator to restore original parameters; and (3) severe damage, in which the pacemaker ceases to generate output pulses. Pulse generator recovery may occur long after the end of the radiation treatment and is mostly incomplete, and the pacemaker cannot be used reliably thereafter.¹⁶⁶ Thus, in pulse generators exposed to radiation, transient loss of function should be regarded as a precursor of permanent damage. Currently available pulse generators that use the complementary metal-oxide semiconductor (CMOS) circuitry may actually be more sensitive to the effects of ionizing radiation than older generators.^{167-170b} Although some studies have shown no adverse effects on pacemakers,^{171,172} it is imperative that guidelines be followed for ensuring the lowest possible radiation dose to the pacemaker¹⁷³ and that careful follow-up be performed during and after completion of the radiation therapy. Therapeutic radiation should be accomplished with the pulse generator shielded, and if the patient is pacemaker-dependent and the pulse generator is situated near or in the radiation field, consideration should be given to relocating the generator to another site. The low-energy x-rays used for diagnostic radiology have not been reported to have any adverse effect in pacemakers.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is generally considered to be contraindicated in pacemaker patients, although controversy exists.¹⁷⁴⁻¹⁷⁸ MRI affects pacemaker function by the development of strong static and time-varying magnetic fields and pulsed radiofrequency fields. The changing magnetic fields can result in actual physical movement of the pulse generator's internal components, or generate transient currents and heating of the components or leads. During MRI, most pacemakers revert to an asynchronous mode of function. Although asynchronous pacing per se may not cause problems in the stable patient, radiofrequency pulsing can result in induced voltage across the pacemaker electrodes that may stimulate myocardial tissue, leading to rates equal to the MRI pulsing rates (cycle lengths of 200 to 1000 milliseconds).¹⁷⁷ Radiofrequency pulses can also cause inhibition of the pulse generator, with resulting bradycardia and asystole. Resetting of DDD pulse generators in the back-up mode can occur as the circuit is activated by a high radiofrequency pulse rate.¹⁷⁵

There will be times when the imaging modality may be essential, in which case consultation with the pacemaker manufacturer and cardiologist is recommended. Device manufacturers have made changes in devices to make them more compatible with MRI (less use of ferromagnetic material in battery construction). Recent studies have evaluated the utility and safety of performing MRI with modern scanners (1.5 Tesla) in animals and humans with modern devices (manufactured after 2000).¹⁷⁹⁻¹⁸³ Table 26-10 gives a list of modern devices

that were tested in a protocol with 1.5 Tesla MRI scanner. They excluded patients with fresh implants (<6 weeks), non-transvenous epicardial leads, leads without fixation (separate SVC coil, abandoned leads) and pacemaker dependent ICD patients.¹⁷⁹ Magnet response, rate response, noise response, ventricular sense response, premature ventricular contraction response, conducted atrial fibrillation response, and tachyarrhythmia functions should be disabled. Pacemaker-dependent patients should be programmed to VOO mode and non-pacemaker-dependent patients can be programmed to the VVI or DDI mode.¹⁷⁹ A case report describes a patient with a pacemaker having a head MRI after the pacemaker was programmed to an OOO mode.¹⁸⁴ While near or in the scanner, the patient should have continuous ECG telemetry and pulse oximetry monitoring and noninvasive blood pressure measurements should be obtained every 3 minutes.

Metabolic Abnormalities

Metabolic and electrolyte disorders are frequent causes of pacemaker dysfunction in an emergent setting and must always be considered when evaluating a patient with apparent pacemaker malfunction. Electrolyte and metabolic abnormalities, especially hyperkalemia, alkalosis, acidosis, and hyperglycemia, increase the pacing threshold, causing failure to capture.⁵⁷ Hyperkalemia increases the myocardial stimulation threshold by decreasing the transmembrane resting potential, decreasing the rate of depolarization, and shortening the action potential duration. These effects are independent of other abnormalities, including hypoxemia, hypercarbia, acidosis, alkalosis, and sodium or calcium concentration,⁵¹ reinforcing the importance of immediate correction of the hyperkalemia. There are numerous reports of many different types of pacing abnormalities,¹⁴⁸ ranging from pacemaker exit block of Wenckebach type¹⁴⁹ to higher grades of heart block¹⁵⁰ with eventual complete pacemaker exit block.¹⁵¹ In theory, reprogramming the pacemaker to higher energy output should be able to overcome this block, although practically the maximal output of the pacemaker is not infrequently insufficient. In addition to immediately restoring normal potassium levels, temporary cardiac pacing may prove beneficial.¹⁵²

Table 26-10. MRI Testing in Newer Implantable Devices

Pacemakers

- St. Jude Pacemaker AFP (262), Trilogy (2360), Entity (5326), Affinity (5130, 5330), Integrity (5142, 5342, 4346), Identity (5172, 5370, 5380, 5386)
- Guidant-Vigor (12320), Discovery (1272), Insignia (1194, 1290)
- Medtronic-EnPulse (AT-500, E2SRO1, E2DRO1), Kappa (701, 901), Prodigy (7860), Insync BiV (8040, 8042)

Implantable Cardioverter-Defibrillators

- St. Jude-Photon (V-194, V-230, V-232), Atlas (V-240), Epic (V-197, V-235, V-239)
- Guidant-Prizm (1850, 1851, 1852, 1860, 1861), Contak (1823, H119, H175), Vitality (T125, T135)
- Medtronic-Maximo (7232), Gem-II (7273), Gem-III (7275), Marquis (7274), Insync (7272)

Adapted from Nazaria S, Rogum A, Zviman MM, et al: Clinical utility and safety of a protocol for noncardiac and cardiac magnetic resonance imaging of patients with permanent pacemakers and implantable cardioverter-defibrillators at 1.5 tesla. *Circulation* 2006;114:1277-1284.

Other electrolyte and metabolic abnormalities also have important effects on pacemaker function, although they are not as common. Hypokalemia can cause increased myocardial stimulation threshold¹⁵³ with resultant pacemaker exit block and can be treated with calcium, isoproterenol, or potassium repletion. Hyperglycemia, metabolic acidosis, metabolic alkalosis, and hypothyroidism can increase the capture threshold^{54,57}; these problems are best treated by aggressive correction of the underlying metabolic disturbance.

Systolic Heart Failure

The presence of a permanent pacemaker has been reported to be an independent predictor of poor outcome in patients with heart failure,^{154,155} and right ventricular apical pacing has been shown in some reports in specific patient populations to increase the incidence of death and hospitalization for heart failure.^{155a} Patients having exacerbations of heart failure symptoms may be manifesting evidence of pacemaker malfunction^{156,157} or suboptimal programming values, and these possibilities must be carefully evaluated.

SECTION II

Implantable Cardioverter-Defibrillator Emergencies

Since the first implant in 1980,¹⁸⁵ the implantable cardioverter-defibrillator (ICD) has become the first line therapy for patients at risk for sudden cardiac death. An ICD consists of pulse generator, pacing/sensing electrodes, and defibrillation coils. It is capable of bradycardia pacing similar to permanent pacemakers; hence the ICDs are susceptible to the same complications and emergencies as discussed in the pacemaker section. In addition, an ICD senses and detects ventricular tachycardia (VT) and ventricular fibrillation (VF) and delivers therapy in the form of overdrive antitachycardia pacing, low-energy cardioversion, and high-energy defibrillation (Fig. 26-17). In this section we discuss unique emergencies related to detection and therapy of VT/VF.

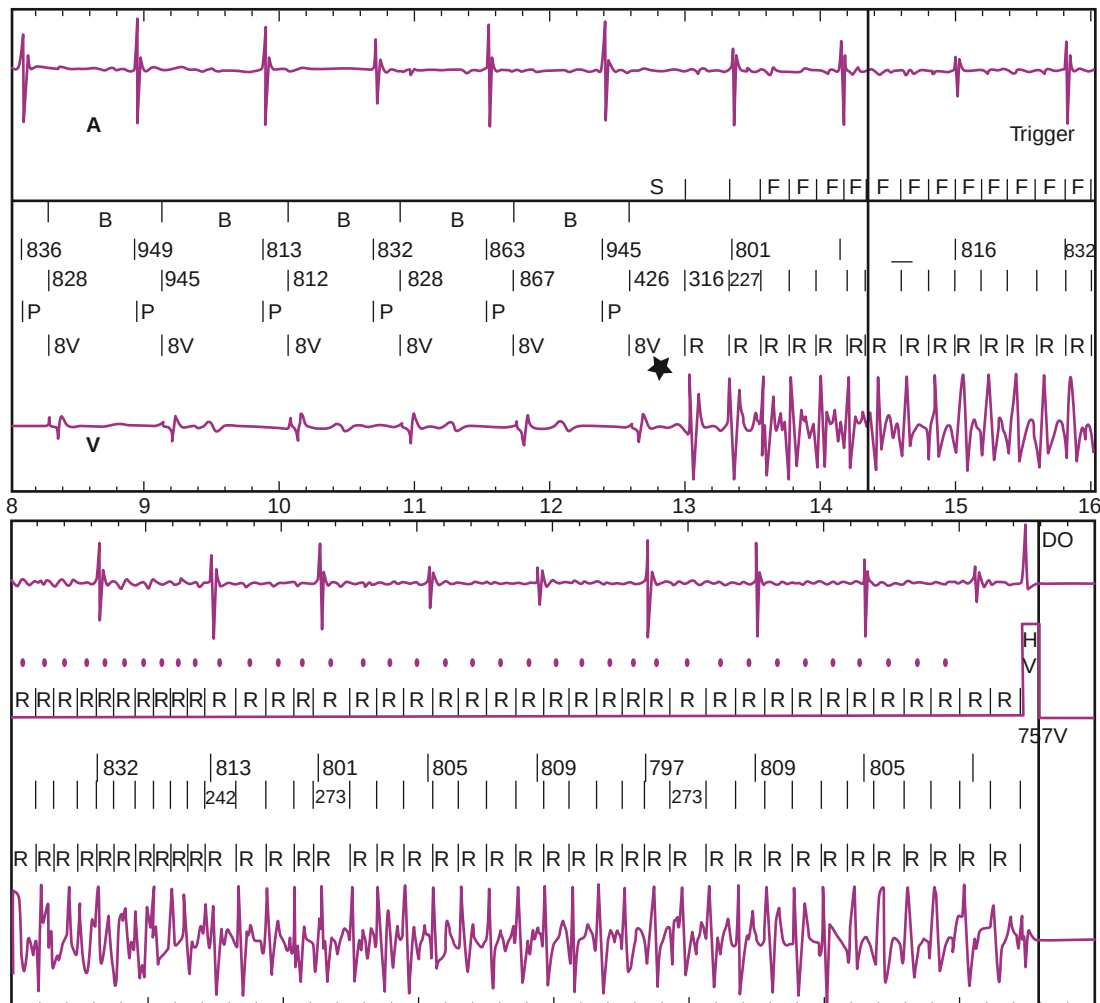


Figure 26-17. Continuous intracardiac electrogram recordings from interrogation of a biventricular implantable cardioverter-defibrillator in a 78-year-old man who received a shock through the device. The atrial electrogram (A) is on the *top* followed by marker channels and ventricular electrogram (V) on the *bottom*. The strip shows sudden onset of a fast rhythm in the ventricular channel (*star*) that is appropriately detected as ventricular fibrillation (F on marker channel) and treated with high-energy defibrillation.

Various randomized clinical trials have shown the effectiveness of ICD therapy for improving mortality in survivors of cardiac arrest (secondary prevention) and patients at risk for sudden death (primary prevention).¹⁸⁶⁻¹⁸⁸ Table 26-11 summarizes the indications for ICD implantation in adults according to the Task Force guidelines.²

Inappropriate ICD Shock

Inappropriate shock refers to delivery of an ICD shock for a rhythm different from VT or VF. This is the most common adverse effect observed among ICD patients; the incidence varies from 13% to 22% in various series.¹⁸⁹⁻¹⁹⁴ Inappropriate shocks can be caused by misdiagnosis of supraventricular tachycardia (SVT) as VT or inappropriate sensing due to lead malfunction or environmental interference (Table 26-12). It is important to understand the detection and therapy programming in the tachycardia zone in the ICD. Sensing is the process by which an ICD determines the timing of electrogram signals caused by cardiac depolarization. Detection is the algorithm by which an ICD processes a series of electrogram signals to classify the

cardiac signal and determine if treatment should be delivered. The sensing in the ICD is similar to the sensing in a pacemaker; the tachycardia zone is programmed based on detected rate on the ventricular channel. The device can be programmed to have more than one VT zone (slow VT, fast VT) and one VF zone. Therapy consists of antitachycardia pacing and low-energy cardioversion that is programmed in the VT zone and high-energy defibrillation that is programmed in the VF zone.

The most common cause of inappropriate shocks is misdiagnosis of SVT (e.g., atrial fibrillation [AF], sinus tachycardia) as VT or VF, as the ventricular rate during these episodes exceeds the programmed rate for VT (Fig. 26-18). Preoperatively documented AF, a maximal heart rate during exercise close to the detection interval, and a low detection rate have been found to be independent risk factors for inappropriate therapy.¹⁹² Various algorithms have been developed to differentiate SVT from ventricular arrhythmias and hence avoid inappropriate shocks.¹⁹⁵⁻¹⁹⁸ Sinus tachycardia is differentiated from VT based on onset criterion (sudden onset in VT while sinus tachycardia is gradual); this criterion might not differentiate slow VT with a cycle length similar to sinus tachycardia. Atrial fibrillation is differentiated from VT by stability criteria (VT is more regular); however, at faster rates AF can be regular and VT can show some irregularity. Dual-chamber devices have simultaneous recordings from the atrial and ventricular channels that can diagnose VT based on AV dissociation. The morphology criterion relies on the fact that the ventricular electrogram during VT will have a different morphology from the sinus and SVT morphologies. It is important to note that these SVT discriminators do not work in the VF zone and hence selection of appropriate rate cut-offs for the VT and VF zones is also very important to avoid inappropriate shocks. The performance of SVT discriminating algorithms used by different manufacturers is comparable.¹⁹⁹

Device-related causes of inappropriate shocks include inappropriate sensing due to lead malfunction or dislodgement, double counting of QRS complex, oversensing of diaphragmatic myopotentials, and T wave oversensing (Fig. 26-19). Rarely, older ICDs can deliver shocks for repetitive self-terminating episodes of VT (committed shock). These shocks can be prevented by increasing the number of beats required for detection of VT or VF or upgrading their devices to those that have noncommitted shock (redetection of VT or VF after the device has been charged). Electromagnetic interference (EMI) refers to noise on the ventricular

Table 26-11. Guidelines for Implantation of Implantable Cardioverter-Defibrillators in Adults: Class I and II Indications

Class I

- A. Cardiac arrest due to ventricular tachycardia (VT) or ventricular fibrillation (VF) not due to a reversible cause.
- B. Spontaneous sustained VT in association with structural heart disease.
- C. Syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or VF induced during electrophysiologic study (EPS) when drug therapy is ineffective, not tolerated, or not preferred.
- D. Nonsustained VT in patients with CAD, prior MI, left ventricular dysfunction, and inducible VF or sustained VT during EPS that is not suppressed by a class I antiarrhythmic drug
- E. Spontaneous sustained VT in patients without structural heart disease that is not amenable to other treatments.

Class II

- A. Patients with left ventricular ejection fraction less than 30% at least 1 month post-MI and 3 months post-CABG
- B. Severe symptoms attributable to sustained ventricular arrhythmias while awaiting cardiac transplantation
- C. Familial or inherited conditions with a high risk for life-threatening ventricular arrhythmias such as long Q-T syndrome and hypertrophic cardiomyopathy
- D. Syncope of unexplained etiology or family history of sudden death in association with Brugada syndrome
- E. Syncope in patients with advanced heart disease in which thorough invasive and noninvasive investigation has failed to define a cause.

Abbreviations: CAD, coronary artery disease; CABG, coronary artery bypass grafting; MI, myocardial infarction.

Adapted from Gregoratos G, Abrams J, Epstein AE, et al: ACC/AHA/NASPE 2002 guidelines for implantation of cardiac pacemakers and antiarrhythmia devices: summary article: report of the American College of Cardiology/American Heart Association task force on practice guidelines (ACC/AHA/NASPE committee to update the 1998 pacemaker guidelines). *Circulation* 2002;106:2145-2161.

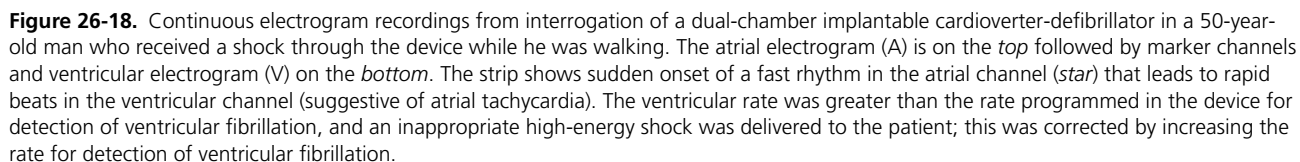
Table 26-12. Causes of Inappropriate ICD Shocks

1. Supraventricular arrhythmias

- Sinus tachycardia
- Atrial flutter and atrial fibrillation
- Paroxysmal supraventricular tachycardia
- Frequent premature atrial or premature ventricular complexes

2. Device-related causes

- Oversensing of T waves and/or P waves
- Double counting of R waves
- Loose setscrew
- Scanning of pacer stimulus artifact
- Oversensing due to lead fracture or insulation failure
- Electromagnetic interference (environmental noise)
- Oversensing of diaphragmatic myopotentials



Patients who receive an isolated shock with no symptoms to suggest a change in health status should be reassured and scheduled for elective evaluation of the ICD. Patients who feel unwell after an ICD shock or who receive more than one shock in a short period of time require emergent evaluation. Interrogation of the ICD with the programmer from the specific device company will immediately give an alert if therapy in the VT/VF zone has been delivered, battery status is close to end of life, and if there is lead malfunction (change in impedance). Analysis of the programmed parameters, episode summary, and the stored intracardiac electrogram during the episode will give clues to the etiology of the inappropriate shock. Multiple shocks can lead to increased anxiety and depression and can negatively impact the quality of life

Electrical Storm

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Figure 26-19. Continuous electrogram recordings from interrogation of a single-chamber implantable cardioverter-defibrillator implanted in a 61-year-old man for sustained ventricular tachycardia. The patient complained of receiving multiple shocks while running. The ventricular electrogram shows oversensing of the T waves (stars) that leads to inappropriate detection of the rhythm as ventricular fibrillation. The patient received multiple shocks; this was corrected by changing the sensing algorithm in the implantable cardioverter-defibrillator so that it would not detect the T wave. Defibrillation testing was repeated at the changed algorithm to ensure appropriate detection of ventricular fibrillation.

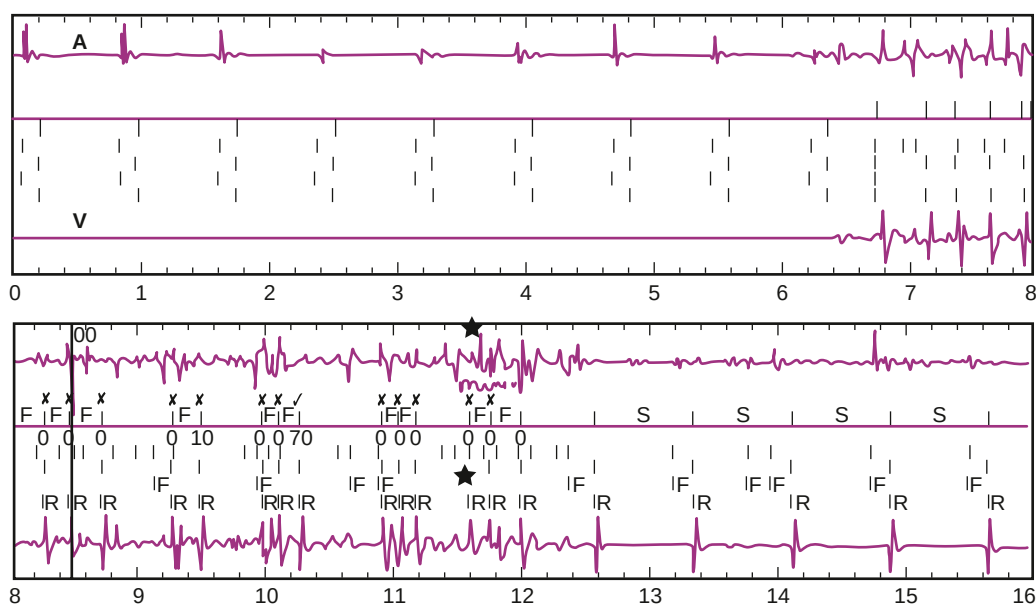


Figure 26-20. Continuous electrogram recordings from routine interrogation of a biventricular implantable cardioverter-defibrillator implanted in a 72-year-old man for advanced heart failure. The atrial electrogram (A) is shown on the top followed by the marker channels and the ventricular electrogram (V) on the bottom. The strip shows sudden onset of rapid and irregular rhythm (stars) recorded in the atrial and ventricular channels that is suggestive of electromagnetic interference. It meets the rate criteria for ventricular fibrillation as denoted by the F markers on the ventricular channel (it was nonsustained, and no therapy was delivered). The patient had undergone a minor procedure using electrocautery that was the cause of the electromagnetic interference.

with an ICD. A patient having multiple shocks should be immediately seen in the emergency room and connected to telemetry to ascertain the appropriateness of the shocks. In a patient with multiple appropriate shocks, intravenous amiodarone is the first line of therapy²⁰⁴ while evaluating for reversible causes such as electrolyte abnormality and ischemia. Amiodarone-induced hyperthyroidism and proarrhythmic effects of antiarrhythmic drugs are other causes of electrical storm. Intravenous

β -blockers to suppress adrenergic drive,²⁰⁵ intubation and sedation with propofol,²⁰⁶ and intra-aortic balloon pump and ventricular assist devices for hemodynamic support have been used to suppress the ventricular arrhythmias. The ICD can be interrogated to ascertain programmed parameters to attempt pace termination of VT. Emergent catheter ablation of VT or VF has been successfully used as a treatment of last resort in selected patients.^{207,208}

Drug Effects on ICD Function

Antiarrhythmic drugs are often initiated in patients with ICDs to decrease the burden of ventricular and supraventricular arrhythmias. Based on data from various ICD trials, more than 50% of the patients with ICDs can be assumed to be taking these drugs.^{209,210} The advantage of adding antiarrhythmic drugs to ICD patients includes: (1) reduction in frequency of ICD discharges by decreasing the episodes of VT/VF; (2) reduction of VT rate that allows antitachycardia pacing to be effective and maintains consciousness during ICD therapy; (3) reduction in burden of SVT to prevent inappropriate shocks; (4) reduction in defibrillation threshold (DFT); and (5) improvement in quality of life. The potential deleterious effects of antiarrhythmic drugs on ICD patients include: (1) increased ICD discharge due to proarrhythmias; (2) slowing of the VT rate below the ICD detection rate, thus preventing therapy and leading to syncope; (3) altering the QRS morphology that interferes with sensing; (4) increased DFT; (5) increased pacing threshold at higher pacing rates (use dependence); and (6) heart failure exacerbation.^{66a,211,212}

An increase in pacing threshold is seen with class IC drugs (especially flecainide); however, in a prospective study of 14 ICD patients, there was no significant increase in pacing threshold with propafenone at clinically used doses.²¹³ Class IC drugs can lead to widening of the QRS electrogram morphology that may cause misclassification of SVT as VT by the device, while class IA and class III drugs can cause QT prolongation that might lead to double counting (R wave and T wave) and inappropriate shocks.^{66a}

The most potentially dangerous effect of drugs on ICD function is an increase in DFT that can lead to ineffective ICD therapy. In general, the drugs that block fast inward sodium current and shorten the action potential duration (e.g., lidocaine) can cause an increase in DFT, whereas potassium channel blocking drugs that prolong the action potential duration (e.g., sotalol) tend to decrease DFTs and are favorable choices in patients with high DFTs. Class IA drugs (procainamide, quinidine, and disopyramide) do not seem to have a significant effect on DFT, whereas class IB drugs (lidocaine and mexiletine) have consistently shown elevation in DFT.²¹⁴ The effects of class IC on DFTs are less clear, with flecainide showing an increase in DFT in animal studies while moricizine and propafenone did not show any effect on DFT.²¹¹ Among the class III drugs, N-acetyl procainamide (an active metabolite of procainamide), clofilium, sotalol, and dofetilide have been shown to reduce DFTs.²¹⁴⁻²¹⁶ Intravenous amiodarone was not found to have any effect on DFT, whereas oral amiodarone was associated with an increase in DFT in animal and human studies.²¹¹ Recent advances in defibrillator technology (use of biphasic waveforms and “active” can) have improved defibrillation efficacy and mitigated some of the adverse pharmacologic effects; however, amiodarone can cause a clinically significant increase in DFT (even in modern devices). DFT in patients after starting amiodarone should be re-evaluated.

Sotalol has been shown to significantly decrease the burden of ventricular arrhythmias and ICD shocks in randomized prospective trials.^{217,218} Azimilide, a novel class III drug, has also been shown to reduce ICD therapies (shocks and antitachycardia pacing) in large randomized placebo-controlled studies^{219,220}; however, it has not yet been approved in the United States by the Food and Drug Administration. Recently, the Optimal

Pharmacological Therapy in Cardioverter Defibrillator Patients (OPTIC) trial randomized ICD patients to receive β -blocker alone, amiodarone plus β -blocker, or sotalol. At 1-year follow-up, amiodarone plus β -blocker was the most effective regimen in reducing ICD shocks.²²¹ Recently, there has been interest in assessing the role of statins and novel antianginal agents such as ranolazine in reducing ventricular arrhythmias.

ICD-Pacemaker Interactions

Although new generation ICDs are equipped with pacemaker capability, patients with older ICDs might have separate pacemakers and ICDs. The potential adverse interaction between ICD and pacemaker can be classified as: (1) ICD effect on pacemaker function; and (2) pacemaker effect on ICD function.²¹²

ICD shock can lead to transient postshock loss of capture and sensing in the pacemaker because of exposure of the myocardium to high current density. This is related to the distance between the pacing and shocking electrodes and the amount of energy delivered. Another potential effect on pacemaker function after ICD shock is reprogramming of the pacemaker mode and/or polarity. These can be avoided by keeping the greatest possible separation between the pacing and shocking electrodes and using bipolar pacing systems in these patients. ICD shocks can potentially damage the pacemaker circuitry; this has not been observed in modern pacemakers. Nevertheless, comprehensive pacemaker interrogation should be performed after ICD shock. Another potential adverse effect is pacemaker reprogramming during ICD interrogation; this can be prevented by keeping adequate spatial separation between the pacemaker and ICD generators.

In patients with ICDs and separate pacemakers, the pacing stimulation artifact (PSA) can cause undersensing or oversensing in the ICD lead (especially in unipolar pacemakers) and hence prevent ICD therapy or cause an inappropriate ICD shock. It is recommended that pacing at the chronic pacing amplitude (maximal amplitude in new pacemakers) in sinus rhythm should cause a PSA amplitude less than 1 mV on the ICD rate sense lead to ensure appropriate ICD sensing during VF. Appropriate ICD sensing should also be documented during VF with simultaneous synchronous pacing from the pacemaker at this amplitude. In addition, the electrical artifact resulting from mechanical contact between the pacemaker and the ICD lead can be oversensed by the ICD and cause inappropriate shocks. Rate responsive pacemaker rates can achieve rates that cross over into the VT detection zone of the ICD, leading to inappropriate shocks. This can be corrected by appropriate ICD programming of the VT/VF zones.

Ineffective ICD Therapy

An ICD is programmed to provide therapy during life-threatening ventricular arrhythmias. Delayed or absent ICD therapy during VT/VF can be lethal for some patients. Ineffective ICD therapy can be due to: (1) inactivated device (some ICDs have a programmable magnet mode that can be triggered by EMI to turn off therapy); (2) undersensing of VT/VF due to change in the myocardial substrate, antiarrhythmic drug-induced decreased sensing, lead malfunction or displacement, generator malfunction, and pacemaker-ICD interaction; (3) lack of detection of VT/VF due to a high rate cut-off for detection, and slower

VT because of antiarrhythmic drugs; (4) ineffective therapy due to battery depletion with prolonged charge time; high DFT, and ICD component failure.

It is imperative that ICD patients undergo routine evaluation (every three months and after each exposure to EMI) to assess the battery status, charge time, lead integrity and function, and analysis of arrhythmia log to evaluate for appropriate and inappropriate therapy. The new generation ICDs have wireless telemetry and remote monitoring that are capable of monitoring the device more frequently at home and notifying the physician of device or lead malfunction.²²² Death due to unpredictable ICD generator failure has been reported recently,^{223,224} which has led to more aggressive reporting of device alerts, recalls, and advisories. The DFT needs to be evaluated appropriately at the time of implant to achieve an adequate safety margin (at least 10 J difference between DFT and maximum energy delivered through the ICD). This might require implantation of a separate SVC coil and subcutaneous array in selected patients. Antiarrhythmic drugs can adversely affect DFTs and also slow the VT rate, leading to underdetection of VT. This emphasizes the need for re-evaluation of DFT, especially after starting antiarrhythmic drugs that have adverse effects on ICD function. Drugs like sotalol and dofetilide that lower DFTs are suitable for patients with high DFTs.

Postshock electromechanical dissociation is the most common mechanism of sudden death in ICD patients after appropriate ICD therapy for VT/VF and it needs further investigation.²²⁵

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Acute Presentations of Valvular Heart Disease

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CHAPTER 27

Acute Aortic Insufficiency
Acute Mitral Regurgitation
Acute Prosthetic Valve Dysfunction
Tricuspid Regurgitation

Aortic Stenosis
Mitral Stenosis
Conclusion

ACUTE DETERIORATION in valvular function represents a tremendous challenge to the practicing clinician. The presentation of valvular emergencies is usually dramatic, and a thorough knowledge of predisposing etiologies, hemodynamic abnormalities, and therapeutic modalities are essential to making appropriate management decisions. Despite an increasing population of patients with prosthetic valves, a resurgence of rheumatic fever, and the continued rise in intravenous drug use-associated infective endocarditis, the overall incidence of valvular emergencies in intensive care settings is low. However, the consequences of a missed diagnosis or a delay in therapy can be devastating. Therefore, an important guideline is to always entertain the possibility of a valvular emergency in a patient having hemodynamic instability or acute congestive heart failure.

This review focuses primarily on acute dysfunction of the aortic and mitral valves leading to severe regurgitation. The unique valvular complications associated with prosthetic valves and acute tricuspid regurgitation will also be discussed. Finally, factors predisposing to acute decompensation of previously stable, chronic, aortic, and mitral stenosis will be addressed.

Acute Aortic Insufficiency

Etiology

Aortic insufficiency occurs as a result of either dilation of the aortic root and annulus or disruption of the valve leaflets. The most common etiologies of acute aortic insufficiency are infective endocarditis and aortic dissection.¹ Infective endocarditis is more likely to occur on a congenitally abnormal or rheumatically involved valve. Infective endocarditis results in acute aortic insufficiency through a process of endothelial damage, development of nonbacterial thrombotic vegetation, adherence of circulating organisms to the vegetation, proliferation of infection within the vegetation, and valve destruction.² Acute, type A, aortic dissection is complicated by some degree of aortic insufficiency in approximately 50% of cases.^{3,4} Abnormal wall stress in the presence of aortic media disease, such as that seen with chronic hypertension or Marfan disease, results in an intimal tear and subsequent dissection.⁵ Other etiologies of acute aortic insufficiency are listed in Table 27-1.

Pathophysiology

The presentation of acute, severe, aortic insufficiency differs significantly from that of chronic aortic insufficiency. The cardiovascular adaptation to acute and chronic left ventricle (LV) overload determines the dramatic difference in hemodynamic and clinical profiles. The basic function of the heart is to maintain cardiac output commensurate with body demands while operating on the flat portion of the LV diastolic pressure-volume relationship, so that filling pressures remain low. Cardiac output is the product of heart rate and forward stroke volume. Forward stroke volume is the total stroke volume minus the regurgitant volume. Under normal circumstances, the latter is negligible, so that total and forward stroke volumes are synonymous.

In acute, severe, aortic insufficiency, the large regurgitant volume imposed on the unprepared ventricle markedly reduces forward stroke volume and shifts the LV diastolic pressure-volume relationship to the steep ascending portion of the curve. Because the LV has limited distensibility, the acute increase in LV end-diastolic volume due to regurgitant flow results in an abrupt rise in LV end-diastolic pressure (LVEDP) (Fig. 27-1) and, subsequently, pulmonary venous pressure. In addition, reflex sympathetic activation, in response to a reduction in cardiac output and systemic blood pressure, produces tachycardia and increases systemic vascular resistance (SVR). This rise in SVR further worsens regurgitant flow and impedes LV ejection so that a rise in aortic systolic pressure is inhibited. As opposed to chronic aortic regurgitation, aortic diastolic pressure does not fall significantly for two reasons: (1) the rapid increase in LVEDP reduces the driving gradient between aorta and LV and (2) peripheral runoff is limited by an increase in SVR.^{6,7} In some cases, the LV and aortic diastolic pressures are equalized.

In contrast, the gradual progression of chronic aortic insufficiency allows the ventricle to dilate and undergo eccentric hypertrophy, which shifts the LV pressure-volume curve rightward (see Fig. 27-1), and maintains a normal LVEDP. This compensatory mechanism also increases total stroke volume to preserve forward stroke volume despite the presence of a large regurgitant volume. As a result, there is no reflex tachycardia or rise in SVR. Aortic systolic pressure rises as a result of the increased stroke volume, and diastolic pressure falls in response to the regurgitant volume, decreased SVR, and rapid peripheral

Table 27-1. Etiologies of Acute Aortic Insufficiency

Infective endocarditis
Aortic dissection—predisposing and associated conditions
Hypertension
Marfan syndrome
Congenital bicuspid aortic valve
Coarctation of aorta
Ehler-Danlos syndrome
Turner syndrome
Chest trauma
Rupture of a myxomatous valve
Systemic connective tissue disorders
Ankylosing spondylitis
Systemic lupus erythematosus
Granulomatous diseases
Tertiary syphilis
Giant cell arteritis
Takayasu arteritis

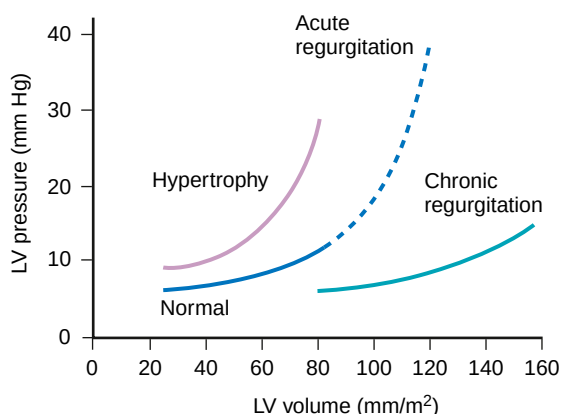


Figure 27-1. Diastolic pressure-volume relationships in the left ventricle. *Acute regurgitation* is sudden volume loading of the left ventricle without the benefit of adaptive ventricular remodeling. It results in the left ventricle functioning on the steep portion of the normal curve (dotted line). *Chronic regurgitation* is volume loading in the presence of a remodeled ventricle. It shifts the curve to the left and allows normalization of left ventricular (LV) filling pressure at significantly increased LV volumes. *Hypertrophy* (e.g., aortic stenosis) shifts the curve to the right and results in a noncompliant ventricle that is highly dependent on atrial booster pump function for LV filling. (From Hall RJ, Julian DG: *Diseases of the Cardiac Valves*. New York, Churchill Livingstone, 1989, p 291.)

runoff. These factors are responsible for the classic finding of a wide pulse pressure in chronic aortic insufficiency.

Clinical Presentation

The clinical features of acute aortic insufficiency are profoundly different from those of chronic disease. These differences result primarily from the presence of markedly elevated LVEDP and absence of a wide pulse pressure in patients with acute severe

Table 27-2. Classic Peripheral Manifestations of Chronic Aortic Insufficiency*

• Musset sign
Head bobbing with each systole
• Corrigan pulse
Water-hammer pulse felt with abrupt distention and quick collapse
• Traube sign
"Pistol shot" sounds—booming systolic and diastolic sounds heard over the femoral artery
• Müller sign
Systolic pulsations of the uvula
• Duroziez sign
Systolic murmur heard over the femoral artery when it is compressed proximally and diastolic murmur when it is compressed distally
• Quincke sign
Visible capillary pulsations in the nail bed (seen by shining light source), fingertips, or lip (detected with glass slide pressed against the lip)
• Hill sign
Popliteal cuff systolic pressure exceeding brachial cuff pressure by more than 60 mm Hg

*Not typically seen with acute aortic insufficiency.

aortic insufficiency as described above. Because the pulse pressure is usually normal in the acute setting, the classic findings of severe aortic insufficiency in the periphery are absent (Table 27-2). In addition, the striking elevation in LVEDP accounts for the often dramatic presentation of congestive heart failure and cardiogenic shock.⁸

Patients typically have severe dyspnea, weakness, or hypotension. They are often tachycardic, and the LV impulse may be normal. Early mitral valve closure, a hallmark of severe acute aortic insufficiency, results from a rapid elevation of LVEDP, which exceeds left atrial (LA) pressure early in diastole. This reversal of pressures between the LV and LA in late diastole results in a soft or inaudible first heart sound (S1). Occasionally, mitral valve closure may be heard during diastole and accompanied by diastolic mitral regurgitation.^{9,10} The Austin-Flint murmur, which is thought to represent turbulent flow from the LA to the LV because of partial mitral valve closure from the aortic insufficiency jet is either absent or brief and ceases when LV pressure exceeds LA pressure in diastole.^{11,12} An accentuated pulmonic closure sound suggests pulmonary hypertension, and a third heart sound (S3) is frequently heard. A fourth heart sound (S4), however, is usually not present because the mitral valve is either closed before atrial systole occurs or LVEDP is already so high that there is little flow to the ventricle during this period. The acute aortic insufficiency murmur is usually short, early, and of medium pitch, which is in contrast to the long, high-pitched murmur of chronic aortic insufficiency. In tachycardic patients, this murmur can easily be overlooked. Edema and weight gain are not often seen in severe acute aortic insufficiency because

there is inadequate time for substantial secondary salt and water retention. The extremities may be cool and mottled, owing to both poor cardiac output and elevated SVR.

Diagnosis

The diagnosis of acute aortic insufficiency should be considered in any individual having pulmonary edema or circulatory collapse. A history of known valvular disease, evidence of infective endocarditis, long-standing hypertension, Marfan syndrome, or chest trauma should make one particularly suspicious. Initial diagnostic testing in patients suspected of having acute aortic insufficiency includes an electrocardiogram (ECG), chest radiograph, blood cultures (if infective endocarditis is suspected or if the patient has a prosthetic valve), and a transthoracic echocardiogram (TTE).

An ECG is important in the evaluation of any patient with pulmonary edema, primarily to rule out myocardial infarction. In the absence of pre-existing heart disease, the chest radiograph generally reveals a normal cardiac silhouette with evidence of pulmonary edema (Fig. 27-2). Noninvasive imaging by TTE provides crucial information regarding the presence, severity, and etiology of aortic insufficiency. With severe aortic regurgitation, in addition to visualizing the regurgitant jet with color Doppler, quantitative measurements, such as jet or vena contracta (narrowest portion of regurgitant jet just distal to valve orifice) width, can be obtained. A jet width greater than 65% of LV outflow tract and vena contracta greater than 0.6 cm are consistent with severe aortic regurgitation.^{12A} Continuous wave Doppler is used to calculate the pressure half-time, which reflects the equilibration between aortic and LV diastolic pressure. With acute, severe aortic regurgitation, the rapid equilibration of pressures results in a short pressure half-time of less



Figure 27-2. Chest radiograph from a patient with acute aortic insufficiency secondary to pneumococcal endocarditis. Note the classic findings of acute pulmonary edema with a normal cardiac silhouette.

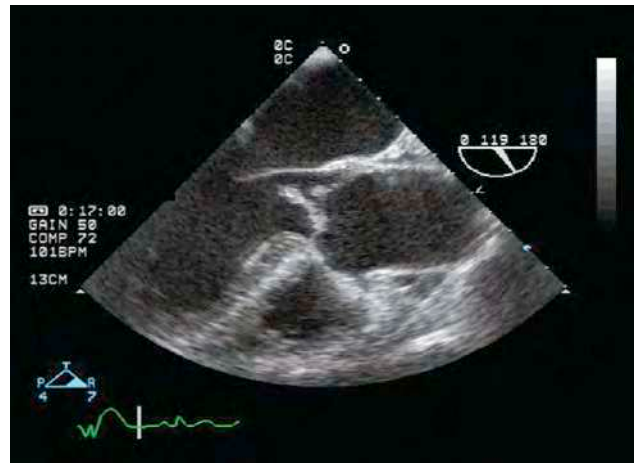


Figure 27-3. Long-axis transesophageal echocardiogram shows the presence of a large aortic valve vegetation. Ao, aorta; LA, left atrium; LV, left ventricle; Veg, vegetation.

than 200 msec.¹³ Other echocardiographic findings supportive of severe aortic regurgitation include premature closure of the mitral valve, detected best by M-mode echocardiography and holodiastolic flow reversal in the descending aorta. Transesophageal echocardiography (TEE) may be required in individuals in whom transthoracic echo windows are limited (Fig. 27-3). In addition, TEE has increased sensitivity for evaluating the underlying etiology of aortic regurgitation, such as endocarditis (vegetations or aortic root abscess) or aortic dissection (dissection flap).^{14,15}

Aortic dissection must be considered in the differential diagnosis of any patient having acute aortic regurgitation. This diagnosis is confirmed either by computed tomography (CT), TEE, or magnetic resonance imaging (MRI). These imaging modalities have largely replaced aortography, the previous gold standard. A recent meta-analysis compared the effectiveness of TEE, CT, and MRI for the diagnosis of aortic dissection. After pooling 16 studies with 1139 patients, TEE, helical CT, and MRI were found to have sensitivities of 98%, 100%, and 98%, respectively, and specificities of 95%, 98%, and 98%, respectively.¹⁶ CT is the most widely used modality given its speed and ease of accessibility to most emergency rooms (Fig. 27-4). CT also may provide identification of the intimal flap and involvement of major branch arteries. TEE has an advantage in that it is a bedside procedure and allows direct visualization of the aortic regurgitant jet. However, it is unable to detect dissections localized to the distal ascending aorta or proximal aortic arch. MRI has the best positive likelihood ratio for the detection of aortic dissections, but is time consuming, often not readily available in an emergent setting, and not feasible for a critically ill patient.

Treatment

In general, most patients with acute severe aortic insufficiency are desperately ill and have evidence of both systemic hypoperfusion and pulmonary edema. Acute aortic regurgitation usually requires urgent surgery. However, medical therapy has an important role in optimizing hemodynamics perioperatively. In the presence of severe hemodynamic compromise, admission to the cardiac intensive care unit is clearly indicated. The principles of management are to recognize the degree of hemodynamic

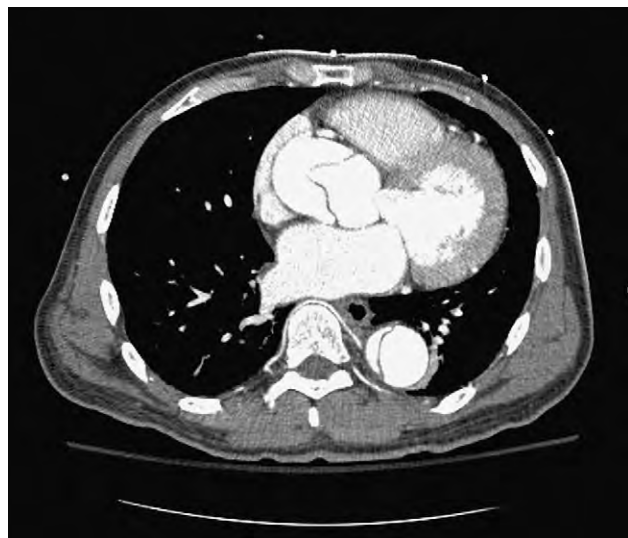


Figure 27-4. CT angiogram reveals a type A aortic dissection with the presence of an intimal flap in the ascending and descending aorta. AscAo, ascending aorta; AV, aortic valve; DscAo, descending aorta; LA, left atrium; LV, left ventricle.

impairment, reduce pulmonary venous pressure, maximize cardiac output, and initiate therapy for any underlying disorder.¹⁷ Invasive hemodynamic monitoring, by placement of a Swan-Ganz pulmonary artery catheter, allows the clinician to assess the response to therapy and gauge the tempo of the illness.

Medical therapy for acute congestive heart failure can usually be achieved with a combination of loop diuretics and intravenous vasodilators. The objectives are to achieve maximum cardiac output with minimum intracardiac filling pressures. The hemodynamic response to medical therapy in large part determines the urgency of surgical intervention.

Intravenous vasodilator therapy significantly reduces pulmonary artery pressures. Nitroprusside is the vasodilator of choice, starting at 0.25 $\mu\text{g/kg/min}$ given intravenously and gradually titrating upward by increments of 0.25 to 0.5 $\mu\text{g/kg/min}$ with the goal of achieving optimal hemodynamics or until systemic hypotension supervenes.¹⁸ The speed of uptitration is dictated by the degree of hemodynamic compromise. In severely ill patients the nitroprusside dose can be increased every 5 minutes, whereas in stable patients, a more gradual approach can be used. During maintenance therapy, one needs to be alert for signs and symptoms of both cyanide and thiocyanate toxicity. These compounds are breakdown products of nitroprusside, which accumulate with prolonged use, especially in the presence of renal insufficiency.

Diuretics should be initiated in sufficient doses to induce a brisk sustained urine output, using pulmonary capillary wedge pressure as a guide to therapy. Titrating the intravenous doses of furosemide (start 40 to 80 mg every 6 to 12 hours; maximum 600 mg/day), bumetanide (start 0.5 to 2 mg every 12 to 24 hours; maximum 10 mg/day), and torsemide (10 to 20 mg daily; maximum 200 mg/day) with or without oral metolazone (2.5 to 20 mg/day) 30 minutes before administering the loop diuretic is extremely effective in most cases of acute heart failure.

In general, inotropic agents do not have a significant role in management because most cases of acute aortic insufficiency occur in the setting of normal or even accentuated LV function.

However, if pre-existing myocardial dysfunction exists, agents such as dobutamine at a dose of 5 to 15 $\mu\text{g/kg/min}$ may assist in maintaining cardiac output.¹⁹ Intra-aortic balloon pumps (IABP) are contraindicated with aortic regurgitation. Additional medical therapy includes appropriate antibiotics in suspected infective endocarditis.²⁰ In the case of aortic dissection, intravenous β -blockers are thought to be useful in reducing the velocity of LV ejection, thereby minimizing aortic wall stress. However, when aortic dissection is complicated by acute aortic regurgitation, β -blockers should be used cautiously, if at all, as the compensatory tachycardia would be blunted, further reducing cardiac output.

If, despite medical therapy, hemodynamic instability persists, emergent surgical valve repair or replacement represents the only definitive option for cure. Indications for surgery in the presence of infective endocarditis are outlined in Table 27-3. Even in the presence of active infective endocarditis, valve surgery should not be delayed to achieve bacteriologic cure. In the International Registry of Acute Aortic Dissection, patients with type A dissection had an in-hospital mortality of 26% with surgery and 58% with medical management.²¹ Of those undergoing surgery for type A aortic dissection, 16% had involvement of the aortic valve requiring valve repair or replacement in conjunction with aortic root/arch surgery.

Acute Mitral Regurgitation

Etiology

The presentation of acute severe mitral regurgitation is not unlike acute aortic insufficiency. Both valve lesions result in sudden, severe LV volume overload. To better understand the underlying pathophysiologic states leading to acute mitral regurgitation, it is important to first recognize the functional components of

Table 27-3. Indications for Surgery in Infective Endocarditis

Native Valve Endocarditis

Congestive heart failure refractory to routine management (Class I)
Elevated LV end-diastolic pressure or LA pressures (Class I)
Fungal or highly-resistant organisms (Class I)
Complications: heart block, annular or aortic abscess, destructive penetration lesions (Class I)
Recurrent emboli and persistent vegetations despite appropriate antimicrobial therapy (Class IIa)
Mobile vegetations is in excess of 10 mm (Class IIb)

Prosthetic Valve Endocarditis

Congestive heart failure (Class I)
Valve dehiscence (Class I)
Increasing valve obstruction or worsening regurgitation (Class I)
Complications, as above (Class I)
Persistent bacteremia or recurrent emboli (Class IIa)
Relapsing infection (Class IIa)

From Bonow RO, Carabello BA, Chatterjee K, et al: ACC/AHA 2006 practice guidelines for the management of patients with valvular heart disease. *J Am Coll Cardiol* 2006;48:1.

the mitral valve apparatus. These components include the LA, mitral annulus, mitral valve leaflets, chordae tendineae, papillary muscles, and the LV wall. All these structures must work in concert to produce effective mitral valve leaflet apposition during systole.

Infective endocarditis may cause acute mitral regurgitation by mechanisms including leaflet perforation, alteration of mitral valve annulus secondary to abscess formation, or chordae tendineae rupture. Other etiologies of chordal rupture are myxomatous degeneration secondary to mitral valve prolapse or Marfan's disease spontaneous rupture, trauma, rheumatic disease, or spontaneous.^{22,23} Coronary artery disease is another major cause of acute mitral regurgitation and may affect valvular function in a number of ways: (1) papillary muscle rupture after myocardial infarction²⁴; (2) ischemic papillary muscle dysfunction²⁵; (3) papillary muscle fibrosis²⁵; (4) dyssynergy of the LV segment adjacent to a normally functioning papillary muscle²⁶; and (5) diffuse LV enlargement with mitral annular dilation. The posteromedial papillary muscle has only one vascular supply arising from either the right coronary or left circumflex artery and is, therefore, more susceptible to ischemic dysfunction or myocardial infarction. With the increasing use of percutaneous balloon valvotomy for rheumatic mitral stenosis, iatrogenic mitral regurgitation requiring valve replacement is more frequent as compared with closed surgical valvotomy.²⁷⁻²⁹ Finally, degeneration of a bioprosthetic valve, impaired closure of a mechanical valve, or paravalvular regurgitation from suture disruption may lead to acute, prosthetic valve, mitral regurgitation.

Pathophysiology

The severity of mitral regurgitation depends on the volume of regurgitant flow, LA compliance, and pre-existing LV function. The volume of regurgitant flow is a function of the size of the incompetent valve orifice and the pressure gradient between the LV and LA.³⁰ In the presence of a relatively noncompliant LA, the abrupt increase in pressure is transmitted to the pulmonary circuit with resultant pulmonary edema.³¹ With continuing acute regurgitation, the LV begins to fail secondary to elevated wall stress due to the mismatch between elevated LV end-diastolic volume/pressure and wall mass. In the presence of mitral regurgitation, there are two outlets to flow from the LV: (1) the relatively high-impedance systemic circulation and (2) the low-impedance LA. In this setting, forward stroke volume is highly dependent on SVR. As SVR increases, a greater proportion of the total LV stroke volume is directed to the LA and the regurgitant fraction increases [(total stroke volume – forward stroke volume)/total stroke volume].³² Thus the reduction in cardiac output increases SVR through neurohormonal activation, which worsens the severity of mitral regurgitation. As regurgitant flow increases further and cardiac output continues to decline, intense peripheral vasoconstriction ensues, leading to a vicious cycle of worsening mitral regurgitation and further impairment in forward stroke volume.

Clinical Presentation

The clinical features of acute mitral regurgitation reflect both the pathophysiology and pathoanatomy of the mitral valve apparatus as described above. A wide spectrum of clinical illness may be seen, ranging from complete papillary muscle rupture with cardiovascular collapse to mild dyspnea after rupture of a secondary or tertiary chordae.

The general appearance of the patient may provide important diagnostic clues regarding the underlying etiology of mitral regurgitation. A specific phenotype, such as Marfan or Ehlers-Danlos syndrome, may suggest a diagnosis of chordal rupture. Alternatively, peripheral manifestations of vascular (emboli, Janeway lesions) or immunologic (Osler nodes, Roth spots) findings consistent with the diagnosis of infective endocarditis may be seen. Finally, the presence of anginal-type chest pain leads one to suspect myocardial ischemia or infarction with resulting papillary muscle disease as the underlying etiology of acute mitral regurgitation.

Most patients with acute mitral regurgitation are tachycardic, which represents a compensatory mechanism to maintain cardiac output in the presence of declining forward stroke volume. The jugular venous pulse may be elevated with 50% of patients having a prominent “a” wave.³³ Precordial examination often reveals a hyperdynamic, nondisplaced apical impulse with a prominent presystolic expansion suggesting LV overload with increased atrial systole. A left parasternal lift is also common and is an indication of severe mitral regurgitation, often in association with elevated right ventricular systolic pressures. A systolic apical thrill may be felt in up to 75% of patients with ruptured chordae tendineae.³³ The presence of a thrill is less common in papillary muscle dysfunction or rupture.³⁴

Cardiac auscultation reveals a normal S1 because in most cases of acute mitral regurgitation the mitral valve leaflets are normal. This is in contradiction to chronic mitral regurgitation in which S1 is soft secondary to intrinsically abnormal mitral valve leaflets. Accentuated pulmonary valve closure suggests pulmonary hypertension³³ and because the LV empties rapidly, the aortic component may close early, giving rise to a widened split.³⁵ The presence of an S4 is common. An S3 gallop is almost universally heard and is related to LV volume overload. The murmur of acute mitral regurgitation differs according to the underlying pathophysiology. In papillary muscle dysfunction, a crescendo-decrescendo murmur may be heard during mid-to-late systole, while papillary muscle rupture results in a pansystolic murmur. Acute chordal rupture results in an ejection murmur that begins in the apex and radiates to the base of the heart.³⁶ Chronic mitral regurgitation, on the other hand, gives rise to a soft blowing holosystolic murmur heard throughout systole that begins at the apex and radiates to the axilla and back. Early termination of the murmur in acute mitral regurgitation results from rapid equalization of LA and LV pressures and suggests a greater degree of regurgitation.³⁷ The severity of the murmur may not reflect the degree of volume overload.³⁸ A summary of the differences in clinical presentation between acute and chronic mitral regurgitation is listed in [Table 27-4](#).

Diagnosis

As in the case of acute aortic insufficiency, immediate assessment of intracardiac filling pressures becomes critical, especially in the patient who is hemodynamically unstable. Initial noninvasive diagnostic maneuvers include a chest radiograph, which typically reveals a normal cardiac silhouette with pulmonary venous congestion or edema.³⁹ However, with pre-existing valvular or myocardial disease, there may be radiographic evidence of cardiac enlargement. Occasionally, an unusual pattern of right upper lobe pulmonary edema⁴⁰ may result that can be confused with pneumonia. However, prompt resolution with diuretic and vasodilator therapy rapidly clarifies the diagnosis

(Fig. 27-5). TEE has demonstrated that this radiologic finding may be related to the regurgitant jet being directed toward the right superior pulmonary vein.⁴¹

The ECG often reveals sinus tachycardia; however, atrial fibrillation with a rapid ventricular response is another

common presenting rhythm. A large negative deflection of the P wave in lead V₁ suggests LA volume overload. Nonspecific ST segment and T wave abnormalities are quite common; however, if acute mitral regurgitation occurs as a result of ischemia or infarction, the ECG becomes invaluable for both diagnosis and treatment.

Because the underlying pathoanatomy of the mitral valve influences prognosis and determines the type of therapeutic intervention, echocardiographic assessment of the mitral valve apparatus becomes essential. In the presence of good echocardiographic windows, transthoracic imaging can be performed quickly and safely at the bedside to determine the underlying etiology and severity of mitral regurgitation. In addition, overall LV function and wall motion abnormalities indicative of ischemia or infarction can be assessed. Finally, structural cardiac disorders that mimic mitral regurgitation, such as ventricular septal rupture, can be ruled out.⁴²

Depending on the etiology of acute mitral regurgitation, a variety of echocardiographic abnormalities may be seen. There may be an obvious flail leaflet, chordal rupture, or vegetation. Papillary muscle rupture is often directly visualized as a mass attached to the involved leaflet with discontinuity of the base of the muscle.⁴³ Despite the accuracy of transthoracic imaging, technical difficulties may impair visualization and limit interpretation. In these circumstances, TEE is a useful alternative modality for assessing acute mitral regurgitation (Fig. 27-6). Compared with TTE, TEE has superior resolution and a significant advantage in terms of visualizing the mitral valve apparatus, especially in the presence of a prosthetic mitral valve. Doppler imaging provides both qualitative and quantitative assessment of the mitral regurgitation severity. A color Doppler jet width at the vena contracta of more than 6 mm by multiplane TEE identifies angiographically severe mitral regurgitation with a sensitivity and specificity of 95% and 98%, respectively.⁴⁴ If systolic retrograde flow into the pulmonary veins is detected, mitral regurgitation is at least moderate. Finally, echocardiography clearly distinguishes acute mitral regurgitation from ventricular septal rupture, which has a very similar clinical presentation (Table 27-5).

If diagnostic studies, including ECG and echocardiography indicate ischemia or infarction as the underlying etiology of acute mitral regurgitation, then urgent cardiac catheterization must be considered depending on the hemodynamic stability

Feature	Acute	Chronic
Congestive heart failure	Rapid and sudden	Insidious
Rhythm	Sinus tachycardia	Atrial fibrillation
Point of maximal impulse	Hyperdynamic and nondisplaced	Hyperdynamic and shifted inferolaterally
Right ventricular lift	Present	Absent
Precordial thrill	Usually present	Absent
Jugular venous pressure	Prominent "a" wave	Normal tracing
Heart sounds		
S1	Normal	Soft
S2	Accentuated P2 with wide split	Normal P2 with wide split
S3	Present	Present
S4	Present	Absent
Mitral regurgitation murmur	Loud, decreasing in late systole	Blowing holosystolic
Radiation of mitral regurgitation murmur	Toward base	Toward axilla
Mitral diastolic flow murmur	Present	Absent

From Depace NL, Nestico PF, Morganroth J: Acute severe mitral regurgitation: pathophysiology, clinical recognition and management. *Am J Med* 1985;78:293.

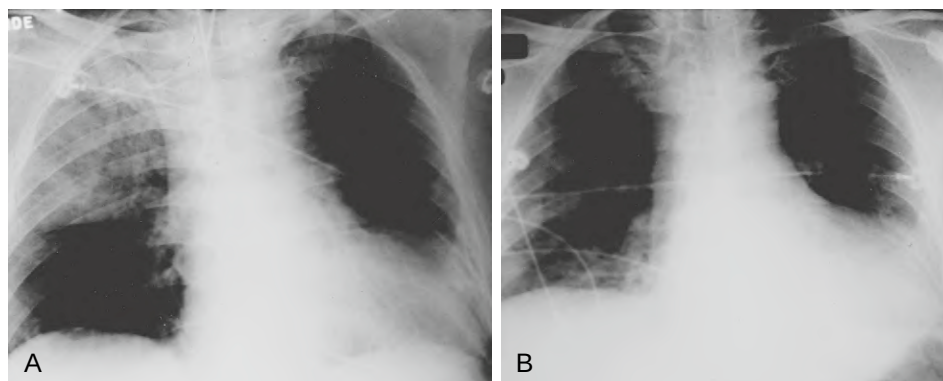


Figure 27-5. Unusual radiographic appearance of acute mitral regurgitation mimicking lobar pneumonia. **A**, Prominent right upper lobe alveolar infiltrate. **B**, Rapid resolution occurred in 48 hours with diuretic therapy. (Courtesy of Steve Primack, MD, Department of Radiology, Oregon Health Sciences University, Portland.)

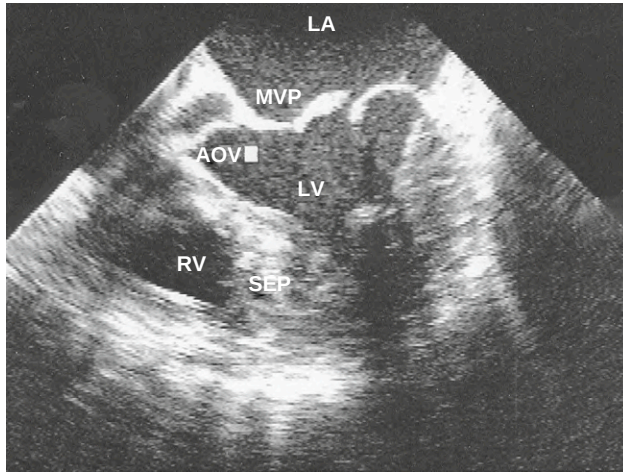


Figure 27-6. Transesophageal echocardiogram in the horizontal plane at the level of the mid-esophagus shows prolapse and loss of coaptation of the anterior mitral valve leaflet suggesting the diagnosis of mitral valve prolapse (MVP) with chordal rupture. AOV, aortic valve; LA, left atrium; LV, left ventricle; RV, right ventricle; SEP, interventricular septum.

Table 27-5. Differentiation of Papillary Muscle Rupture and Ventricular Septal Rupture

Feature	Papillary Muscle Rupture	Ventricular Septal Rupture
Age (mean, years)	65	63
Days post myocardial infarction	3-5	3-5
Anterior myocardial infarction	25%	66%
Murmur	Variable systolic	Pansystolic at lower sternal border
Palpable thrill	Rare	Yes
"v" wave in pulmonary capillary wedge tracing	++	++
Oxygen step-up from right atrium to pulmonary artery	±*	++
Echocardiographic findings	Flail or prolapsing leaflet	Visualize defect
Doppler	Regurgitant jet in LA	Detect shunt
Mortality		
Medical	90%	90%
Surgical	40%-90%	50%

*Oxygen step-up may occasionally be seen in papillary muscle rupture as a result of the regurgitant "v" from left atrium contaminating the mixed venous sample from the pulmonary artery.

From Antman EM: ST-elevation myocardial infarction: management. In Zipes DP, Libby P, Bonow RO, et al (eds): Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine, 7th ed. Philadelphia, WB Saunders, 2005, p 1204.

++ , invariably present; + , occasionally present; ± , rarely present.

of the patient. Coronary angiography defines coronary anatomy and may delineate a culprit lesion amenable to catheter-based or surgical intervention.

Treatment

The management of acute severe mitral regurgitation is similar to that of acute aortic insufficiency. The principles of treatment focus on reducing LVEDP, decreasing aortic impedance to LV ejection so that blood flow can be directed in a forward rather than retrograde direction, and initiating specific therapy for the precipitating etiology. As with acute aortic insufficiency, right heart catheterization is an integral component in the management of acute mitral regurgitation. The clinical severity of the regurgitation and the tempo of the illness as dictated by serial hemodynamic measurements, determine the rapidity with which one proceeds with emergent valve surgery. In the case of papillary muscle rupture, which is the cause of death in 1% to 5% of fatal myocardial infarctions, urgent surgical intervention is mandatory.⁴⁵ However, barring this catastrophic event, the majority of patients having acute, severe mitral regurgitation can often be stabilized initially with medical therapy.

Vasodilator therapy is the key component of medical management, and the preferred agent is intravenous nitroprusside (for dosage, see therapy for aortic insufficiency).⁴⁶ Its rapid onset and offset of action allow careful titration to optimize the hemodynamic response. Nitroprusside improves forward stroke volume directly by decreasing aortic impedance and also indirectly by decreasing LV volume, which reduces the area of the incompetent mitral valve orifice, thereby minimizing regurgitant flow.⁴⁷ Reduction of mean LA pressure and the regurgitant "v" wave reduce pulmonary congestion. Optimal therapy is defined as the maximal increase in cardiac output and reduction in pulmonary artery wedge pressure that can be obtained without provoking symptoms of systemic hypotension. An additional degree of afterload reduction may be provided by placing an IABP.⁴⁸ Improvement in diastolic coronary flow that occurs in response to an IABP may also have some salutary effects on LV function, especially in the presence of myocardial ischemia. If there is significant hypotension, dopamine (start at 1 to 3 µg/kg/min to a maximum of 10 to 20 µg/kg/min) may be a useful agent to maintain systemic blood pressure. However, at doses greater than 5 µg/kg/min, α-adrenergic-induced peripheral vasoconstriction may actually worsen the degree of regurgitation by increasing afterload. If LV contractility is impaired and cardiac output is significantly reduced, the addition of dobutamine (start at 1 to 2 µg/kg/min to a maximum 10 to 15 µg/kg/min) can be beneficial. Finally, diuretics (as outlined under therapy for aortic insufficiency) are useful to reduce pulmonary congestion.

Infective endocarditis complicated by chordal rupture or leaflet perforation should be treated with appropriate antibiotics in addition to medical therapy as noted above to optimize the hemodynamics of acute mitral regurgitation. The decision to proceed with emergent valve surgery is based on the hemodynamic response to medical management of the acute congestive heart failure and other factors (see Table 27-3). Recurrent systemic emboli, despite appropriate antimicrobial therapy, and infection with resistant organisms or fungi are additional indications for valve replacement. Finally, more complex infections, such as those complicated by valve ring abscess or fistula formation, also require surgical intervention.

Ischemic Mitral Regurgitation

Significant ischemic mitral regurgitation occurs in 3% of patients with acute myocardial infarction⁴⁹ and 8% of those having cardiogenic shock.⁵⁰ Patients with ischemic mitral regurgitation have a worse prognosis than those with other etiologies of mitral regurgitation. In addition, despite the significantly improved survival after acute myocardial infarction with thrombolytic therapy or percutaneous intervention, 1-year mortality for patients with concomitant severe ischemic mitral regurgitation is 52% compared with 11% in a cohort without mitral regurgitation.⁴⁹

Papillary muscle rupture in the setting of myocardial infarction represents the most dramatic presentation of ischemic mitral regurgitation and is a surgical emergency. Although this occurs in only 1% to 3% of patients with acute myocardial infarction, it accounts for up to 5% of infarct-related deaths.⁴⁵ Despite aggressive medical management, previous studies have documented the dismal prognosis of these patients with an up to 95% mortality in the first 48 hours without surgical intervention.^{51,52} In a series of 22 patients from the Mayo Clinic, there was significant improvement of functional class with an overall survival of 47% at 7 years with mitral valve replacement. This survival advantage occurred despite an overall decrease in LV function. Of note was the observation that the addition of coronary artery bypass surgery appeared to confer significant benefit in long-term outcome.⁴⁵ From the Shock Trial Registry, an observational study of 1190 patients with acute myocardial infarction complicated by cardiogenic shock, 98 patients were determined to have acute mitral regurgitation as the underlying etiology of shock. Acute mitral regurgitation occurred more frequently in patients with inferior or posterior myocardial infarction. In-hospital mortality for this subset of patients was 55%; and was reduced to 39% if undergoing surgical repair.⁵⁰

Ischemic mitral regurgitation may also be secondary to papillary muscle dysfunction without rupture. The mechanism actually involves ischemic apical and posterior papillary muscle displacement and wall motion abnormalities, which result in tethering of mitral valve leaflets and systolic tenting with incomplete closure. This condition can occur intermittently or continuously. Intermittent papillary muscle dysfunction classically presents as recurrent episodes of dyspnea associated with pulmonary edema. Several small case series suggest that percutaneous coronary intervention can improve acute regurgitation without requiring valve surgery.⁵³⁻⁵⁵ However, a report from the Thrombolysis in Myocardial Infarction (TIMI) phase I trial did not show a statistically significant relationship between coronary artery patency and the resolution or prevention of acute severe mitral regurgitation.⁵⁶ To further complicate this issue, a nonrandomized study from Duke University also failed to show significant reversal of valvular incompetence with either thrombolytics or angioplasty.⁴⁹ Finally, coronary artery bypass grafting as the sole treatment for ischemic mitral regurgitation resulted in a resolution (9%) and reduction to mild severity (51%) of mitral regurgitation.⁵⁷ Based on current data, correction of severe, ischemic mitral regurgitation often requires valve surgery in addition to revascularization. The combination of complete coronary revascularization with either mitral valve repair or replacement with preservation of the chordal apparatus is the current standard of care for acute ischemic mitral regurgitation refractory to medical management and nonsurgical reperfusion strategies.⁵⁸

Table 27-6. Acute Complications of Prosthetic Valves

Structural Valve Dysfunction

Bioprosthesis

Valvedegeneration—usually associated with leaflet calcification and tear

Mechanical prosthesis

Ballor disk variance—change in ball or disk size and function due to infiltration of by lipid

Strutfracture (particularly with the older Bjork-Shiley valves)

Nonstructural Valve Dysfunction

Perivalvular leak

Thrombosis or pannus formation

Embolization

Hemolysis

Prosthetic valve endocarditis

Early($\leq$ 60 days postsurgery)—occurs before endothelialization of valve, usually caused by *Staphylococcus epidermidis* or *S. aureus*; occasionally gram-negative organisms or fungi may be implicated

Late($\geq$ 60 days post surgery)—occurs after endothelialization of valve; caused by typical endocarditis organisms (i.e., viridans streptococci, enterococci, etc.)

Acute Prosthetic Valve Dysfunction

Prosthetic heart valves have been in use for over half a century. They are primarily implanted for hemodynamically significant valvular stenosis or regurgitation. A tremendous amount of experience with these devices has been gained over the past several decades. What has become apparent is that prosthetic valves, despite their obvious benefit, constitute another type of valvular heart disease. It is therefore important to remember that prosthetic valve implantation represents a palliative intervention.

Prosthetic valves are either mechanical or bioprosthetic. Mechanical bioprosthetic valves are further classified based on their structure as caged-ball (Starr-Edwards), single-tilting disk (Bjork-Shiley), or bileaflet-tilting-disk (St. Jude Medical) valves. Bioprosthetic valves are either heterografts (Carpentier-Edwards), which are formed from porcine or bovine tissue, or homografts, which are human aortic valves. Although bioprosthetic valves have better hemodynamic characteristics and do not require long-term anticoagulation, they are less durable and deteriorate over time. Mechanical valves, on the other hand, have tremendous durability but require life-long anticoagulation and are inherently stenotic.⁵⁹

Etiology and Clinical Presentation

Acute prosthetic valve complications, which affect both mechanical and bioprosthetic valves, may be classified as either structural or nonstructural (Table 27-6). Although bioprosthetic valves sustain a high structural failure rate within 15 years, mechanical valves may last more than 30 years. However, mechanical prosthetic valves are more thrombogenic

with caged-ball valves having the highest thrombogenicity and bileaflet-tilting disk valves the lowest.

The usual clinical presentation of acute prosthetic valve dysfunction is that of rapidly progressive heart failure with evidence of either prosthetic valvular regurgitation or stenosis. Other manifestations include thromboembolism (cerebral or peripheral),⁶⁰ which suggests prosthetic valve thrombosis (PVT)⁶¹ or prosthetic valve endocarditis (PVE).⁶² Normally functioning prosthetic valves are associated with various opening and closing clicks and systolic and occasionally diastolic flow murmurs.⁶³ A new or changing murmur may therefore signal a pathophysiologic alteration in prosthetic valve function. In addition, the absence or damping of normal valve clicks also suggests abnormalities in valve function.

Diagnosis

As part of the initial evaluation, determining the class, type, and model of the implanted valve and the date of implantation is extremely important. The chest radiograph can be invaluable in assessing for the presence of heart failure and may provide confirmatory radiologic evidence as to the type of valvular prosthesis.⁶⁴ The ECG may show signs of LV overload, but these findings are not specific in detecting prosthetic dysfunction because these ECG changes may antedate valve replacement. However, in the setting of aortic PVE, the development of new atrioventricular conduction delay is specific for the presence of a valve ring abscess.⁶⁵ Anemia and an elevated serum lactic dehydrogenase level greater than 600 IU, suggesting hemolysis are virtually never found in a normal functioning prosthesis and should always raise the suspicion of a paravalvular leak.⁶⁵

Echocardiography is an essential tool in the evaluation of prosthetic valve dysfunction.⁶⁶ It serves the dual purpose of identifying the etiology of the valve abnormality and assessing LV function. Continuous-wave Doppler imaging is effective in assessing valvular stenosis by virtue of the modified Bernoulli equation:

$$\text{Pressure gradient} = 4 \times \text{maximum transvalvular velocity}^2$$

In general, there has been an acceptable correlation between echo-derived and catheterization-based valvular gradients. Although transvalvular pressure differences are proportional to the degree of stenosis, variables such as heart rate, contractility, and cardiac output, and the size and type of prosthesis, can significantly alter the measured gradient.⁶⁷ Because there is a potential for underestimating the degree of prosthetic aortic stenosis, especially in the presence of low cardiac output, it has been suggested that it may be more appropriate to calculate prosthetic valve area using the continuity equation^{68,69}:

$$\text{Area}_1 \times \text{Time Velocity Integral}_1 = \text{Area}_2 \times \text{Time Velocity Integral}_2$$

It should also be remembered that there is a wide variation in valvular gradients depending on the class, type, and model of the valve. This highlights the importance of obtaining a baseline echocardiogram after valve replacement, which then serves as a control for comparison of pressure gradients with future follow-up studies. Caution must be exercised when using non-invasive hemodynamic data to make clinical decisions regarding prosthetic valve dysfunction. It is therefore essential to interpret echocardiographic data in light of the presenting clinical illness.

Color Doppler flow mapping has several important applications in prosthetic valve disease: (1) directing continuous-wave Doppler cursor parallel to the stenotic flow jet, allowing more accurate estimation of transprosthetic velocities and gradients⁷⁰; (2) semiquantitative evaluation of prosthetic valve regurgitation, which has been shown to correlate well with angiographically derived measurements^{71,72}; and (3) differentiating valvular from paravalvular leaks.⁷⁰

When transthoracic imaging is limited secondary to reverberatory artifacts caused by metallic components of a mechanical valve or technically difficult echocardiographic windows, TEE is a useful adjunctive tool.⁷³⁻⁷⁹ Because imaging is performed without intervening cardiac structures, excellent delineation of valvular anatomy and function may be obtained. This is particularly true in the case of the mitral valve because the esophageal "window" is not obstructed by the metallic valve components. In addition, several studies have suggested that TEE may, in fact, be more sensitive and specific than transthoracic echocardiography in the evaluation of partial valve thrombosis,^{80,81,82} PVE with aortic ring abscess,⁸³ paravalvular leaks,⁷⁸ Starr-Edwards prosthesis function,⁷⁷ and bioprosthetic valve degeneration.⁷⁹ TEE may also be appropriate when transthoracic echocardiographic findings are not consistent with the observed clinical syndrome. However, it should be emphasized that the combined approach of using transthoracic with transesophageal echocardiography facilitates a more complete evaluation of LV function.

In the case of acute prosthetic valve dysfunction with heart failure, a bedside right heart catheterization is an essential monitoring tool that allows continuous hemodynamic assessment and appropriate therapeutic interventions. Because echocardiography has in large part replaced traditional catheterization measurements for valvular insufficiency and stenosis, cardiac catheterization is withheld unless the available echocardiographic data are inconclusive or there is a suspicion of significant coronary artery disease. In some cases, simple fluoroscopy may be used to identify prosthetic valve dysfunction and assess the effects of thrombolytic therapy.⁸⁴⁻⁸⁶ When frank dehiscence is present, a rocking motion of the valve ring may be seen. In the case of mechanical valves, the excursion and movement of the ball, leaflet, or disc may be limited, suggesting PVT.

Treatment

Congestive Heart Failure

Therapy for acute prosthetic valve dysfunction depends on the type and severity of hemodynamic abnormality, the valve involved, and the underlying etiology. If the valve becomes obstructed acutely, the clinical presentation is likely to be dramatic with syncope and death in the absence of immediate surgical intervention. On the other hand, stenotic lesions that develop more gradually present as progressive heart failure and a low cardiac output state. Medical management consists of reducing LA pressure and maximizing ventricular performance with inotropic agents. Acute regurgitant lesions are managed according to the guidelines outlined under the treatment for aortic, mitral, and tricuspid regurgitation. Usually this will involve a combination of vasodilators, diuretics, and inotropic support. Definite therapy usually involves reoperation and replacement of the dysfunctional valve. The mortality for reoperation will depend primarily on the preoperative functional class, the underlying etiology of the valve dysfunction (endocarditis and

valve thrombosis carrying the highest risk), and the need for emergency surgery.

Prosthetic Valve Endocarditis (PVE)

Specific management of PVE consists of obtaining blood cultures and initiating empiric antibiotic therapy. Because there is a fairly well-defined difference between the pathophysiology and type of organisms responsible for early and late PVE, the initial choice of antibiotics will depend on the time of presentation relative to the date of surgical valve replacement; that is, “early” PVE (<60 days) and “late” PVE (>60 days). Staphylococcal, particularly *Staphylococcus epidermidis*, infections predominate in early PVE, whereas in late PVE there are equal percentages of streptococcal and staphylococcal infections.⁸⁷ In addition to progressive heart failure, PVE may also have embolic phenomena, para-valvular leak, or hemolytic anemia. Therefore, in patients with prosthetic valves who have these complications it is appropriate to obtain blood cultures and initiate empiric antibiotic therapy. Invariably, the vast majority of patients with PVE will require valve replacement. Table 27-3 lists indications for surgery for prosthetic valve endocarditis. The reoperative mortality for PVE ranges from 20% to 80%, but these figures have shown improvement since 1965.⁸⁸ Recently, a prospective cohort of 556 patients with definite prosthetic valve endocarditis as determined by the modified Duke criteria reported advanced age, health-care associated infection *Staphylococcus aureus* and complications (CHF, cerebrovascular accident, abscess, persistent bacteremia) as predictors of in-hospital mortality.⁸⁹ Although overall in-hospital mortality is no different, subsets of patients with staphylococcal endocarditis (27% vs 73% mortality) or complications of endocarditis (18% vs 48% mortality) benefit from early surgical treatment as compared with conservative medical management.⁹⁰ This trend toward enhanced survival may be related to improvements in both surgical technique and myocardial preservation.

Prosthetic Valve Thrombosis (PVT)

Valvular obstruction may occasionally be secondary to bacterial vegetations but more commonly is the result of pannus ingrowth or thrombus. The incidence of PVT with currently available mechanical devices varies from 0.03% to 4.3% per year.⁸⁵ Although a major risk factor for PVT is inadequate anticoagulation, approximately 40% of patients have adequate prothrombin times at the time of presentation.⁶³ This may be explained by the fact that PVT is a complex process that consists of a significant component of fibrous tissue ingrowth with associated secondary thrombosis. However, the percentage of valves involved with fibrous pannus varies significantly and depending on the study may range from 20% to 80%.⁹¹⁻⁹³ PVT may present acutely with heart failure or as a slowly progressive disorder with protean symptomatology.^{91,94} A high level of suspicion must be maintained in any patient with a valvular prosthesis who has nonspecific cardiac symptoms. As described above, TTE provides assessment of hemodynamic severity, whereas TEE or fluoroscopy is often used to delineate valve motion and clot burden. In general, the mortality for reoperation is high but tends to be variable, ranging from 4.5% to 35%, depending on the functional class. It does, however, appear that PVT has an independent effect on operative mortality.⁶⁷

Medical options to potentially restore prosthetic valvular function include thrombolytic therapy and anticoagulation with heparin. Thrombolytic therapy for hemodynamically

stable right-sided prosthetic valve thrombosis is relatively safe. If emboli occur in this setting, they tend to be small and confined to the pulmonary vasculature.^{95,96} However, in the case of prosthetic mitral and aortic thrombosis, there have been concerns regarding thrombolysis because of the increased risk of cerebral or systemic embolization arising from dissolution of the obstructive clot. Several studies have demonstrated that in patients selected for thrombolytic therapy there is a 70% to 88% hemodynamic success rate with an approximately 20% risk of complications, including hemorrhage and emboli.^{85,91,97-99} Thrombolytic therapy remains a viable option in those individuals whose operative mortality would be unacceptably high with surgical intervention or who have right-sided PVT. Streptokinase, urokinase, and recombinant tissue plasminogen activator have been used in various studies for PVT, but it should be noted that none of these agents have been approved by the Food and Drug Administration for use in this setting. Incomplete resolution of the obstruction or complete failure of therapy with thrombolytics may be related to the presence of pannus formation. In cases in which medical therapy fails, surgical intervention is required to restore complete forward flow.

In summary, PVT is a clinically and pathologically complex process that despite its relatively low incidence represents a serious complication in individuals with prosthetic heart valves. The 2006 American College of Cardiology/American Heart Association guideline for valvular disease endorses a class IIA recommendation for emergent surgery of left-sided or fibrinolytic therapy of right-sided PVT that is complicated by either New York Heart Association (NYHA) class III-IV CHF or a large thrombotic burden. Class IIB indications for fibrinolytic therapy include: left-sided PVT with both NYHA class I-II CHF (class III-IV CHF if high surgical risk) and small clot burden; and obstructed left-sided PVT with CHF and large clot burden but high surgical risk. Finally, unfractionated heparin for small thrombus and class I CHF is also a Class IIB indication.⁸⁷

Tricuspid Regurgitation

In general, the hemodynamic impact of acute tricuspid regurgitation is less significant than that of acute left-sided valvular lesions. However, in the setting of acute massive RV overload, hypotension and shock may ensue. More commonly, persistent, severe, chronic tricuspid regurgitation results in salt and water retention leading to peripheral edema, ascites, and congestive hepatomegaly. Massive RV volume overload secondary to acute tricuspid regurgitation may also lead to a significant reduction in LV ejection fraction due to paradoxical early systolic septal motion that results from ventricular interdependence.¹⁰⁰ Despite the hemodynamic instability at initial presentation, many of these patients can be effectively managed with a combination of diuretics and inotropic agents, provided that pulmonary arterial pressure remains normal and RV function is preserved. Once stabilized the long-term prognosis of these patients tends to be favorable. In general, the clinical presentation, response to medical therapy, and underlying pathology determine the need for surgical intervention.

Etiology

It should be emphasized that isolated, acute tricuspid regurgitation is a relatively uncommon medical emergency. The chronic form of tricuspid regurgitation predominates and usually

results from annular dilation secondary to left-sided valvular pathology, severe LV dysfunction, or pulmonary hypertension. In the current era, infective endocarditis remains the most common cause of acute tricuspid regurgitation and is almost exclusively a disease of intravenous drug users.¹⁰¹ Despite antibiotic sterilization of the valve lesion, these individuals frequently develop ruptured chords or leaflet perforation. Occasionally, a large, healed vegetation may impair leaflet apposition leading to tricuspid regurgitation. Rarer causes of acute tricuspid regurgitation include nonpenetrating chest trauma^{102,103} and RV infarction.^{104,105} With the growing number of cardiac transplant recipients, an iatrogenic form of tricuspid regurgitation has been recognized with increasing frequency.¹⁰⁶⁻¹⁰⁹ These patients undergo repeated endomyocardial biopsies for evaluation of cardiac allograft rejection; and occasionally during these procedures the biptome may inadvertently damage the tricuspid valve chordae or leaflet, resulting in acute tricuspid regurgitation.

Clinical Presentation

The physical findings in acute tricuspid regurgitation are dependent, in part, on the severity of the RV volume overload. In the case of papillary muscle rupture or RV infarction, there may be hypotension and cardiovascular collapse. Most patients, however, maintain blood pressure within the normal range and typically demonstrate findings consistent with right-sided heart failure. There is usually a prominent “v” wave visible in the jugular venous pulse and a holosystolic murmur along the left sternal border. The tricuspid regurgitation murmur increases in intensity with inspiration and, by this variation with respiration, can be differentiated from mitral regurgitation. An S3 gallop originating from the RV can be heard; and abdominal examination reveals pulsatile hepatomegaly. In general, peripheral stigmata of infective endocarditis are absent when the tricuspid valve is affected and, if present, suggest paradoxical emboli or additional, left-sided valvular lesions. In the case of intravenous drug users, track marks and evidence of “skin popping” may be seen.

Diagnosis

The diagnostic modality of choice is two-dimensional and Doppler echocardiography.¹¹⁰ The echocardiogram provides structural information about the tricuspid valve, including detection of vegetations (Fig. 27-7). In addition, the severity of tricuspid regurgitation and RV dysfunction can be assessed. Most importantly, pulmonary artery pressures can be estimated using the modified Bernoulli equation:

$$PAS = RAP + 4 \times V^2$$

where PAS = pulmonary artery systolic pressure, RAP = right atrial pressure measured by physical examination [5 cm + JVP (cm above clavicle)], and V is the peak velocity of the tricuspid regurgitation jet measured by continuous-wave Doppler.¹¹¹ In general, transthoracic echocardiography is satisfactory for assessing tricuspid valve structure and RV function. Transesophageal echocardiography may not offer any significant diagnostic advantage. In a prospective study by San Román and colleagues, transthoracic echocardiography was equivalent to transesophageal echocardiography in the diagnosis of tricuspid valve infective endocarditis; however, the relationship of the vegetation to the leaflet was better characterized by transesophageal echocardiography.¹¹²

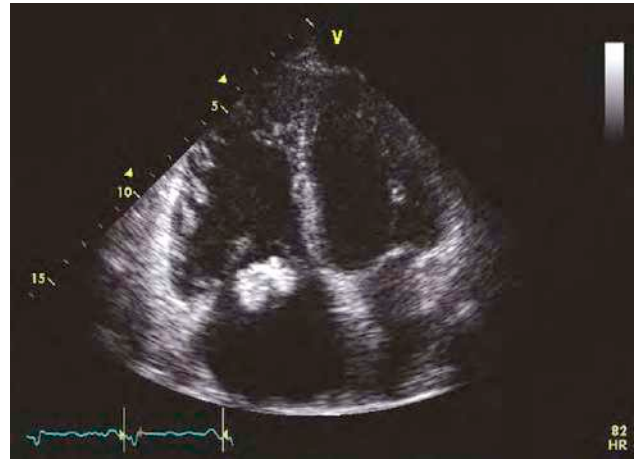


Figure 27-7. Transthoracic echocardiogram of an apical four-chamber view shows a large vegetation present on the tricuspid valve, preventing coaptation of valve leaflets with subsequent severe, tricuspid regurgitation.

The ECG in cases of trauma may show right bundle branch block. If the tricuspid regurgitation has been of long standing, there may be ECG criteria for RV hypertrophy. RV infarction with acute tricuspid regurgitation rarely occurs in isolation and typically presents in conjunction with inferior myocardial infarction, which can be diagnosed by the characteristic ST segment elevation in leads II, III, and aVF. The presence of ST segment elevation in the right-sided lead V₄R confirms the diagnosis of an RV infarct and suggests that the patient may be at high risk for complications.¹¹³

The chest radiograph may show signs of cardiomegaly that represent RV and right atrial (RA) enlargement. The presence of cavitary septic pulmonary emboli may also be seen with tricuspid valve endocarditis. In addition, blood cultures form an essential component of the diagnostic work-up for patients with suspected infective endocarditis. In patients with infective endocarditis from intravenous drug use, staphylococcal organisms are the predominate isolate.

Right heart catheterization can be extremely helpful in confirming the diagnosis of pure tricuspid regurgitation and ruling out significant LV abnormalities. The presence of a large “v” wave in the RA tracing with concomitant elevation in mean RA pressure usually signifies the presence of significant tricuspid regurgitation. In addition, if the pulmonary artery and capillary wedge pressures are normal, the tricuspid regurgitation is likely to be related to primary dysfunction of the valvular apparatus and not secondary to left-sided heart function or pulmonary hypertension.

Treatment

The management strategy for acute tricuspid regurgitation should be focused primarily on medical therapy. In general, most patients can be effectively treated with a diuretic alone or in combination with an inotropic agent, such as dobutamine. In rare instances of acute massive tricuspid regurgitation, the patient who is refractory to medical therapy may require immediate surgical intervention. When possible, tricuspid valve repair, often with ring annuloplasty is preferred over valve replacement. However, when valve replacement is required,

a bioprosthetic valve is often used.¹¹⁴ The choice of a bioprosthesis is based on the extremely high incidence of valve thrombosis when mechanical valves are implanted in the tricuspid position. In the case of tricuspid regurgitation related to infective endocarditis, the decision to implant a prosthetic valve becomes even more complex. Because many of these patients are young, noncompliant, and often return to intravenous drug use, their risks for adverse events—whether self-induced or iatrogenic—are significant. The operative mortality for reoperation particularly for recurrent prosthetic valve endocarditis can be extremely high. Furthermore, if a bioprosthesis is used, the risk of valve failure is higher because of the younger age of the intravenous drug using population. The choice of a mechanical valve for durability is also fraught with complications, from both the inherently higher thrombotic risk despite anticoagulation and the general trend of medication noncompliance among these patients. Although treatment cannot be generalized for the intravenous drug use population, these recurring problems have fostered the development of several unique surgical approaches. These options include complete valve excision with no prosthetic replacement,¹¹⁵ valve repair after sterilization of the infection,¹¹⁶ and “vegetomy,”¹¹⁷ which refers to isolated resection of the bacterial vegetation with preservation of the valvulochordal apparatus. Many of these patients, even with complete valve excision, continue to do well, with minimal symptoms of right-sided heart failure. This is particularly true when the pulmonary vascular resistance is normal and RV function is preserved. Naturally, any management plan for infective endocarditis must include appropriate antibiotic coverage for an adequate period of time.

The treatment goal for tricuspid regurgitation secondary to an inferior myocardial infarction with RV involvement is revascularization. The type of revascularization procedure will depend on the nature of the coronary anatomy, the extent of atherosclerotic disease, the myocardial territory at risk, and the status of LV function.

Aortic Stenosis

Etiology

Aortic stenosis presents as a slowly progressive disorder characterized by narrowing of the aortic valvular orifice resulting in dyspnea, angina, or syncope.¹¹⁸ The etiology varies, but the lesion is usually the result of a degenerative, calcific process of the aortic leaflets. This disease process commonly presents in the sixth or seventh decade; however, if the valve is congenitally bicuspid, then the manifestations may occur earlier. Aortic stenosis may also be the result of commissural fusion secondary to chronic rheumatic heart disease.

Clinical Presentation

Physical examination reveals a small volume, slowly rising, sustained pulse, and an apical impulse that may be displaced downward and to the left with a marked presystolic impulse or “a” wave. The harsh ejection systolic murmur of aortic stenosis is best heard at the base and is transmitted to the carotids but may also be heard at the apex. In general, late peaking murmurs of longer duration signify more severe stenosis.^{119,120} However, it is important to remember that with decreasing cardiac output, there is a fall in the gradient with an associated diminution in the intensity of the murmur.

Diagnosis

The ECG usually reveals LV hypertrophy with strain, and there may be evidence of atrioventricular conduction delay in patients with calcific aortic stenosis involving the conduction system.¹²¹ The chest radiograph demonstrates LV enlargement, and some degree of aortic calcification is noted in most adults with significant aortic stenosis. Poststenotic dilation of the proximal ascending aorta may also be noted along the right heart border in the posteroanterior chest film.

Echocardiography has replaced cardiac catheterization for the initial assessment of valvular aortic stenosis. This noninvasive modality can accurately predict the severity of the valvular stenosis and estimate the valve area using the continuity equation.¹²² In addition, the anatomy of the valve leaflets can be assessed along with LV function.

When there is an inability to obtain adequate echocardiographic windows, it is likely that cardiac catheterization will be required to invasively assess the severity of valve stenosis. In addition, when the suspicion of coronary disease exists, angiography is imperative before valve replacement to determine the need for concomitant coronary artery bypass surgery.

Acute Complications

Several conditions may predispose to an acute deterioration in patients with aortic stenosis. To discern the inciting events leading to acute decompensation in valvular aortic stenosis, it is important to understand the underlying pathophysiologic state. Progressive valvular aortic stenosis leads to increasing LV systolic pressure and wall stress. In an effort to normalize this afterload mismatch, the LV hypertrophies. Initially, this normalizes wall stress, but it also results in a shift of the LV pressure-volume curve upward and to the left (see Fig. 27-1). This necessitates higher filling pressures for a given ventricular volume leading to elevated pulmonary venous pressures with consequent dyspnea on effort. Because of this abnormal LV pressure-volume relationship, any diminution in preload will seriously impair stroke volume. Therefore conditions that lead to acute volume shifts (e.g., dehydration or acute blood loss) will result in a significant impairment of cardiac output. The altered LV pressure-volume relationship reduces passive LV filling, making LV preload critically dependent on atrial contraction.¹²³ Any impairment in the contribution of diastolic filling by atrial systole, such as atrial fibrillation or atrioventricular dyssynchrony, can lead to acute decompensation. In addition to atrial arrhythmias and conduction abnormalities, increasing heart rate may also impair LV filling simply by decreasing the diastolic filling period. It is also important to realize that a markedly reduced heart rate will also impair forward cardiac output because the stroke volume is limited by the severe valvular stenosis. This is particularly true in the setting of impaired LV function. Any condition that further impairs LV relaxation will also have a significant impact on diastolic filling (e.g., acute coronary ischemia). Relative ischemia may also occur in the setting of normal coronary arteries or nonobstructive coronary artery disease when myocardial oxygen demands have exceeded coronary reserve.¹²⁴

Treatment

The treatment of severe aortic stenosis is valve replacement that corrects the underlying pathophysiology of afterload mismatch. Improvement in LV function and long-term survival will

follow valve replacement in the vast majority of patients.¹²⁵ In the event of rapid clinical deterioration, the inciting event must be identified and treated promptly. In the case of volume depletion (e.g., dehydration, blood loss), volume replacement must be judicious to avoid pulmonary edema. In some cases, this may require a pulmonary artery catheter to monitor pulmonary capillary wedge pressure. Systemic hypoperfusion unresponsive to increased preload should be treated with inotropic agents, which have the dual effect of increasing stroke volume and systemic vascular resistance to maintain tissue perfusion. A combination of dobutamine and dopamine may be particularly useful in this regard. If pulmonary congestion occurs, loop diuretics can be used cautiously to decrease pulmonary capillary pressure.

Atrial fibrillation should be treated with urgent synchronized cardioversion, particularly if systemic hypotension or pulmonary congestion has supervened. Atrioventricular conduction abnormalities should be managed with temporary pacing followed by a permanent pacemaker if the conduction disturbance persists. Once the patient is stabilized, urgent valve replacement should be undertaken. If there is a question of coronary artery disease, cardiac catheterization should be performed, focusing specifically on coronary anatomy. Occasionally when the patient is gravely ill from LV failure, it may be necessary to proceed directly to valve replacement without preoperative coronary angiography.

Mitral Stenosis

Etiology

Mitral stenosis generally results as a sequela to group A streptococcal infections. Goldstein and colleagues¹²⁶ were the first to demonstrate that group A streptococci have antigens that cross react with the structural glycoprotein of heart valves, thus directly linking this organism with rheumatic valvular disease. The classic pathologic features include fusion of the commissures, thickening of the valve leaflets, and shortening of the chordae tendinae.¹²⁷ These abnormalities of valve structure result in progressive narrowing of the valve orifice, leading to restriction of LV inflow. The predicted pathophysiologic effects are that of progressive LA enlargement accompanied by elevation in LA pressure. This results in pulmonary venous hypertension with the clinical accompaniment of progressive dyspnea. Secondary pulmonary arteriolar constriction may also occur, which worsens pulmonary hypertension. Rheumatic heart disease overwhelmingly represents the most common cause of mitral stenosis¹²⁸; however, other rare etiologies include congenital mitral stenosis¹²⁹ and Lutembacher syndrome (atrial septal defect associated with mitral stenosis).¹³⁰

Clinical Presentation

Typically symptomatic mitral stenosis presents in the fourth or fifth decade; however, in socioeconomically disadvantaged areas it may occur much earlier.¹³¹⁻¹³³ Patients have progressive dyspnea on exertion, orthopnea, and paroxysmal nocturnal dyspnea. Hemoptysis may also occur secondary to rupture of bronchopulmonary venous connections. With long-standing mitral stenosis, patients frequently develop atrial fibrillation,¹³⁴ and this, in turn, may lead to thrombus formation in the LA. The development of clot in the LA poses considerable risks to

Table 27-7. Physical Findings in Mitral Stenosis

• Low volume pulse
• Jugular venous pulse with prominent “a” wave
• Point of maximal impulse is not displaced and is “tapping” in quality (reflecting a loud S1)
• Palpable localized apical diastolic thrill
• Midsystolic rumbling apical murmur with presystolic accentuation (if the patient is in sinus rhythm)
• Loud S1 with accentuated P2 (if pulmonary hypertension is present)
• Opening snap at the lower left sternal border (signals mitral valve opening and the presence of pliable leaflets)
• Graham Steell murmur of pulmonary regurgitation (a feature of pulmonary hypertension)

the patient, including systemic thromboembolic events and acute valvular obstruction. In most cases, the physical findings are quite striking and reflect both the restriction to LV filling and the accompanying signs of pulmonary hypertension (see Table 27-7).

Diagnosis

In more severe cases of mitral stenosis, the ECG may show characteristic changes suggestive of LA enlargement. With progressive pulmonary hypertension, the frontal axis shifts rightward and is accompanied by ECG evidence of RV hypertrophy.^{135,136} The chest radiograph may reveal the presence of LA enlargement and dilation of the main pulmonary artery. These findings, plus a normal aortic arch, give the characteristic radiographic appearance of a straight left heart border. Cardiac catheterization with simultaneous pulmonary capillary wedge (a surrogate for LA pressure) and LV pressure measurements demonstrates a gradient from LA to LV. The valve area may be calculated using the Gorlin equation, based on the diastolic pressure difference between LA and LV, cardiac output, and the diastolic flow period. In the evaluation of uncomplicated mitral stenosis, echocardiography has replaced the use of cardiac catheterization. Echocardiography not only accurately estimates the degree of valvular stenosis but also gives additional information about the anatomy of the valve.¹³⁷ However, coronary angiography is still a prerequisite before surgical therapy in individuals with known or suspected coronary artery disease.

Treatment

Over the past several years, the treatment of mitral stenosis has evolved in a dramatic fashion. The original surgical treatment for mitral stenosis was described by Cutler and Levine at the Peter Bent Brigham Hospital in 1923.¹³⁸ The procedure was initially fraught with a high mortality. However, by 1948, with Harken's report in the *New England Journal of Medicine*, it became apparent that closed mitral valvuloplasty was an acceptable form of treatment for symptomatic mitral stenosis.¹³⁹ Since then, surgical techniques have evolved to include open surgical commissurotomy with cardiopulmonary bypass and, more recently, percutaneous balloon mitral valvuloplasty. Several

recent randomized clinical trials have demonstrated percutaneous balloon mitral valvuloplasty to be equivalent to surgical therapy.^{140,141}

Several different conditions may be superimposed on the substrate of mitral stenosis, resulting in acute emergencies. Atrial fibrillation occurs commonly in mitral stenosis and classically with deterioration in functional class, and marked dyspnea and fatigue. These symptoms result from an elevation in LA pressure and a fall in cardiac output. The increased ventricular rate associated with atrial fibrillation causes a significant rise in LA pressure, much more so than the loss of atrial booster pump function.¹⁴² In addition, the shortened diastolic filling time and loss of atrial systole compromises stroke volume leading to impaired cardiac output. This pathophysiology also occurs with other tachyarrhythmias complicating mitral stenosis.^{142,143} Hemodynamic deterioration may also present in mitral stenosis during pregnancy. Other important and often life-threatening complications include obstruction of the mitral orifice with thrombus or infected vegetation¹⁴⁴⁻¹⁴⁵ and massive hemoptysis¹⁴⁶⁻¹⁴⁸ from rupture of dilated bronchial veins. The literature with reference to treatment of these dire complications remains limited; however, anecdotal studies suggest that urgent treatment of the valvular obstruction surgically or percutaneously can be life saving. An interesting report from South Africa describes a young patient with severe mitral stenosis and hemodynamic collapse secondary to overwhelming sepsis with high obligate flow rates.¹⁴⁹ Emergent percutaneous balloon mitral valvuloplasty was performed with marked improvement in hemodynamics and clinical status. This patient subsequently succumbed to other complications unrelated to mitral stenosis, but this case study does demonstrate the feasibility of percutaneous balloon mitral valvuloplasty in an acutely ill patient with compromised cardiac output secondary to sepsis. A similar strategy has been employed during pregnancy complicated by mitral stenosis.¹⁵⁰

Conclusion

Acute heart failure secondary to valvular dysfunction remains an extremely difficult clinical dilemma from the standpoint of both diagnosis and treatment. In this review, we have focused primarily on acute aortic insufficiency and acute mitral regurgitation with some additional information about prosthetic valve dysfunction and acute tricuspid regurgitation. A brief description of acute hemodynamic decompensation in aortic stenosis and mitral stenosis has also been discussed. Our intention has been to emphasize the importance of prompt recognition of these clinical syndromes by understanding their underlying pathophysiology. Emphasis has been placed on expeditious treatment with appropriate diagnostic testing. In most cases of acute heart failure secondary to valvular disease, the use of a bedside pulmonary artery catheter is invaluable, allowing the clinician to assess both the degree of hemodynamic embarrassment and to guide therapy. In conclusion, for the treating physician to effectively manage these patients he or she must not only understand the pathophysiology of the disease but also be cognizant of the limitations of medical therapy. It is essential to understand that, in general, surgical intervention represents the most definitive intervention and, therefore, early cardiothoracic surgical consultation is a critical step in the management algorithm of these desperately ill individuals.

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Hypertensive Emergencies

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CHAPTER 28

Definition

Prognosis

Definition

HYPERTENSIVE EMERGENCIES are characterized by severe elevations in blood pressure (BP) ($>180/120$ mm Hg) complicated by evidence of impending or progressive target-organ dysfunction.¹ The major types of hypertensive emergencies are summarized in Table 28-1. In reality, however, it is not the absolute level of BP that is hazardous, but the rate of rise of BP. Patients with chronic hypertension can tolerate much higher BP than previously normotensive persons. Diastolic BP (DBP) of 140 mm Hg or higher may be well tolerated in a patient with chronic hypertension without symptoms, whereas a DBP of 110 mm Hg may be devastating in a previously normotensive woman with preeclampsia or a child with acute glomerulonephritis. The diagnosis of hypertensive emergency, whatever the BP level, requires immediate reduction of BP, generally with an intravenous antihypertensive agent in an intensive care unit for continuous monitoring of BP. In contrast, a severe elevation in BP without evidence of progressive end-organ damage, considered an urgent hypertensive crisis, can usually be managed with oral medication in an outpatient setting. In this case, gradual reduction in BP over a period of 24 to 48 hours is usually sufficient.

Included among hypertensive emergencies is the syndrome of malignant or accelerated hypertension. As first described by Volhard and Fahr in 1914, malignant hypertension was characterized by severe hypertension, retinopathy with papilledema, renal insufficiency, fibrinoid necrosis of renal arterioles, and a rapidly progressive and fatal clinical course.² Later, the definition was generalized to include severe hypertension accompanied by papilledema (grade IV Keith-Wagener retinopathy). In contrast, accelerated hypertension was considered severe elevation of BP in the presence of retinal hemorrhages and exudates but without papilledema (grade III Keith-Wagener retinopathy). Subsequent

studies showed that severe hypertension complicated by retinal hemorrhages and exudates with or without papilledema had similar clinical features and prognosis, so that the terms *malignant* and *accelerated hypertension* are used interchangeably.³ Presently, these terms are not used, and, instead, *hypertensive emergency* is used to refer to the syndrome of elevated BP complicated by acute end-organ damage, including grade III or IV retinopathy.

Incidence and Prevalence

In spite of improvements in the diagnosis and treatment of hypertension, the control rate remains low. In the National Health and Nutrition Examination Survey III (NHANES III) only 37% of patients with hypertension had controlled BP levels.⁴ However, widespread outpatient antihypertensive treatment has reduced the incidence of hypertensive emergencies, and nonadherence to prescribed medication now accounts for most cases.⁵ Hypertensive emergencies occur in approximately 1% of hypertensive patients.⁶ In a Brazilian retrospective study of 76,723 patients admitted to the emergency department, 273 (0.35%) were considered hypertensive urgencies and only 179 (0.23%) had a diagnosis of hypertensive emergency.⁷ Similarly, 118 of 17,952 (0.65%) patients admitted to an emergency department in Spain were diagnosed as having a hypertensive crisis (defined as BP $\geq 210/120$ mm Hg), but only 28 (0.15%) were diagnosed as a hypertensive emergency.⁸ In an Italian series, 108 hypertensive emergencies comprised 0.76% of visits to the internal medicine section of an emergency department during 1 year.⁹ The estimated prevalence of hypertensive crisis in the general hypertension population is 1% in the United States.¹⁰ Two major university hospitals in the United States have reported similar findings: in New York, 0.6% of 9851 medical service admissions were for hypertensive emergency, whereas in Miami, 1.1% of 2898 medical emergency department visits resulted in hospital admissions for hypertensive emergency.^{11,12} This contrasts with a 7% incidence of accelerated hypertension with papilledema in patients with untreated essential hypertension in the era before the development of effective antihypertensive therapy.^{13,14} The reduction in incidence of hypertensive emergencies has generally been attributed to the success of antihypertensive therapy in preventing progression from the early stages of hypertension to more advanced disease with target-organ damage. Poor access to health care and noncompliance to medications are generally associated with hypertensive crisis and should be assessed in patients having hypertensive emergencies before hospital discharge.

Table 28-1. Types of Hypertensive Emergencies

- Hypertensive encephalopathy
- Intracerebral hemorrhage
- Acute myocardial infarction
- Acute left ventricular failure with pulmonary edema
- Unstable angina pectoris
- Dissecting aortic aneurysm
- Eclampsia

Table 28-2. Conditions Related to Hypertensive Emergencies

Essential hypertension
Renal parenchymal disease
• Acute glomerulonephritis • Aasculitis • Hemolytic uremic syndrome • Thrombotic thrombocytopenic purpura
Renovascular disease
Pregnancy
Endocrine
• Pheochromocytoma • Cushing syndrome • Renin-secreting tumors • Mineralocorticoid hypertension
Drugs
• Cocaine, sympathomimetics, erythropoietin, cyclosporin, antihypertensive withdrawal • Interactions with monoamine-oxidase inhibitors (tyramine), amphetamines, lead intoxication
Autonomic hyperactivity
• Guillain-Barré syndrome, acute intermittent porphyria
Central nervous system disorders
• Head injury, cerebral infarction/hemorrhage, brain tumors

From Vaughan CJ, Delanty N: Hypertensive emergencies. *Lancet* 2000;356:411-417.

Etiology and Pathogenesis

The etiology of malignant or accelerated hypertension is unknown, but many conditions are related to hypertensive emergencies and urgencies (Table 28-2). The degree of BP elevation does not correlate closely with the severity of end-organ deterioration, and it is uncertain whether malignant or accelerated hypertension is a nonspecific consequence of very high BP or is triggered by a specific constellation of neurohumoral factors and cytokines.¹⁴⁻¹⁷

The primary abnormality in patients with hypertensive emergencies is the impaired autoregulatory capacity (i.e., the ability of blood vessels to dilate or constrict to maintain normal perfusion, particularly in the cerebral and renal beds). An initial abrupt rise in vascular resistance in response to excess production of catecholamines, angiotensin II, vasopressin, aldosterone, thromboxane and/or endothelin, or deficient production of endogenous vasodilators—such as nitric oxide and prostacyclin—seems to precipitate increased vasoreactivity and resultant hypertensive emergency (Fig. 28-1).¹⁷

Autoregulatory function is compromised, resulting in end-organ ischemia, which triggers the release of additional vasoactive substances, thus initiating a vicious cycle of further vasoconstriction, myointimal proliferation, and end-organ ischemia.¹⁸ Preclinical studies have provided evidence that activation of renin-angiotensin-aldosterone system (RAAS) plays an important role in the pathophysiology of severe hypertension,

leading to hypertensive crisis. Animals that are double transgenic for the human renin and angiotensinogen genes develop severe hypertension plus inflammatory vasculopathy similar to that seen in severe human hypertension.¹⁹ Angiotensin II has direct cytotoxic effects on the vessel wall through activation of expression of genes for proinflammatory cytokines and the transcription factor nuclear factor κ B (NF- κ B).^{20,21} The RAAS also induces expression of proinflammatory cytokines and vascular cell adhesion molecules, which may contribute to the vascular injury and target-organ damage.¹⁷ Arteriolar fibrinoid necrosis ensues, precipitating endothelial damage, platelet and fibrin deposition, and thromboxane release. Some studies have also reported a relation between genetic polymorphisms in components of the RAAS and hypertensive crisis. For example, the DD and ID genotypes of the angiotensin-converting enzyme (ACE) gene are more frequent in patients having malignant hypertension or hypertensive crisis.^{22,23}

Malignant or accelerated hypertension is more prevalent among patients with secondary hypertension, particularly hypertension secondary to renal artery stenosis or renal parenchymal disease, than among essential hypertensive patients. However, essential hypertension is the most common underlying cause of malignant or accelerated hypertension because of its greater prevalence. Based on postmortem analysis, Kincaid-Smith found that of 124 cases of malignant hypertension, 44% occurred in the setting of primary hypertension; 13% had chronic glomerulonephritis; 9% had polyarteritis nodosa; and 6% had unilateral renal artery stenosis.²⁴ In a study of 123 patients without evidence of primary renal parenchymal disease referred to a tertiary care center for evaluation of severe hypertension with grade III or IV retinopathy, Davis and associates found that 43% of the white patients and 7% of the black patients had renal artery stenosis documented by renal arteriography.²⁵ Of the 242 patients with malignant hypertension identified by Lip and associates, 97 (40%) had secondary hypertension, most commonly related to renal parenchymal disease. Twenty-five patients (10%) had pregnancy-induced hypertension.²⁶ Aldosterone excess has also been detected in patients with hypertensive crisis. Labinson and colleagues reported eight patients with a clinical diagnosis of primary aldosteronism whose course was complicated by hypertensive emergencies.²⁷ All of these responded well to laparoscopic adrenalectomy or medical treatment with aldosterone receptor blockers. Accordingly, any patient who has experienced malignant or accelerated hypertension should undergo evaluation for secondary hypertension.

Diagnosis

The common presenting symptoms and target organ complications of hypertensive emergencies are listed in Table 28-3.²⁶ The physician evaluating a patient for hypertensive emergency should focus on the history, physical examination, and laboratory evaluation to assess the severity of BP elevation and related end-organ damage.¹⁶ This includes a determination of the duration, severity, and level of control of preexisting hypertension, antihypertensive drug treatment, and the extent of preexisting end-organ damage. The presence of concomitant illnesses and all medications, including prescription drugs, over-the-counter preparations such as sympathomimetic agents, and illicit drugs such as cocaine, should be noted. The physician should assess specific symptoms suggesting end-organ damage such as chest pain (myocardial ischemia or aortic dissection), back pain (aortic

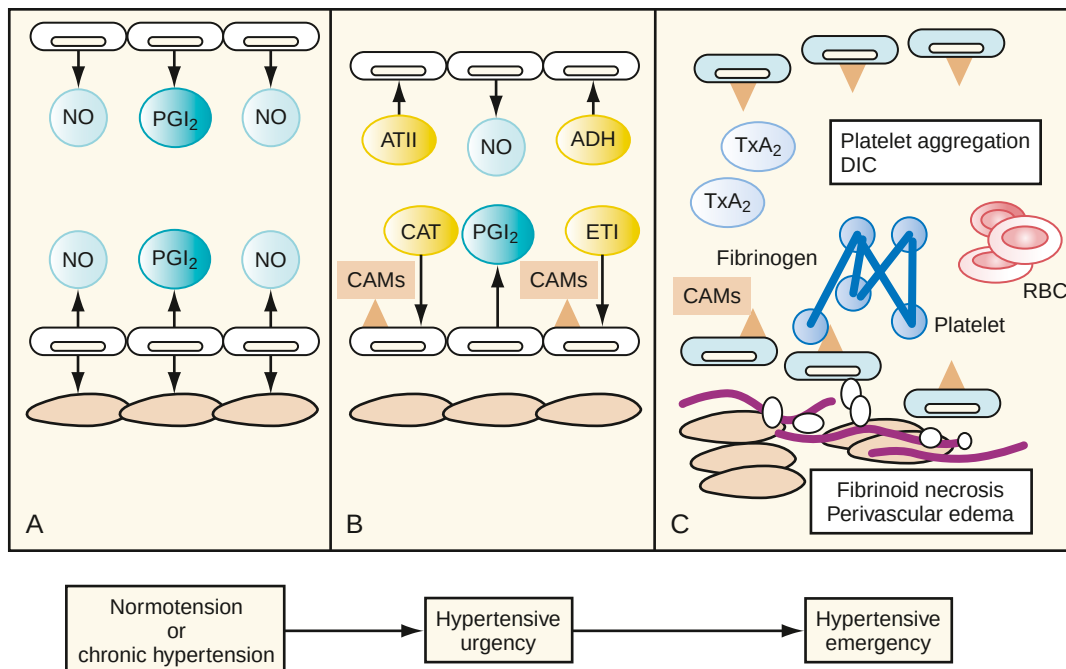


Figure 28-1. Putative vascular pathophysiology of hypertensive emergencies. **A**, The endothelium modulates vascular resistance through the autocrine/paracrine release of vasoactive molecules such as nitric oxide (NO) and prostacyclin (PGI₂). **B**, Acute changes in vascular resistance occur in response to excess production of catecholamines (CAT), angiotensin II (ATII), vasopressin (ADH), aldosterone, thromboxane (TxA₂), and endothelin 1 (ET1), or low production of endogenous vasodilators such as NO and PGI₂. Acute or severe increases in blood pressure can also promote expression of cellular adhesion molecules (CAMs) by the endothelium. **C**, During a hypertensive emergency, endothelial control of vascular tone may be overwhelmed, leading to end-organ hyperperfusion, arteriolar fibrinoid necrosis, and increased endothelial permeability with perivascular edema. Loss of endothelial fibrinolytic activity coupled with activation of coagulation and platelets promotes disseminated intravascular coagulation (DIC). RBC, red blood cell. (From Vaughan CJ, Delanty N: Hypertensive emergencies. *Lancet* 2000;356:411-417.)

Table 28-3. Most Common Presenting Symptoms and Complications of Hypertensive Emergencies

Symptoms/Complications	Frequency
• Visual disturbance	26%
• Headache	12%
• Headache and visual disturbance	10%
• Heart failure	8%
• Stroke and transient ischemic attack	7%
• Dyspnea	5%
• No symptoms	10%
• Heart failure	11%
• Stroke	10%
• Angina	4%
• Myocardial infarction	4%
• Chronic renal failure	32%
• None	61%

From Lip GYH, Beevers M, Beevers G: The failure of malignant hypertension to decline: a survey of 24 years' experience in a multiracial population in England. *J Hypertens* 1994;12:1297-1305.

dissection), dyspnea (pulmonary edema or congestive heart failure), and neurologic symptoms (hypertensive encephalopathy).

The signs of hypertensive emergency that should be assessed on physical examination are listed in Table 28-4. Supine and upright BP should be measured to assess volume status. The BP should also be measured in both arms because a significant difference increases the suspicion of aortic dissection. The ocular fundi should be examined for evidence of acute hypertensive retinopathy. The heart and lungs should be auscultated for signs of acute left ventricular dysfunction. The presence of an abdominal bruit suggests renal artery stenosis and palpation of the abdomen may reveal evidence of an aortic aneurysm. Discrepancies in peripheral pulses and the murmur of aortic regurgitation suggest aortic dissection. The neurologic examination may yield evidence of encephalopathy or stroke, including disorientation, localized weakness, and visual field deficits.

Basic diagnostic evaluation for patients with hypertensive crisis is listed in Table 28-5. Urinalysis and determination of serum electrolytes, urea nitrogen, and creatinine levels should be obtained to confirm or exclude acute renal insufficiency; a complete blood cell count with peripheral blood smear should be performed to look for evidence of microangiopathic anemia; and a serum glucose test should be done to identify concomitant diabetes.^{5,17} An electrocardiogram to help identify or rule out myocardial ischemia and chest radiograph to look for pulmonary edema secondary to left ventricular failure and for widening of the mediastinum secondary to thoracic aortic dissection are indicated.^{5,17} In some cases, measurement of plasma renin

Table 28–4. Physical Examination in Patients with Hypertensive Emergency

Blood pressure measurements
• Supine and upright • Both arms
Fundoscopy
• Hemorrhages • Exudates • Papilledema
Heart and lungs auscultation
• S3 gallop • New murmurs • Pulmonary rales
Abdomen
• Bruits • Mass palpation
Palpation of peripheral pulses
Neurologic examination

Table 28–5. Diagnostic Tests for Evaluation of Patients with Hypertensive Crisis

Blood
• Urea • Creatinine • Glucose • Electrolytes • Full blood count (including peripheral blood smear)
Urine analysis
Electrocardiogram
Chest radiography

activity and aldosterone drawn at the time of admission can be useful in making a retrospective diagnosis. If aortic dissection is suspected, computed tomography, magnetic resonance imaging, and transesophageal echocardiography may be needed.²⁸

Any evidence of acute or rapidly progressive end-organ deterioration in the history, physical examination, or laboratory evaluation distinguishes a hypertensive emergency from an urgent hypertensive crisis.⁶ As soon as the physician diagnoses or suspects target organ damage from the history, physical examination, or laboratory analysis, the patient should be placed on a cardiac monitor and have intravenous access established. BP reduction (usually with an intravenous drug) should begin during the arrangements for hospital admission.

Treatment

Patients with a hypertensive emergency should be admitted to an intensive-care unit and require immediate but controlled reduction in BP to protect end-organs from further damage. In general, the goal of therapy is to lower the mean arterial pressure

by approximately 25% or to reduce the DBP to 100 to 110 mm Hg over a period of several minutes to hours, depending on the clinical situation.^{1,6} Precipitous reductions in BP and rapid reductions to normotensive or hypotensive levels should be avoided because they may provoke end-organ ischemia or infarction. BP should be maintained at the initial target level for 2 to 6 hours. If the BP is tolerated and the patient is clinically stable, further gradual reductions can be implemented in the next 24 to 48 hours.¹ Ischemic stroke and aortic dissection are exceptions. There is no evidence from clinical trials to support immediate antihypertensive treatment in patients with ischemic stroke.²⁹ Oral or intravenous antihypertensive treatment should be instituted if DBP greater than 120 mm Hg or if the patient is eligible for thrombolysis.³⁰ Aortic dissection is a dramatic and fatal complication, and these patients should have their systolic BP (SBP) reduced to less than 100 mm Hg if tolerated.¹ Therapy for acute dissection aims to reduce stress on the aortic wall by lowering BP and heart rate. These goals are achieved with a combination of β -blockers (labetalol is most commonly used) and vasodilators. Nitroprusside can cause reflex tachycardia and thus β -blockers should be started first.¹⁷

The goal of therapy is to interrupt the cycle of impaired autoregulatory capacity and vasoreactivity by reducing peripheral vascular resistance.⁶ Sodium nitroprusside is the drug of choice for the treatment of most hypertensive emergencies because it allows for the controlled reduction of BP. In all situations in which an antihypertensive agent is being delivered intravenously, constant BP monitoring, preferably through an arterial line, is mandatory. Most patients who have a hypertensive crisis are volume-depleted, presumably secondary to a pressure-related diuresis. Accordingly, diuretics should be reserved for patients in whom there appears to be fluid overload, such as pulmonary edema.

Parenteral antihypertensive agents should be gradually withdrawn after BP has been controlled for 12 to 24 hours, with concomitant introduction of oral agents. Evaluation for secondary hypertension may be started during hospitalization while oral antihypertensives agents are titrated. Attempting to ensure adherence to antihypertensive therapy during long-term follow-up is an important step to prevent recurrent hypertensive crisis.⁵

Prognosis

The development of successful antihypertensive therapy has greatly improved the prognosis of patients with hypertensive emergencies.⁵ In 1939, Keith and colleagues found that mean survival of patients with hypertension and grade IV retinopathy was 10.5 months, with no survivors at 5 years.³¹ More recently, authors have reported that the survival of patients with malignant hypertension approaches that of patients with uncomplicated primary hypertension.^{32,33} Using life-table analysis, the estimated survival of patients with malignant hypertension was 18 years, versus 21 years in patients with uncomplicated hypertension.³² The leading cause of death (50%) in patients with accelerated hypertension was myocardial infarction. In Birmingham, UK, 74% of 315 patients with malignant hypertension were alive after 5-year follow-up and renal failure was the most common cause of death.³³ Acute target-organ damage secondary to hypertensive emergency (e.g., acute renal failure may return toward normal if BP is controlled in the long term).⁵

An exception to this rule is eye and central nervous system damage, which tends to be irreversible.

Specific Hypertensive Emergencies

Hypertensive Encephalopathy

Hypertensive encephalopathy is the most difficult neurologic emergency to diagnose and frequently it is a diagnosis of exclusion.¹⁷ With better diagnosis and treatment of primary hypertension, hypertensive encephalopathy is infrequent. However, prompt recognition and treatment is essential to prevent progression to hemorrhage. This becomes a particularly difficult issue when hypertensive encephalopathy occurs in previously normotensive persons, as with preeclampsia or “crack” cocaine

abuse. Hypertensive encephalopathy is also associated with secondary causes of severe hypertension, such as renal disease, immunosuppressive therapy,^{34,35} erythropoietin use,³⁶ and thrombotic thrombocytopenic purpura.³⁷

Ordinarily cerebral blood flow is autoregulated (i.e., cerebral resistance vessels constrict and dilate in response to changes in systemic pressure) to maintain a constant perfusion pressure (Fig. 28-2).^{17,38-41} In normotensive subjects, perfusion pressure is maintained over a wide range of mean arterial pressure (60 to 120 mm Hg). With chronic hypertension, the mean BP range over which cerebral perfusion is maintained is shifted upward (160 to 180 mm Hg), such that persons with long-standing hypertension can tolerate greater elevations in BP without compromising cerebral perfusion. When elevations in systemic BP exceed the brain's ability to locally autoregulate cerebral perfusion, overperfusion ensues, resulting in cerebral edema, small vessel damage, and microinfarctions. As indicated earlier, breakdown in autoregulation of cerebral perfusion occurs at much lower BP levels in previously normotensive subjects than in persons with chronic hypertension.

Hypertensive encephalopathy most commonly develops over a period of several days. The patient usually complains of headache, nausea, visual changes, or focal neurologic symptoms. Physical examination generally reveals disorientation, obtundation, focal neurologic signs, seizures, and retinopathy, including papilledema. Hypertensive encephalopathy is a diagnosis of exclusion after ruling out stroke, subarachnoid hemorrhage, seizure disorder, encephalitis, and drug overdose.¹⁷

The drug of choice for treatment of hypertensive encephalopathy is nitroprusside (Table 28-6). It should be titrated to reduce

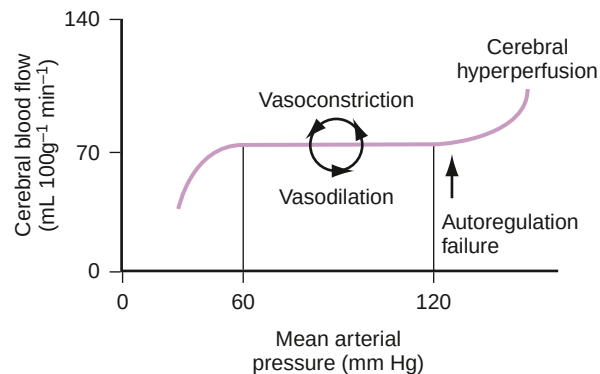


Figure 28-2. Autoregulation of cerebral blood flow. (From Vaughan CJ, Delanty N: Hypertensive emergencies. *Lancet* 2000;356:411-417.)

Table 28-6. Types of Hypertensive Emergency and Treatment Recommendations

Type of Hypertensive Emergency	Recommended Treatment	Drugs to Avoid
Hypertensive encephalopathy	Nitroprusside, labetalol	β -blockers, methyldopa, clonidine, nicardipine, diazoxide, nitroglycerin
Stroke	Labetalol, nitropaste, nicardipine	β -blockers, methyldopa, clonidine, diazoxide, hydralazine, nitroglycerin
Intracerebral hemorrhage, subarachnoid hemorrhage	Nimodipine,* nitroprusside, nicardipine, labetalol	β -blockers, methyldopa, clonidine, diazoxide, hydralazine, nitroglycerin
Myocardial ischemia, myocardial infarction	Nitroglycerin, labetalol, nitroprusside, β -blockers†	Hydralazine, diazoxide, minoxidil
Acute pulmonary edema	Nitroprusside or nitroglycerin‡ and loop diuretic	Hydralazine, diazoxide, β -blockers, labetalol
Aortic dissection	Nitroprusside, β -blockers, labetalol	Hydralazine, diazoxide, nicardipine, minoxidil
Acute renal insufficiency	Fenoldopam, nitroprusside, labetalol, calcium channel β -blockers	β -blockers, ACE inhibitors, angiotensin receptor blockers
Preeclampsia, eclampsia	Hydralazine, labetalol	Diuretics, β -blockers, ACE inhibitors
Postoperative hypertension	Nitroprusside, nitroglycerin, calcium channel blockers, β -blockers	—
Hyperadrenergic states	Labetalol, phentolamine, calcium channel blockers,§ nitroprusside	β -blockers (in cocaine overdose)

*Nimodipine is used to reduce cerebral artery vasospasm, not to lower BP in subarachnoid hemorrhage.

†Should not be used if left ventricular function is compromised.

‡Drug of choice if left ventricular failure is due to or complicated by ischemia.

§Useful for treating associated coronary spasm.

mean arterial pressure by about 20% or to a DBP of 100 mm Hg within the first hour.¹⁷ Particular caution is needed in elderly patients and in those with preexisting hypertension in whom overaggressive reduction in BP may be accompanied by worsening of neurologic status and even stroke. Neurologic function should improve with BP reduction. If not, a diagnosis other than hypertensive encephalopathy should be entertained. Labetalol can be used as an alternative to nitroprusside. Agents that suppress central nervous system function, such as β -blockers and central nervous system active agents, and agents that increase cerebral blood flow, such as nicardipine and nitroglycerin, should be avoided.

Subarachnoid Hemorrhage

Subarachnoid hemorrhage is caused by ruptured aneurysms in 85% of patients and the fatality rate is 50%.⁴² Headache is the most characteristic symptom of subarachnoid hemorrhage and focal neurologic deficits occur when the aneurysm compresses a cranial nerve or bleeds into the brain parenchyma or from local ischemia due to acute vasoconstriction. Acute BP reduction in this setting, regardless of the presenting BP, has not been shown to improve morbidity and mortality.⁴² Therefore, antihypertensive therapy should not be prescribed unless mean arterial pressure is 130 mm Hg.^{43,44}

Patients having subarachnoid hemorrhage should receive nimodipine, a calcium channel blocker.^{42,44,45} The evidence for nimodipine is based on a single large trial in which patients treated with nimodipine had a 40% reduction in poor outcomes defined as severe disability, vegetative state, and death.⁴⁶ Nimodipine should be dosed at 60 mg orally or per nasogastric tube every 4 hours for 21 days, starting within 96 hours of the subarachnoid hemorrhage.⁴⁵ The benefits of nimodipine are likely secondary to inhibiting cerebral artery vasospasm and not to BP reduction because there is no significant change in BP with the above doses.

Stroke

Approximately 80% of patients with stroke are hypertensive on presentation and 30% have a prior history of hypertension.⁴⁷ The elevated BP usually falls spontaneously without treatment after a few days, and 10 days after a stroke approximately, two thirds of patients are normotensive.^{48,49} BP regulation after a stroke can be precarious, particularly in the elderly, with even minimal intervention causing precipitous drops in BP. Optimum management of hypertension in acute ischemic stroke remains controversial.²⁹ Aggressive treatment of BP may lead to neurologic worsening by reducing perfusion pressure of the penumbra area and extension of the damage.⁵⁰⁻⁵³ A prospective study conducted in 115 patients admitted within 24 hours of stroke noted that each 10% decrease in SBP was associated with an increased odds ratio of 1.89 for developing an unfavorable outcome.⁵⁴ However, a trial has reported significantly reduced cumulative mortality and number of cardiovascular events in patients treated with candesartan from the first day after stroke.⁴⁹ Because BP tends to decrease spontaneously in the first few days after a stroke, antihypertensive therapy should be withheld unless some other target organ is being compromised.⁵⁵

Although the appropriate treatment of arterial hypertension in the setting of acute ischemic stroke remains controversial, the American Heart Association (AHA) recommends no antihypertensive treatment unless BP elevations are extremely high (SBP >220 mm Hg or DBP >120 mm Hg) or if the patient is

eligible for thrombolysis.^{55,50} If antihypertensive therapy is necessary, the BP should be gradually reduced by 15% to 25% during the first 24 hours.⁵³ Drug therapy is similar to that for hypertensive encephalopathy (see Table 28-6). Inducing hypertension in hypotensive patients is theoretically beneficial (i.e., increasing cerebral blood flow in the ischemic penumbra of the brain could potentially salvage ischemic tissue). However, a study in patients with intracranial arterial stenosis showed that increased BP is associated with increased risk of ischemic stroke and stroke in the territory of the stenotic vessel.⁵⁶ Further data from large clinical trials are not available and therefore pressor therapy is not currently recommended.⁵³ Two randomized studies on BP management during acute stroke are under way and may help with clinical decision making.^{57,58}

Intracerebral Hemorrhage

The clinical benefit of BP reduction after intracerebral hemorrhage remains controversial. It has been difficult to determine whether elevated BP in the setting of intracerebral hemorrhage is a cause of hemorrhagic extension or an effect of increasing intracranial volume and pressure. It has been customary to recommend BP reduction in patients with severe hypertension after an intracerebral hemorrhage in an effort to prevent further bleeding, but to do so may precipitate cerebral hypoperfusion. Controlled studies have not shown benefit from reducing BP after intracerebral hemorrhage. Therefore, AHA recommends intravenous antihypertensive therapy based on peripheral BP and if elevated intracranial pressure is suspected (Fig. 28-3).⁵⁹

Myocardial Ischemia or Infarction

The target BP is less than 130/80 mm Hg in patients with acute coronary syndromes.⁶⁰ All patients with unstable angina and hypertension should receive oxygen, aspirin, and nitroglycerin. Nitroglycerin is indicated to promote coronary dilation, improve coronary perfusion, and reduce symptoms, and should be used as needed to reduce BP. β -blockers reduce heart rate and myocardial oxygen consumption and are useful in combination with nitrates unless ventricular function is compromised. BP should be reduced gradually to less than 130/80 mm Hg until the symptoms subside. In patients with elevated DBP, the BP should be lowered slowly and caution is advised in inducing reductions in DBP to below 60 mm Hg.⁶⁰ If nitroglycerin is ineffective or contraindicated, labetalol can be used to reduce BP while improving myocardial oxygenation (see Table 28-6). Nitroprusside should be used only if the hypertension is refractory to other agents because of the possibility of the coronary steal phenomenon (i.e., in the setting of fixed coronary obstruction, blood flow can be redirected from ischemic areas, worsening myocardial ischemia). Agents that may reflexively increase myocardial oxygen demand, such as hydralazine, should be avoided.

Once the BP is reduced below 180/110 mm Hg, thrombolytic therapy can be considered if evidence of ongoing ST-elevation myocardial infarction persists⁶¹ and primary angioplasty is not readily available. Risk of bleeding is increased in patients who are very hypertensive acutely, particularly if they are ordinarily normotensive.

Renal Insufficiency

Acute renal insufficiency may be either a cause of severe hypertension, as in renal parenchymal disease, acute glomerulonephritis, vasculitis, or renal artery stenosis, or a consequence of

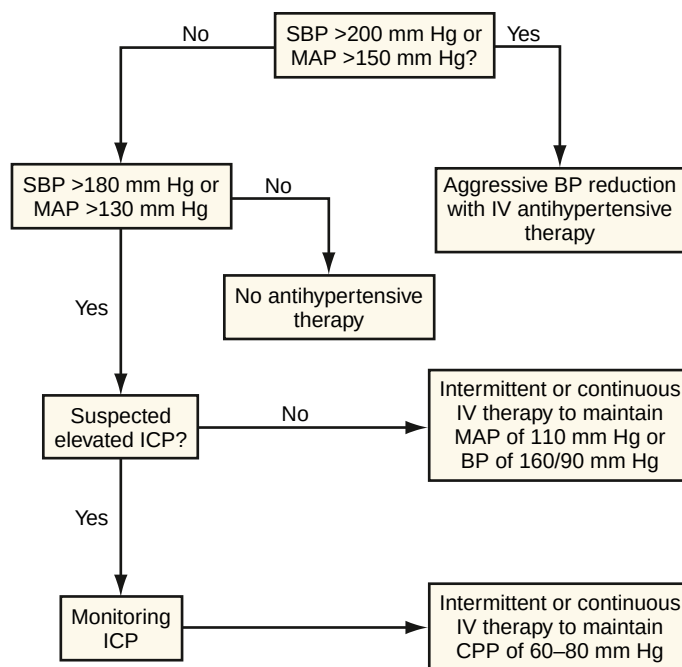


Figure 28-3. Guidelines suggested by the American Heart Association for treating hypertension in patients with intracerebral hemorrhage. BP, blood pressure; CPP, cerebral perfusion pressure; ICP, intracranial pressure; IV, intravenous; MAP, mean arterial pressure; SBP, systolic blood pressure.

severe BP elevation.⁶ Patients having severe hypertension and microscopic hematuria or acutely worsened renal function should be diagnosed as a hypertensive emergency. A urinalysis and measurement of serum creatinine should be performed in these patients and the latter compared with recent values to establish whether the deterioration in renal function is acute.⁵ In patients with kidney transplants, additional causes of severe elevations in BP include stenosis of the graft site, the use of cyclosporine, corticosteroids, or both, and excessive secretion of renin by the native kidney.⁶² A renal sonogram should be obtained in all patients with acute renal insufficiency to evaluate kidney size and to rule out obstructive uropathy because obstruction of the urinary tract at any level, including the bladder outlet, can raise BP. In patients with severe hypertension and renal insufficiency, the goal of medical therapy is to reduce BP without compromising renal blood flow. High-dose loop diuretic treatment may be necessary to maintain urine flow. Sodium nitroprusside is cost-effective in controlling BP in this setting, but the risk of cyanide and thiocyanate toxicity is increased. Fenoldopam is an attractive alternative in renally impaired patients.^{63,64} Calcium channel blockers are effective and well tolerated, particularly in renal transplant recipients.⁶⁵ β -blockers reduce blood flow and glomerular filtration rate and should be avoided. ACE inhibitors and angiotensin receptor blockers may be effective but can be hazardous, precipitating hypotension or worsening renal function.

Preeclampsia or Eclampsia

Hypertension in pregnant women is defined as SBP =140 mm Hg and/or DBP = 90 mm Hg after 20 weeks of gestation in a woman with previously normal BP.⁶⁶ Preeclampsia is a syndrome characterized by hypertension and proteinuria (urinary protein excretion of 300 mg/24 hr) and may be associated with visual disturbances, headache, and epigastric pain. Seizures indicate progression to eclampsia. It is more common in nulliparous women, multiple gestations, women with hypertension for

4 years, family history of preeclampsia, hypertension in previous pregnancy, and women with renal disease.

Preeclampsia is caused by impaired placentation of the trophoblast and incomplete vascular remodeling. This failure of vascular invasion compromises blood flow to the maternal-fetal interface and reduces placental perfusion, causing systemic hemodynamic changes through activation of soluble fms-like tyrosine kinase 1 (sFlt1) and soluble endoglin (sEng) (Fig. 28-4). The clinical manifestation of preeclampsia is due to systemic maternal endothelial cell dysfunction, resulting in reduced organ perfusion caused by vasospasm, activation of the coagulation cascade, and loss of vascular integrity.⁶⁷ sFlt1 is a potent antagonist of VEGF (vascular endothelial growth factor) and placental growth factor (PlGF), a related proangiogenic protein.⁶⁸ Glomerular endotheliosis, the classic renal lesion in preeclampsia, is a consequence of suppressed levels of VEGF. VEGF also induces nitric oxide and prostacyclin release by endothelial cells, favoring vasodilation. The functional significance of overexpression of sEng and sFlt1 has been demonstrated in a rodent model: pregnant rats expressing high levels of these proteins develop nephrotic-range proteinuria, severe hypertension, biochemical evidence of HELLP syndrome (elevated lactate dehydrogenases [LDH] and aspartate aminotransferase [AST], low platelets) and intrauterine growth restriction.⁶⁹ Histology reveals severe glomerular endotheliosis in the kidney, infarction in the placenta, areas of necrosis in the liver, and schistocytes in the peripheral blood.

Decreased levels of urinary PlGF during midgestation predict subsequent development of clinical preeclampsia and endoglin levels are most elevated in women who develop preterm preeclampsia and preeclamptic pregnancies with small-for-gestational-age infants.⁶⁸

Definitive treatment of preeclampsia and eclampsia is delivery of the placenta. However, the decision to deliver a patient with preeclampsia must balance both the maternal and fetal risks.⁷⁰ The patient with eclampsia requires prompt intervention.

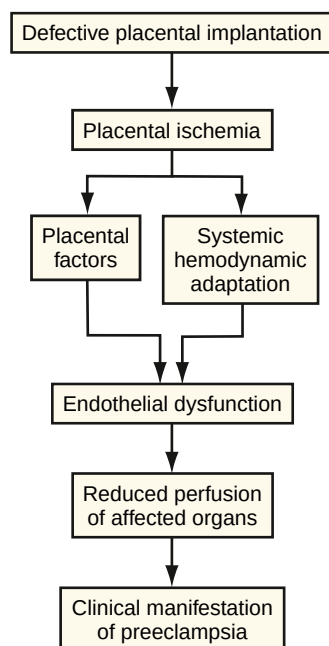


Figure 28-4. Pathophysiology of preeclampsia. (Adapted from Noris M, Perico N, Remuzzi G: *Mechanisms of disease: pre-eclampsia*. *Nat Clin Pract Nephrol* 2005;1:98-114.)

Temporizing measures for preeclampsia include bed rest, hydration, and magnesium sulfate administration to reduce central nervous system irritability. If delivery is imminent, acute treatment of hypertension is required for DBP of 105 to 110 mm Hg or higher. The DBP goal is 95 to 105 mm Hg (Table 28-7).^{70,71} Hydralazine is considered the first-line agent. Labetalol is considered second line and nifedipine use is controversial. However, a meta-analysis of randomized trials reported greater maternal and fetal complication rates with hydralazine compared with labetalol or nifedipine.⁷² Thus the choice of antihypertensive agent is somewhat controversial. Nitroprusside can be used when other agents fail, but generally should be avoided because of potential risk of fatal cyanide poisoning. If delivery is likely to be delayed for more than 48 hours, an oral agent such as methyldopa or labetalol is required. Women who develop preeclampsia are at increased risk of long-term cardiovascular complications, such as coronary heart disease, stroke, and cardiovascular disease in general.⁷³

Postoperative Hypertension

Postoperative hypertension is common, particularly following vascular surgical procedures. It is reported in upward of 30% to 50% of patients following coronary artery bypass graft surgery.⁷⁴ Complications of postoperative hypertension include bleeding from suture sites, myocardial infarction, and stroke. Postoperative hypertension is characterized by increased sympathetic tone and a high systemic vascular resistance. BP in this setting is generally easily controlled with a number of easily titratable agents, including nitroprusside, labetalol, and nicardipine. Nitroglycerin is also effective and is preferable when coronary ischemia is suspected. Nicardipine and isradipine have been evaluated in clinical trials and have been reported to safely and effectively reduce BP after cardiac and noncardiac surgery.⁷⁵⁻⁷⁷

Table 28-7. Treatment of Hypertension in Preeclampsia

Hydralazine	5 mg IV bolus, then 10 mg every 20 to 30 min to a maximum of 25 mg, repeat in several hours as necessary
Labetalol (second line)	20 mg IV bolus, then 40 mg 10 min later, 80 mg every 10 min for two additional doses to a maximum of 220 mg
Nifedipine (controversial)	10 mg PO, repeat every 20 min to a maximum of 30 mg. Caution when using nifedipine with magnesium sulfate; can see precipitous BP drop. Short-acting nifedipine is not approved by FDA for managing hypertension.
Sodium nitroprusside (used rarely, when others fail)	Fetal cyanide poisoning may occur if used for more than 4 hr.

From Taler S: Hypertension in pregnancy. In Oparil S, Weber MA (eds): *Hypertension: a Companion to Brenner and Rector's the Kidney*, 2nd ed. Philadelphia, Elsevier, 2005, pp 596-602.

Hyperadrenergic States

Severe BP elevation can be caused by hyperadrenergic states, including cocaine overdose (which can be complicated by drug-induced seizures, stroke, myocardial infarction, or encephalopathy),⁷⁸ clonidine or β -blocker withdrawal, monoamine oxidase inhibitor crisis, and pheochromocytoma.⁶ Cocaine is a sympathomimetic agent that blocks the presynaptic reuptake of norepinephrine and dopamine, resulting in an excess of these neurotransmitters at postsynaptic receptor sites. This leads to sympathomimetic effects, including tachycardia, hypertension, mydriasis, and hyperthermia. Cocaine can also release norepinephrine stores in sympathetic nerve terminals and stimulate the release of catecholamines from the adrenals. Patients with cocaine-associated myocardial infarction should be treated with aspirin, nitrates, and benzodiazepines.⁷⁹ Hypertension and vasospasm related to cocaine toxicity can be treated with benzodiazepines alone or combined with calcium channel blockers or the α -adrenergic antagonists labetalol and phentolamine. Nitroprusside can be used for severe hypertension. β -adrenergic receptor antagonists should be avoided due to the potential of aggravating the hypertension as a result of unopposed α -adrenergic stimulation.^{79,80}

Other sympathomimetic drugs, such as amphetamines, phencyclidine hydrochloride (PCP), lysergic acid diethylamide (LSD), and diet pills may also precipitate hypertensive crisis. Adrenergic antagonists such as phentolamine and labetalol are also effective in this setting.⁸⁰ Nitroprusside can be used alternatively or in refractory cases.

Pheochromocytoma is a rare but dangerous catecholamine-producing neuroendocrine tumor originated from chromaffin cells of the adrenal medulla or extra-adrenal paraganglia. Catecholamine excess can cause severe hypertension, headache, inappropriate sweating, and palpitations in patients with pheochromocytoma. Hypertensive crisis can be precipitated by stress related to stimuli, such as surgery or trauma in these patients. Thus failure to diagnose pheochromocytoma can be fatal for

Table 28-8. Parenteral Drugs for Treatment of Hypertensive Emergency

Drug	Dosing (Intravenous)	Onset of Action	Duration of Action	Adverse Effects
Nitroprusside	0.25-10 µg/kg/min; increase by 5-10 µg/kg/min q5-10 min	Immediate	2-3 min	Hypotension, nausea, vomiting, cyanide and thiocyanate toxicity
Nitroglycerin	5-100 µg/min; increase q3-5 min	2-5 min	5-10 min	Hypotension, headache, nausea, vomiting
Labetalol	20-80 mg as IV bolus every 10 min; up to 2 mg/min continuous infusion	5-10 min	3-6 hr	Hypotension, heart block, bronchospasm, nausea, flushing, headache, scalp tingling
Nicardipine	5-15 mg/hr; increase by 1-2.5 mg/hr q15 min	5-10 min	1-4 hr	Increase in heart rate, headache, nausea, vomiting
Phentolamine	2-5 mg q5-10 min	1-2 min	3-10 min	Hypotension, tachycardia, angina, headache, nausea, vomiting
Esmolol	200-500 µg/kg loading dose over 1 min, then 50 µg/kg for 4 min, then increase dose by 50 µg/kg q5 min up to 200 µg/kg/min	1-2 min	10 min	Hypotension, nausea, heart block, heart failure, apnea, bronchospasm, dry mouth
Enalaprilat	0.625-1.255 mg q6h	15 min	6 hr	Hypotension, angioedema, rash
Hydralazine	10-20 mg as IV bolus or 10-40 mg IM, repeat every 4-6 hr	10-20 min	3-8 hr	Tachycardia, angina, worsening aortic dissection, fluid retention, headache, nausea, flushing, rash, dizziness
Fenoldopam	0.1-0.6 mg/kg/min	5-10 min	10-15 min	Headache, dizziness, reflex tachycardia, excessive hypotension, flushing

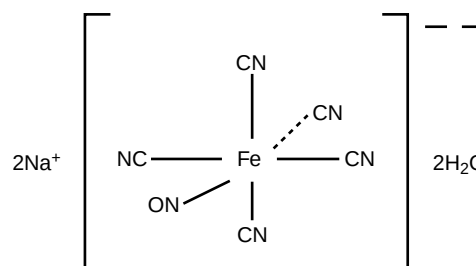
patients undergoing surgical procedures or in pregnant women. The diagnosis can be made by measurement of plasma and 24-hour urine metanephrines. Free plasma metanephrines is the best screening test due to its high sensitivity (99%) and should be performed when pheochromocytoma is suspected.^{81,82} Patients with pheochromocytoma who have very severe hypertension can be treated with intravenous administration of sodium nitroprusside, nitroglycerin, labetalol, or phentolamine to control BP in preparation for surgery.^{82,83} Surgical removal of the tumor is the definitive treatment.

Specific Therapeutic Considerations

Sodium Nitroprusside

Sodium nitroprusside is the most widely recommended and used antihypertensive agent for treatment of hypertensive crisis (Table 28-8). Its rapid onset of action and short half-life allow for minute-by-minute titration of BP, and it is efficacious and generally safe.⁸⁴ However, potentially life-threatening side effects can occur with nitroprusside use. A clear understanding of the mechanism of action of nitroprusside is essential to appreciating these risks.

Nitroprusside consists of a ferrous core, five cyanide groups, and a nitrosyl group (Fig. 28-5). Sulfhydryl groups in the cell walls of vascular smooth muscle donate electrons to the ferrous group in nitroprusside, destabilizing it and causing it to break up into cyanide and NO, the active component of nitroprusside. NO is a free radical that activates guanylate cyclase, causing levels of cyclic guanosine monophosphate to increase in smooth muscle cells. Cyclic guanosine monophosphate inhibits calcium influx, causing venous and arterial smooth muscle relaxation. Venous dilation results in increased venous capacitance, peripheral pooling of blood, and consequent preload reduction. Arterial

**Figure 28-5.** Structural formula of nitroprusside.

dilation results in decreased systemic vascular resistance and lowers arterial BP. NO dilates coronary arteries, resulting in increased myocardial perfusion. However, in the setting of fixed coronary obstruction, blood flow can be redirected from ischemic areas, a phenomenon known as “coronary steal.” When this occurs, nitroprusside therapy can worsen myocardial ischemia.

The most common adverse effect of nitroprusside is hypotension. Nitroprusside is potent and has a rapid onset of action that allows for rapid and precise modulation of BP but also, if used injudiciously, predisposes to potentially catastrophic hypotension. Continuous monitoring of BP, preferably with an arterial line, is obligatory during nitroprusside infusion. If hypotension does occur, the nitroprusside infusion should be discontinued immediately. BP will generally return to pretreatment levels in 1 to 10 minutes.

Cyanide Toxicity

Cyanide, when released from nitroprusside, first binds all available methemoglobin in the circulation.⁸⁵ After saturating methemoglobin, cyanide binds the sulfhydryl group of endogenous

Table 28–9. Signs and Symptoms of Cyanide Toxicity

Central Nervous System
• Headache • Anxiety • Disorientation • Lethargy • Seizures • Coma
Cardiovascular
• Hypertension (tachyphylaxis) • Electrocardiographic changes • Tachycardia/bradycardia • ST-T wave changes • Dysrhythmias • Atrioventricular block
Oxygenation/pH
• Tachypnea • Venous hyperoxemia ◦ Red venous blood ◦ Increased mixed venous O₂ content (SVO₂) ◦ Decreased O₂ consumption (VO₂) ◦ Narrow arteriovenous oxygen difference (AVO₂ difference) ◦ Brick-red skin (occasional cyanosis) • Metabolic acidosis ◦ Elevated blood lactate or elevated lactate/pyruvate ratio
Other
• Nausea, vomiting, abdominal pain • Increased salivation

thiosulfate in the liver to form thiocyanate, which is excreted by the kidney. A normal adult generally has sufficient thiosulfate stores to combine with 50 mg or one vial of nitroprusside. In the absence of renal dysfunction, the normal elimination half-life of thiocyanate is approximately 2.7 days.

Once all available methemoglobin is saturated and all stores of thiosulfate are depleted, free cyanide begins to accumulate in blood and tissues and binds the ferric moiety of cytochrome oxidase, inactivating it. Cytochrome oxidase is an essential enzyme in the oxidative phosphorylation process, forming adenosine triphosphate. With cytochrome oxidase inactivated, tissue anoxia, anaerobic metabolism, and lactic acid formation ensue. In addition, inactivation of oxidative phosphorylation, ordinarily an important buffer, leads to worsening metabolic acidosis.

Symptoms and signs of cyanide toxicity (Table 28-9) reflect central nervous system deterioration, cardiovascular instability, and alteration of oxygenation and pH. An early indication of impending toxicity is tachyphylaxis (i.e., requiring larger and larger doses of nitroprusside to maintain BP control). Acidosis often occurs late in the course of cyanide toxicity; its absence does not preclude cyanide accumulation and the development of toxicity. Cyanide levels should be followed to forewarn of subclinical toxicity, but waiting for results should not delay confirmation of the diagnosis (Table 28-10). If cyanide

Table 28–10. Cyanide Levels and Associated Symptoms

Level	Symptoms
<0.05 µg/mL	None
>0.15 µg/mL	Headache, palpitations, tachypnea
>0.25 µg/mL	Seizures, acidosis, coma
>0.3 µg/mL	Death

toxicity is suspected, the nitroprusside infusion should be stopped immediately. The patient should be placed on 100% oxygen even in the absence of signs of hypoxia and even if arterial partial pressure of oxygen is normal because tissue oxygenation may be inadequate.

Current dosing recommendations for nitroprusside are 0.25 to 10 µg/kg/min. The duration of infusion at the maximal rate should not exceed 10 minutes. Cyanide accumulation can occur if more than 1.5 mg/kg of nitroprusside is given over 3 to 4 hours, and potentially lethal toxicity can occur if 5 to 10 mg/kg/min of nitroprusside is given over 5 to 10 hours. However, individual differences do exist, and toxicity can occur very quickly, even when nitroprusside is dosed per recommendations. Malnutrition, stress, and volume depletion tend to deplete thiosulfate stores, accelerating the accumulation of cyanide.

In cases of nitroprusside toxicity, the Lilly Cyanide Antidote Kit (Eli Lilly, Indianapolis), which contains sodium nitrite, amyl nitrite, and thiosulfate, should be used. The sodium nitrite should be given first: one 10 mL vial of 3% sodium nitrite administered intravenously over 2 to 4 minutes. If intravenous access is not available, the amyl nitrite should be given orally. Both sodium nitrite and amyl nitrite induce methemoglobinemia, providing a source of iron to which the cyanide can bind. The thiosulfate (12.5 g vial given intravenously over 2 to 4 minutes) should be administered second. Thiosulfate acts as a sulfur donor, facilitating conversion of cyanide to thiocyanate. If symptoms of thiocyanate toxicity persist 2 hours after the initial dosing of thiosulfate, half of the original dose can be readministered.

Thiocyanate Toxicity

As discussed earlier, thiocyanate is formed from the binding of cyanide and thiosulfate. Thiocyanate is 100-fold less toxic than cyanide and is excreted by the kidney with an approximate elimination half-life of 2.7 days. Renal insufficiency prolongs elimination. Symptoms of thiocyanate toxicity are primarily neurologic. In persons with normal renal function, toxicity is unlikely before 9 days of nitroprusside infusion, whereas in persons with renal dysfunction, thiocyanate toxicity can occur as early as 3 days after initiation of infusion. Thiocyanate can be removed by dialysis, but this is rarely necessary.⁸⁶

Nitroglycerin

At low doses (5 µg/min), intravenous nitroglycerin predominantly dilates venous capacitance vessels, reducing venous return to the heart, whereas at higher doses both venous and arterial dilation occur. The overall hemodynamic effect of nitroglycerin is to decrease myocardial oxygen demand while increasing myocardial oxygen supply. Myocardial oxygen demand is decreased by decreasing preload and afterload, and myocardial oxygen supply is increased by improving myocardial perfusion

primarily through dilation of coronary arteries. BP is reduced as a consequence of arterial dilation.

Because of its favorable effects on myocardial oxygenation, intravenous nitroglycerin is the agent of choice for treatment of hypertensive crisis complicated by myocardial ischemia or infarction.⁸⁷ It can also be used as an alternative to nitroprusside to reduce afterload for treatment of pulmonary edema and postoperative hypertension.⁸⁸ Prolonged intravenous use of nitroglycerin can induce tolerance but is not associated with toxicity.⁸⁸ Nitroglycerin and nitroprusside are both effective in most patients with hypertensive emergency,⁸⁸ but nitroprusside appears to be more universally effective.⁸⁹ Therefore, in the setting of severe BP elevation, nitroprusside is the drug of choice for most hypertensive emergencies. Nitroglycerin tends to increase intracranial pressure, so it should not be used to treat hypertensive encephalopathy, stroke, or subarachnoid or intracerebral hemorrhage.

Labetalol

Labetalol is a nonselective β -antagonist with some α_1 -antagonist activity.⁹⁰ The ratio of β - to α -blockade is approximately 7:1. BP is reduced primarily through decreases in peripheral vascular resistance, whereas cardiac output is preserved and heart rate is maintained or slightly reduced owing to blockade of reflex tachycardia.

Labetalol is used preferentially in cases in which mixed adrenergic antagonism is desirable, including treatment of aortic dissection, and in situations of catecholamine excess, such as pheochromocytoma, rebound hypertension secondary to clonidine withdrawal, and crack cocaine overdose.⁹¹ Labetalol is also widely used as the primary alternative to nitroprusside for treatment of other types of hypertensive crisis. Because of its β -blocking properties, labetalol is contraindicated in patients with decompensated heart failure, reactive airway disease, and heart block.

Nicardipine

Nicardipine, a dihydropyridine calcium antagonist, has been approved for intravenous treatment of severe BP elevation.^{75,92} Intravenous nicardipine effectively lowers BP with minimal adverse effects, making it a reasonable first-line agent for most types of hypertensive crisis. It is particularly effective in treatment of postoperative hypertension.⁷⁵ By inhibiting the transmembrane influx of calcium ions, nicardipine facilitates the relaxation of cardiac and smooth muscle cells. The predominant effect is on arterial smooth muscle cells, causing reductions in systemic vascular resistance, afterload, and arterial BP. Cardiac output increases with little effect on left ventricular end-diastolic pressure. Nicardipine induces coronary artery dilation, thereby improving myocardial perfusion, but it also increases heart rate, thus tending to increase myocardial work and oxygen demand. Given this tendency and the overall worse outcome of patients receiving dihydropyridine calcium antagonists in the setting of acute myocardial infarction, it seems prudent to avoid the use of nicardipine to treat hypertensive crisis complicated by myocardial ischemia or infarction.

Phentolamine

Phentolamine is a competitive α -adrenergic receptor antagonist with greater affinity for the α_1 - than the α_2 -receptor subtype. Systemic vascular resistance is decreased, whereas heart rate,

cardiac output, and myocardial oxygen demand are increased during phentolamine administration.

Phentolamine is effective for treatment of severe hypertensive states associated with catecholamine excess, such as pheochromocytoma, clonidine withdrawal, and crack cocaine overdose. Adverse effects, including reflex tachycardia, fluid retention, and precipitous falls in BP, and its short duration of action, limit its use.⁷⁴ Because of associated increases in myocardial work and oxygen demand, phentolamine is contraindicated in situations of myocardial ischemia. A test dose of 0.5 to 1 mg infused over 1 minute is generally advised before starting a continuous infusion (see Table 28-3).⁷⁴

Esmolol

Esmolol is an intravenous ultra-short-acting β -adrenergic receptor antagonist that is used intraoperatively or postoperatively for short-term control of BP.⁹³ It should not be used in patients with second- or third-degree heart block, congestive heart failure, or a history of asthma. Esmolol selectively antagonizes the β_1 -adrenergic receptor. Like other β -blockers, it reduces heart rate and cardiac output through its negative inotropic properties without significantly affecting systemic vascular resistance.

Enalaprilat

Enalaprilat, an intravenous ACE inhibitor, is the active metabolite of orally administered enalapril.⁹⁴ Enalaprilat inhibits ACE, suppressing formation of angiotensin II, thus reducing systemic vascular resistance and arterial BP. As with other ACE inhibitors, the degree of BP reduction is directly related to circulating renin levels, such that persons with low renin levels may develop only minimal decreases in BP during enalapril treatment, whereas persons with high levels of renin, as in volume depletion secondary to diuretic treatment or dialysis, may experience precipitous hypotensive effects.⁹⁵ Intravenous enalaprilat is effective in conditions of severe hypertension complicated by high renin levels—in particular, scleroderma and other forms of renal vasculitis—but otherwise its efficacy is variable, precluding its general use in most hypertensive emergencies.

Hydralazine

Hydralazine is a direct arterial vasodilator that has little effect on venous capacitance, thus it preferentially relaxes arterial smooth muscle cells with little effect on veins. This reduces peripheral vascular resistance, afterload, and arterial BP with little or no change in preload or venous capacitance. The decrease in BP provokes a profound reflexive increase in sympathetic activity, causing reflex tachycardia and increased cardiac output, myocardial work, and myocardial oxygen demand. The increase in sympathetic activity also causes significant sodium and fluid retention, resulting in volume expansion.

The clinical use of hydralazine is limited by an associated reflexive increase in cardiac output and heart rate that increases myocardial oxygen demand, and by marked fluid retention. The only advantage of hydralazine is that it improves uterine blood flow and maintains fetal perfusion better than other antihypertensive agents and so is recommended for reduction of BP during preeclampsia or eclampsia.^{70-72,74} Hydralazine is specifically contraindicated in myocardial ischemia and aortic dissection because of its reflex increase in sympathetic nervous system

tone and myocardial inotropic activity. Hydralazine tends to increase intracranial pressure and should not be used to treat hypertensive crisis complicated by stroke or subarachnoid or intracerebral hemorrhage.

Fenoldopam

Fenoldopam is a selective dopamine-1 receptor agonist that effectively lowers BP while improving renal function.^{63,64,96} It provides selective vasodilation of renal, splanchnic, and coronary beds, and has specific benefits in patients with chronic kidney disease, providing short-term increases in natriuresis, diuresis, and creatinine clearance.^{64,65} Fenoldopam is approved for inpatient short-term management of severe hypertension. Headache, dizziness, reflex tachycardia, excessive hypotension, and flushing are reported side effects of fenoldopam.

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Acute Aortic Syndromes: Diagnosis and Management

Peter C. Spittell

CHAPTER 29

Introduction Acute Aortic Dissection

Penetrating Aortic Ulcer Aortic Intramural Hematoma

Introduction

Acute thoracic aortic syndromes comprise a spectrum of medical and surgical emergencies, including acute aortic dissection, penetrating aortic ulcer, and aortic intramural hematoma. All of these conditions are potentially life-threatening and warrant prompt diagnosis and emergent management. The clinical presentation of acute aortic syndromes is highly variable, ranging from occult disease to classic clinical presentations. Numerous etiologic factors, acting singly and in combination, have been identified. Diagnosis is possible by noninvasive imaging in the majority of patients, but in some patients complementary noninvasive tests (transesophageal echocardiography [TEE], computed tomography [CT], and magnetic resonance imaging [MRI]) are required for diagnosis. The management of acute aortic syndromes continues to be a therapeutic challenge, while diverse surgical and percutaneous strategies for the treatment of aortic syndromes are continuously evolving. As a result of increasing knowledge and better management strategies in this area, the outcomes of patients treated for acute aortic syndromes have improved. Therefore, awareness of the clinical features of acute aortic syndromes and familiarity with currently available diagnostic techniques is basic to their effective treatment.

Acute Aortic Dissection

Acute dissection of the thoracic aorta is one of the most common catastrophic aortic conditions encountered in clinical practice. The incidence of aortic dissection has been reported to be approximately 2.9/100,000/yr.¹ The variable clinical presentations of aortic dissection, in combination with a mortality rate in untreated cases as high as 1% per hour during the first 48 hours after the onset of symptoms, underscore the importance of a high index of suspicion and prompt diagnosis and therapy.²⁻⁴ Noninvasive testing (TEE, CT, and MRI) allows an accurate diagnosis to be made in the majority of patients.⁵ Effective treatment exists so that future improvements in initial and long-term survival in acute aortic dissection depend on increased clinical awareness, rapid noninvasive diagnosis, and the early institution of appropriate medical and/or surgical therapy.

Pathogenesis

Aortic dissection originates at the site of an intimal tear in more than 95% of patients.^{2,6} The resultant intimal tear exposes the media to pulsatile aortic flow, creating a second or “false” aortic

lumen that then dissects in the outer layer of aortic media, propagating distally and, occasionally, proximally. One feature differentiating proximal and distal aortic dissection is the greater frequency of hypertension in patients with distal dissection, a possible factor in pathogenesis.⁷

The primary intimal tear is located, in decreasing order of frequency, in the ascending aorta 1 to 5 cm above the right or left sinus of Valsalva (65%), in the proximal descending thoracic aorta just beyond the left subclavian artery origin (20%), in the transverse aortic arch (10%), and more distally in the thoracic aorta or abdominal aorta (5%).^{2,6}

Once initiated, the dissection usually extends distally and, occasionally, proximally for a variable distance. As the dissecting process encounters branches of the aorta it may pass around their origins, extend into their walls, or occlude them.^{2,6} Reentry of the dissection through a second, more distal intimal tear may occur, usually in one of the iliac arteries. External rupture of the dissecting process into the pericardial space is the most common cause of death in aortic dissection; congestive heart failure, usually due to aortic regurgitation, is the second most common cause of death.

Predisposing Factors

Multiple risk factors for aortic dissection have been identified, the most common being advanced age, systemic hypertension, congenital abnormalities of the aortic valve, and heritable disorders of connective tissue.

Aortic dissection most frequently affects patients in the fifth to seventh decades of life (mean age 63 years) and is more common in men (65.3% male).⁸ In patients younger than 40 years, the incidence between men and women is equal due to the occurrence of aortic dissection in women during pregnancy, with approximately 50% of all aortic dissections occurring during the third trimester of pregnancy.⁹

Systemic hypertension is the most frequently encountered predisposing factor for aortic dissection, being present in more than 70% of patients.^{2,3,10-12} Hypertension may play a role in initiating the intramural hematoma along with having a direct weakening effect on the aortic media.^{6,12} The causative role of systemic hypertension is further supported by the finding that coarctation of the aorta predisposes to aortic dissection.¹³

Other major risk factors for aortic dissection, especially proximal aortic dissection, are congenitally bicuspid or unicommissural aortic valves,^{10,12} and the congenital disorders of connective tissue such as Marfan syndrome¹⁴ and Ehlers-Danlos

syndrome. Additional predisposing factors for acute aortic dissection include pre existing aortic aneurysm¹⁵ and a positive family history (as many as 19% of patients).

Iatrogenic aortic dissection is an uncommon but potentially serious complication of invasive angiographic procedures and cardiac surgery. Angiographic procedures such as coronary angiography, percutaneous transluminal coronary angioplasty, intra-aortic balloon insertion, and translumbar aortography have been complicated by aortic dissection.^{12,16-19} Catheter-induced dissection can originate at any location, and it is most common in the sinus of Valsalva, brachiocephalic arteries, descending thoracic aorta, abdominal aorta, and iliac or femoral arteries. The majority of catheter-induced dissections are retrograde dissections and tend to decrease in size over time due to thrombosis of the false lumen, whereas anterograde dissections tend to persist on follow-up. Nearly all iatrogenic aortic dissections can be treated medically with serial clinical examinations and noninvasive testing used to identify those in need of surgical therapy.¹⁷

Cardiac surgical procedures complicated by aortic dissection include those that require cross-clamp or cannulation of the ascending aorta, such as aortic valve replacement^{12,20,21,15} and/or coronary artery bypass grafting.^{12,22,23} Dissection can arise at the site of ascending aortic cannulation, aortosaphenous vein anastomosis, aortic cross-clamp, or as a result of direct arterial injury. Dissection in association with these procedures usually occurs intraoperatively and is promptly diagnosed and treated, but chronic dissection in the postoperative period has been reported.²¹

Aortic dissection has also been reported in association with inflammatory diseases (giant cell aortitis,^{12,24} Takayasu aortitis, rheumatoid arthritis, syphilitic aortitis, systemic lupus erythematosus,²⁵ Noonan syndrome,²⁶ Turner syndrome,²⁷ fibromuscular dysplasia,¹¹ annuloaortic ectasia,¹¹ aortic coarctation, cocaine use,^{28,29} methamphetamine use, polycystic kidney disease,³⁰ polyarteritis nodosa,³¹ trauma,³² high-intensity weight lifting.³³

Classification

There are two different anatomic systems—the DeBakey and Daily (Stanford) systems—used to classify aortic dissection. The DeBakey system³⁴ is based on the site of origin of the dissection and recognizes three types of dissection (Fig. 29-1): type I—the dissection arises in the ascending aorta and extends distally; type II—the dissection is limited to the ascending aorta; and type III—the dissection arises at or just distal to the origin of the left subclavian artery and extends distally or, rarely, retrogradely into the arch of the ascending aorta.

For clinical purposes, because types I and II have a similar prognosis, aortic dissection can be broadly divided into those with the tear in the ascending aorta and those with the tear in the descending aorta, also called “proximal” and “distal,” respectively.³⁵ A similar classification system, proposed by Daily and associates,³⁶ designates all dissections involving the ascending aorta as type A, regardless of the site of the primary intimal tear. All other dissections are designated type B.

An important aspect of classification is the duration of the dissection at the time of first presentation. Dissections are categorized as “acute” if the diagnosis is made within 2 weeks of symptom onset and as “chronic” if more than 2 weeks have elapsed. The distinction is important due to the fact that

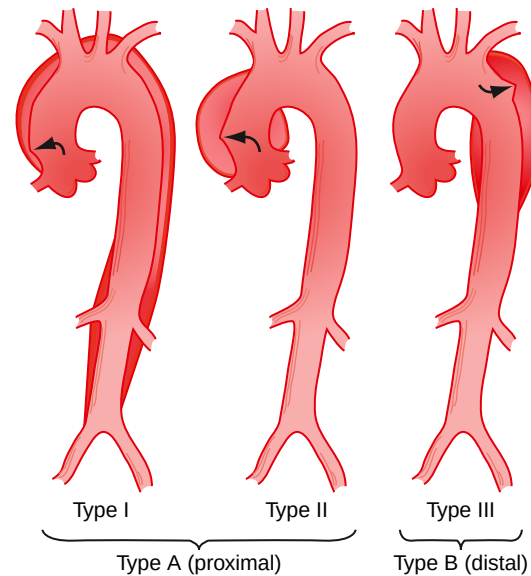


Figure 29-1. Classification of aortic dissection. Type I refers to a primary tear in the ascending aorta and dissection involving the aortic arch and descending thoracic aorta for a variable distance. Type II refers to dissection involving only the ascending aorta. Type III refers to a primary tear distal to the subclavian artery origin, extending distally for a variable distance. (Modified from DeBakey ME, Henly WS, Cooley DA, et al: *Surgical management of dissecting aneurysms of the aorta*. *J Thorac Cardiovasc Surg* 1965;49:130-149.)

approximately 65% to 75% of patients with untreated aortic dissection die in the first 2 weeks after the onset of symptoms.²

Intimal tear without hematoma is an uncommon variant of aortic dissection characterized by a localized intimal tear exposing the underlying media or adventitial layers to pulsatile aortic flow. There is no progression or separation of the medial layers.³⁷

Clinical Features

Due to variable involvement of the aorta and its branches by the dissecting process, the patient with acute aortic dissection may have clinical manifestations of ischemia of various organ systems, singly or in combination, and symptoms and signs of cardiac disease. The diverse presentations of aortic dissection can provide for difficult diagnosis, and misdiagnosis commonly occurs.^{2,12} Despite major advances in the noninvasive diagnosis of aortic dissection and in medical and surgical therapy, up to 55% of patients in reported series die without a correct antemortem diagnosis.^{1,2,12,38,39} For these reasons, a high index of clinical suspicion for acute aortic dissection in any likely setting is imperative.

The classic presentation of a patient with acute aortic dissection, occurring in more than 70% of patients, is the sudden onset of severe pain, usually beginning in the anterior chest, radiating to the back, and moving distally as the dissection progresses.^{1,35} The pain is most commonly described as sudden in onset with a “ripping,” “tearing,” or “stabbing” quality; this is in contrast to the crescendo nature of the discomfort of acute myocardial infarction. Chest pain is significantly more common in patients with proximal (type A, type I, and type II) dissection (79% versus 63% in distal [type B, type III] dissection). In contrast, both back pain (64% versus 47%) and abdominal pain (43% versus 22%) are significantly more common with distal (type B) aortic dissection.⁸

Patients with acute aortic dissection often appear to be in shock, although blood pressure is elevated in one half to two thirds of cases, especially with distal dissection.⁸ Hypotension in aortic dissection is usually attributable to rupture of the dissection into the pericardial space with resultant cardiac tamponade or, less commonly, the pleural space or mediastinum and is more common with proximal dissection.

It should be remembered, however, that painless dissection occurs in 14% to 21% of patients.^{2,12,40} Patients with painless aortic dissection tend to be slightly older, have a prior history of diabetes, aortic aneurysm, or prior cardiac surgery, and more often have type A dissection. Syncope, congestive heart failure, or stroke are also more common in this group. Importantly, in-hospital mortality was significantly higher than for patients having pain (33% versus 23%).⁸

A cardiac murmur may be present, usually at the cardiac base, and may be systolic, diastolic, or both. A diastolic decrescendo murmur of aortic regurgitation indicates involvement of the ascending aorta and is heard in one half to two thirds of patients with type A aortic dissection.⁸ Congestive heart failure, when present in association with proximal aortic dissection, is most often due to severe aortic regurgitation,^{10,35} but cases of congestive heart failure due to rupture of the dissecting process into the right or left atrium or right ventricle have also been reported.⁴¹⁻⁴³ Myocardial infarction, most commonly inferior infarction, occurs in 1% to 2% of patients and is due to compromise of the coronary ostium by a hematoma or intimal flap. Peripheral pulse deficits are noted in 19% to 30% of patients,^{3,8,35} more commonly with proximal aortic dissection, and is associated with a higher rate of in-hospital complications and mortality.⁴⁴ Pulse deficits may be transitory due to oscillation of the intimal flap or distal reentry of the hematoma into the true lumen. Acute lower extremity ischemia, with or without chest pain, as a result of dissection extending into the iliac arteries occurs in 6% to 12% of patients,^{3,45,46} and may provide an important clue to the diagnosis.⁴⁵ Other cardiovascular findings include a difference in systolic blood pressure between the arms (>20 mm Hg), tachycardia, friction rubs, bruits, pulsus paradoxus, and cardiac tamponade.

Syncope in a patient with aortic dissection is an important event as it is associated with a worse prognosis. Syncope most commonly results from rupture of the dissecting process into the pericardial space producing cardiac tamponade.^{12,35} Less commonly, rupture occurs into the left pleural space producing a left hemothorax.¹² Neurologic deficits, including cerebrovascular accident, disturbances of consciousness, ischemic paraparesis, and ischemic peripheral neuropathy, occur in more than 40% of patients, more commonly with proximal aortic dissection.^{1,47}

Other less frequent findings that occur in association with acute aortic dissection include Horner syndrome, a pulsatile sternoclavicular joint,⁴⁸ vocal cord paralysis, hemoptysis,⁴⁹ superior vena cava syndrome,⁵⁰ upper airway obstruction,⁵¹ hematemesis,⁵² pleural effusion, unilateral pulmonary edema,⁵³ signs of mesenteric or renal infarction, fever,⁵⁴ and deep venous thrombosis.¹²

As a general rule, aortic dissection should always be considered in the differential diagnosis of a patient with unexplained syncope, stroke, congestive heart failure, acute arterial occlusion, or an abnormal aortic contour on chest radiography, even in the absence of chest pain.

Diagnosis

Aortic dissection is usually suspected from the initial history and physical examination. The majority of patients with aortic dissection can be identified based upon some combination of three clinical factors: (1) sudden onset of chest or abdominal pain with a sharp, tearing, and/or ripping character; (2) mediastinal and/or aortic widening on chest radiograph; (3) a pulse variation (absence of a proximal extremity or carotid pulse) and/or blood pressure (>20 mm Hg difference between the arms).⁵⁵ The incidence of aortic dissection was 83% when a pulse or blood pressure differential or any combination of the three variables occurred.

Routine laboratory studies are nonspecific and play a minor role in the initial assessment of patients with suspected acute aortic dissection. Their main value lies in the exclusion of other diseases. A mild to moderate leukocytosis occurs in two thirds of patients, and anemia may occur as a result of leakage of the dissection or from sequestration of blood in the false lumen. Serum lactate dehydrogenase and bilirubin levels are sometimes increased because of blood sequestered within the false lumen, but serum glutamic oxaloacetic transaminase and creatine phosphokinase are usually normal.³⁵ Hematologic studies consistent with disseminated intravascular coagulation can also occur. In one small study, D-dimer was positive in all patients with proximal aortic dissection, suggesting a negative test makes the presence of disease unlikely.⁵⁶

The most common electrocardiographic abnormality in patients with aortic dissection is left ventricular hypertrophy from chronic systemic hypertension.³ Acute electrocardiographic changes occur in up to 55% of patients and include ST segment depression, T-wave changes, and ST segment elevation, in decreasing order of frequency.⁵⁷ Acute ischemic changes can occur when one or both coronary ostia become obstructed, either by the intimal flap or from external compression by the dissecting hematoma. The electrocardiographic changes of acute pericarditis may be seen if there has been leakage of blood into the pericardial space. Heart block resulting from proximal extension of the hematoma into the area of the atrioventricular node has also been reported.⁵⁸ The chief value of the electrocardiogram is in distinguishing aortic dissection from acute myocardial infarction, although the two conditions can coexist.

Chest radiography may be helpful in suggesting the diagnosis of aortic, with abnormalities of the aortic dissection silhouette being the most common finding.^{8,59} Additional findings include pleural effusion, mediastinal widening, displacement of intimal calcification greater than 6 mm inside the outer edge of the aortic shadow, and the radiographic findings of congestive heart failure (Fig. 29-2). Nonetheless, it is important to remember that normal chest radiographic findings (present in 11% to 16% of patients) do not exclude the diagnosis of aortic dissection.⁸

Currently available noninvasive imaging modalities that are accurate in the diagnosis of acute aortic dissection include echocardiography (combined transthoracic echocardiography [TTE] and TEE), CT, and MRI. The choice of test depends on which imaging modality is most readily available at a particular institution and the hemodynamic stability of the patient. Most patients have multiple imaging studies performed; in the initial IRAD review, the initial study performed was CT in 61%, echocardiography in 33%, aortography in 4%, and MRI in only 2%.⁸

TTE can be very useful in some patients with suspected aortic dissection (Fig. 29-3). When the findings of a dilated aortic root

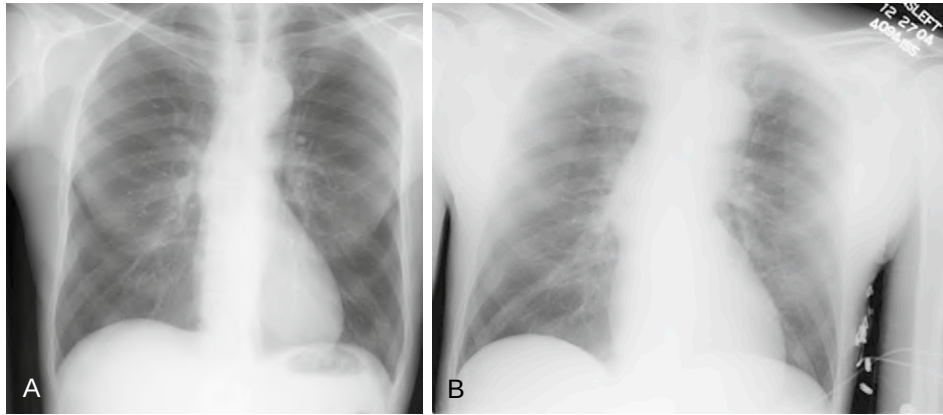


Figure 29-2. Chest radiographs in a patient with aortic dissection. **A**, Baseline anteroposterior chest radiograph before presentation with aortic dissection. **B**, Chest radiograph 1 year later when the patient presented with acute aortic dissection. Note the increased diameter of the ascending aorta and aortic arch and new widening of the superior mediastinum.

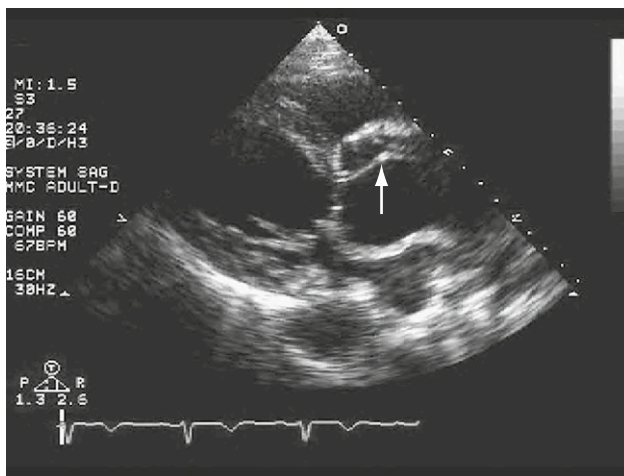


Figure 29-3. Transthoracic echocardiogram (left parasternal long-axis view) shows severe dilation of the ascending aorta and an intimal flap originating in the right coronary sinus of Valsalva (arrow).

(end-diastolic diameter >42 mm), widening of the aortic walls (16 to 20 mm for the anterior wall and 10 to 13 mm for the posterior wall), and a linear undulating echo representing the intimal flap are present, the positive predictive value for TTE is 100%.⁶⁰⁻⁶² Advantages of TTE are its portability, rapid “online” diagnosis, and ability to identify associated aortic regurgitation and other valvular disease, and to assess left ventricular function, regional wall motion abnormalities, pericardial effusion, and cardiac tamponade. The diagnosis of cardiac tamponade in a patient suspected of having aortic dissection deserves special mention. Echocardiographically guided pericardiocentesis should be avoided in this setting because the rapid withdrawal of pericardial fluid can result in a prompt improvement in left ventricular systolic function, left ventricular dp/dt , and systolic blood pressure, producing aortic rupture.^{63,64} The patient with aortic dissection complicated by cardiac tamponade should be taken emergently to surgery for institution of cardiopulmonary bypass followed by evacuation of blood from the pericardial space. Disadvantages of TTE limiting its utility in the diagnosis

of aortic dissection include difficulty in adequately visualizing the descending thoracic aorta,⁵ and in patients with suboptimal echocardiographic “windows” due to obesity or chronic obstructive pulmonary disease. Overall, the sensitivity and specificity of TTE are inferior to TEE, CT, and MRI in the diagnosis of aortic dissection.⁶

Multiplane TEE, in combination with TTE, has a sensitivity of 99% and a specificity of 98% in the diagnosis of aortic dissection.⁶⁵ TEE is portable, minimally invasive, and can accurately determine the type and extent of dissection safely in an emergent setting, allowing rapid triage of patients to either surgical or medical therapy^{66,67} (Fig. 29-4). Color flow Doppler imaging significantly improves the sensitivity of TEE by allowing visualization of the intimal flap, dissection entry site, the true and false lumens, the presence of thrombus, associated aortic regurgitation, and the proximal coronary arteries⁶⁷ (see Fig. 29-2). In addition, multiplane TEE provides a comprehensive assessment of left ventricular systolic function, regional wall motion, pericardial effusion, and cardiac tamponade. The overall sensitivity of TEE is comparable with CT,⁶⁸ MRI,^{5,69,70,71} and aortography⁷² in the diagnosis of aortic dissection. Current multiplane TEE probes have largely overcome impediments in the ascending aorta having monoplane and biplane transducers, although artifacts in this region continue to be a diagnostic challenge.

CT with intravenous iodinated contrast enhancement is also an accurate noninvasive screening test in patients with suspected aortic dissection.⁷³ Advantages of CT include ready availability at most hospitals, even on an emergency basis, and improved accuracy with spiral (helical) CT and with electron beam (ultrafast) or multidetector (multislice) CT.⁷⁴ CT can reliably demonstrate the intimal flap, pericardial and pleural effusion, associated mediastinal hemorrhage, and involvement of the aortic arch vessels and branches of the abdominal aorta⁵ (Fig. 29-5). Disadvantages of CT include the need for iodinated contrast exposure and nonportability, limiting its use in patients with significant renal insufficiency and in hemodynamically unstable patients, respectively. In addition, the site of entry is rarely identified.

Although less commonly used,⁸ MRI is a highly accurate noninvasive technique in the evaluation of patients with suspected aortic dissection.⁷⁵ MRI is superior to TEE and CT in detecting

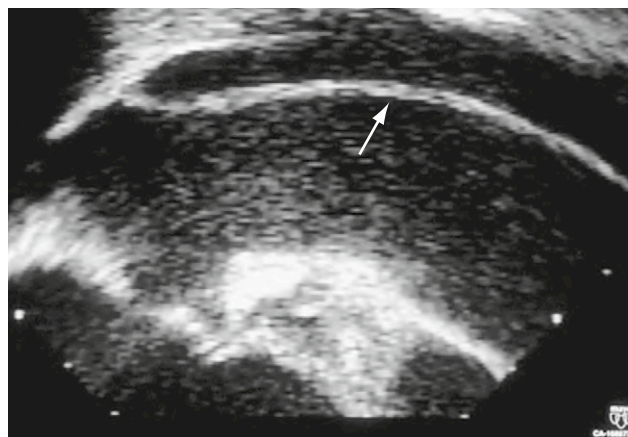


Figure 29-4. Transesophageal echocardiogram (125 degrees longitudinal plane) shows an intimal flap (*arrow*) in a markedly dilated ascending aorta.

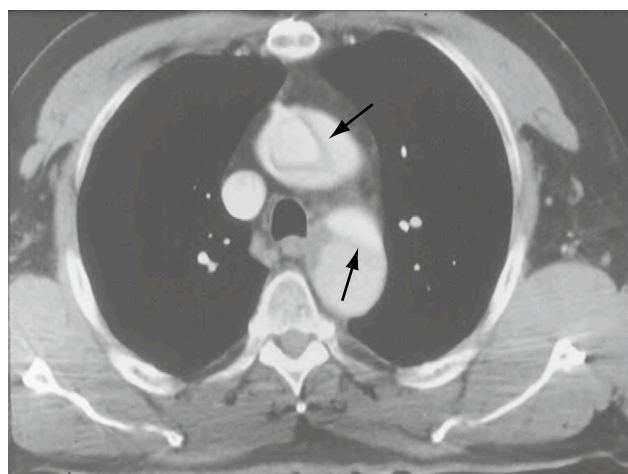


Figure 29-5. CT scan in a patient with type A aortic dissection. Note the complex intimal flap seen within the distal ascending aorta and descending thoracic aorta (*arrows*), and differential opacification of the true and false lumens.

arch vessel involvement and in identifying the anastomosis in patients managed with surgical therapy and may facilitate comparison of serial studies.^{5,69,76} Gated spin-echo MRI accurately demonstrates the entry site and intimal flap,⁷⁷ and may be the optimal method for demonstrating thrombus formation and entry site location within all segments of the aorta⁷⁸ (Fig. 29-6). The ability to obtain oblique and longitudinal planes of section makes MRI especially valuable in demonstrating dissection without intimal tear.^{5,70,79} Disadvantages of MRI include cost, examination time, reduced availability, and standard contraindications to MRI. The most important limitation of MRI in acute aortic dissection is its nonportability, limiting its use in hemodynamically unstable patients.

Of the definitive noninvasive imaging modalities in suspected acute aortic dissection (TEE, CT, MRI), a systematic review of the diagnostic accuracy of these imaging techniques has demonstrated a pooled sensitivity (98% to 100%) and specificity (95% to 98%) that is comparable between the three imaging techniques.⁷¹



Figure 29-6. MRI in the sagittal plane shows type A aortic dissection with an intimal flap extending into the distal abdominal aorta (*arrow*).

Aortography, the traditional definitive diagnostic method in aortic dissection, is able to localize the site of origin of the dissection, delineate the extent of the dissection, and the circulation to vital organs. Diagnostic aortographic features include opacification of the false lumen, deformity of the true lumen by the false lumen, widening of the aorta, narrowing or occlusion of branches of the aorta, and the presence of an intimal flap⁸⁰ (Fig. 29-7). Disadvantages of aortography include nonportability, invasive technique, exposure to ionizing radiation, the use of intravenous iodinated contrast agents, and an inherent delay in diagnosis. False-negative aortogram results can occur if there is simultaneous and equal opacification of the true and false lumina or if the false channel is very faintly opacified.⁸¹ For these reasons, aortography has generally been replaced by noninvasive imaging tests in the diagnosis of acute aortic dissection. Intravascular ultrasound, in combination with standard aortographic technique, greatly improves the accuracy of aortography, can be performed rapidly and safely, and could serve as an accessory diagnostic procedure in selected patients with suspected aortic dissection.^{82,83}

In view of the increased early mortality of untreated acute aortic dissection, the screening test chosen depends on which test is most readily available at a particular institution and the patient's hemodynamic status. Noninvasive diagnosis of acute dissection by TEE, CT, or MRI, if readily available, is preferred as it avoids the risks and delays inherent in invasive angiography.⁸⁴

Management

Treatment for acute aortic dissection is initiated when the diagnosis is first suspected clinically. After the patient is stabilized, the diagnosis is pursued with definitive noninvasive imaging (Fig. 29-8).

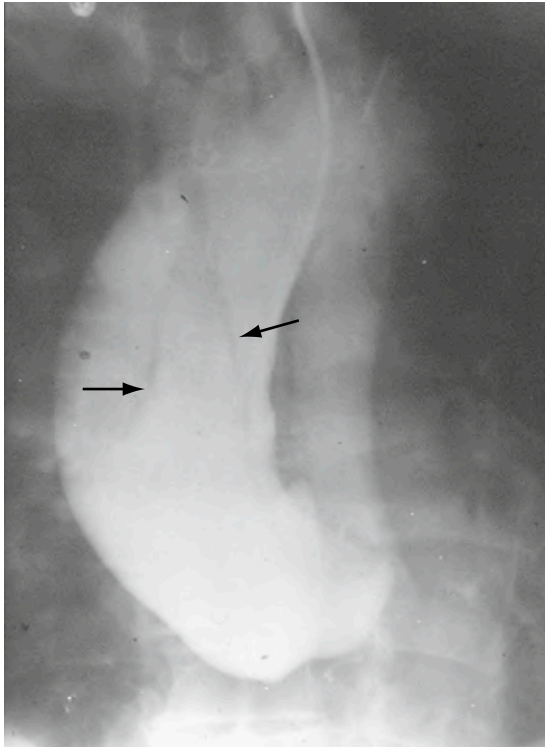


Figure 29-7. Aortogram shows a spiraling intimal flap (arrows) in the ascending aorta and aneurysmal dilation of the ascending aorta.

The initial treatment objectives in suspected aortic dissection are to control pain, reduce systemic blood pressure, and lower the rate of change of pressure development (dP/dT) to the lowest level compatible with maintenance of adequate visceral, renal, and cerebral perfusion.⁸⁵ In hypertensive patients, treatment consists of an intravenous (IV) β -adrenergic blocking agent, often in combination with IV sodium nitroprusside. Beta-blockade before nitroprusside therapy is essential because the latter increases the velocity of left ventricular ejection, increases aortic shear stress, and may promote propagation of the dissection.⁸⁶ Intravenous labetalol in place of a β -blocker and sodium nitroprusside is an alternative, but it has the potential for hepatotoxicity with long-term therapy.⁸⁷ In normotensive patients, an intravenous (IV) β -adrenergic blocking agent may be used alone. Intravenous verapamil or diltiazem are an alternative in patients who cannot tolerate beta-blockers. To assist in monitoring blood pressure and renal perfusion, an intra-arterial cannula and in dwelling bladder catheter are advisable. Following initial patient stabilization, noninvasive diagnosis is pursued (as discussed in the previous section). If the patient continues to require close monitoring and support, an emergency bedside TEE is the test of choice.

Patients with acute type A (type I and II) aortic dissection should undergo emergent surgical repair.^{88,89} Coronary angiography before surgery is not indicated because it does not improve survival and it results in a delay to surgical intervention.⁹⁰⁻⁹² Resection of the ascending aorta and replacement with Dacron is the usual procedure in type I or type II aortic dissection.^{88,89} The objectives of surgery include excision of the intimal tear, obliteration of the entrance into the false lumen, repair of

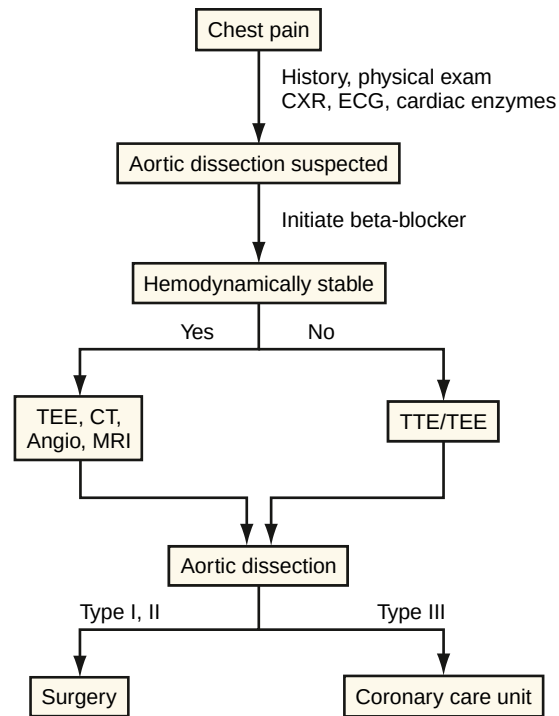


Figure 29-8. Algorithm for initial management of suspected acute aortic dissection. Angio, angiography; CXR, chest radiography; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

aortic regurgitation (if present), and restoration of patency to any major arteries occluded by the dissection. With associated aortic regurgitation, resuspension of the valve, if possible, is preferred. Intraoperative TEE can define the severity and mechanisms of aortic regurgitation and can assist the surgeon in identifying patients in whom valve repair is likely to be successful.⁹³ If there is associated annuloaortic ectasia or destruction of the aortic wall, a valved conduit may be used. The coronary arteries are reimplanted, or if they are involved by the dissection, they are reattached using vein bypass grafts anastomosed proximally to the aortic graft and distally to the uninvolved coronary arteries.^{89,94,95} If compromise of a branch of the aorta supplying a vital organ is present and is not relieved by closing the false channel, then direct repair or surgical replacement of that branch is indicated. Aortic fenestration may be indicated in patients with severe organ or limb ischemia complicating either acute or chronic aortic dissection. Fenestration, either surgical and percutaneous techniques, can effectively relieve the ischemia and can be performed safely in chronic aortic dissection.^{96,97} Operative mortality for ascending aortic dissections at experienced centers varies from 7% to 36%, which is well below the more than 50% mortality with medical therapy.^{8,58,98,99} In-hospital mortality is approximately 14% to 27%, patients with cardiogenic shock and those requiring concomitant coronary artery bypass grafting being the highest risk subgroup.^{98,99}

With acute type B (type III) aortic dissection, urgent surgical intervention is reserved for patients who have a complicated course (rupture, acute expansion or impending rupture, or vascular occlusion).¹⁰⁰ Independent predictors of surgical mortality include those 70 and older, and hypotension or stroke

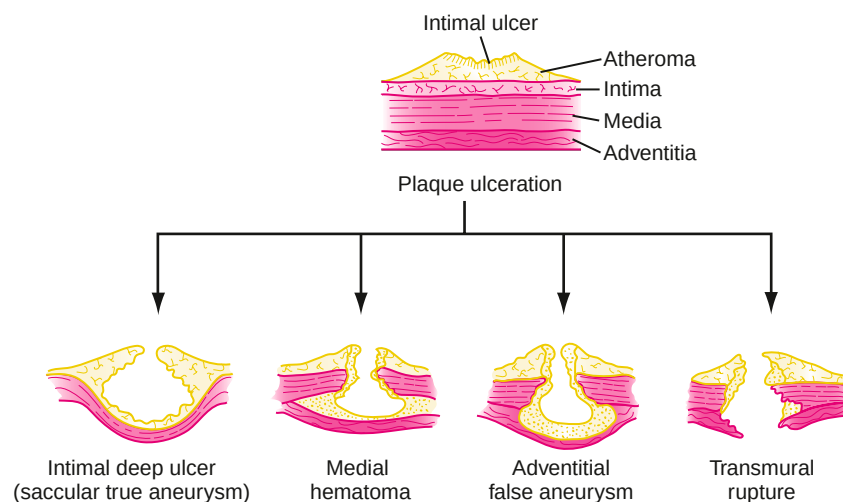


Figure 29-9. Pathologic consequences of penetrating atherosclerotic ulcer of the aorta. Atheromatous ulceration that burrows deeply into an atheroma can result in one of four potential outcomes (*from left to right*): true saccular aneurysm, medial hematoma, adventitial false aneurysm, or transmural rupture. An intramural (medial) hematoma is the most commonly observed consequence of a penetrating aortic ulcer.

on admission.¹⁰¹ The best treatment for uncomplicated type III aortic dissection is less well-defined, but the majority of patients are best treated with medical therapy.¹⁰² Overall in-hospital mortality for these patients is approximately 10%.¹⁰³ Long-term medical therapy focuses on control of blood pressure, using a beta-blocker if possible, and periodic evaluation for evidence of any progression of dissection, patency of the false lumen, progression of aortic diameter to greater than 5 cm, or development of saccular aneurysm.¹⁰⁴⁻¹⁰⁶ The reported long-term survival rate with medical therapy is approximately 60% to 80% at 4 to 5 years and approximately 40% to 45% at 10 years.¹⁰³ Survival is best in patients with noncommunicating and retrograde dissections. The proximal descending thoracic aorta is the major site of aneurysm development and an enlarged false lumen in this region predicts poor outcome and subsequent aneurysm development.¹⁰⁷ Furthermore, partial false lumen thrombosis (34% of patients) predicts a significantly worse 3-year mortality rate.¹⁰⁸ An alternate approach is 2 to 3 weeks of pharmacologic therapy followed by surgical repair if the dissection becomes stable and the patient's general condition does not contraindicate surgery.^{109,110} Transluminal placement of an endovascular stent-graft device in type III aortic dissection is being successfully performed with increasing frequency and will likely provide an alternative to surgery in highly selected patients in the future.¹¹¹⁻¹¹³

Postoperatively, continuation of a beta-blockade, if possible, is essential, as hypertension and left ventricular ejection velocity play an important role in the recurrence of aortic dissection. Following hospital dismissal, emphasis is placed on adequate blood pressure control, avoidance of strenuous physical activity, and serial clinical evaluations. Noninvasive testing is performed at periodic intervals to detect the development of an anastomotic aneurysm or saccular aneurysm, extension of the dissection, patency of the false lumen, or progressive aortic dilation.^{114,115} Initial follow-up noninvasive imaging at 3, 6, and 12 months is warranted. Subsequent follow-up is performed every 1 to 2 years if there is no evidence of disease progression. MRI is generally preferred for follow-up (a baseline MRI before hospital discharge should be performed).

Penetrating Aortic Ulcer

Penetrating aortic ulcer shares several clinical features with aortic dissection, especially type III aortic dissection, but the absence of certain clinical signs favors a diagnosis of penetrating aortic ulcer. Results of noninvasive imaging studies are usually distinctive, allowing differentiation of penetrating aortic ulcer from typical aortic dissection.^{116,117} Differentiation between the two disorders is important in view of the fact that the natural history of penetrating aortic ulcer is less well-defined; therefore, treatment may differ from that currently used for classic aortic dissection.^{116,117}

Pathogenesis

Penetrating aortic ulcer refers to an atherosclerotic lesion of the thoracic aorta that undergoes ulceration, which penetrates the internal elastic lamina of the thoracic aorta, resulting in formation of one of the following: intramural hematoma within the media of the aortic wall, a true saccular aneurysm, a pseudoaneurysm, or transmural aortic rupture¹¹⁸ (Fig. 29-9).

Predisposing Factors

Risk factors for penetrating aortic ulcer are similar to those for aortic dissection, the most common being advanced age, chronic systemic hypertension, and evidence of advanced atherosclerotic disease.¹¹⁹ In contrast to aortic dissection, men and women are equally affected. Long-standing hypertension is present in the majority of patients and likely contributes to the advanced atherosclerotic disease that is universally evident. More than one half of the patients with penetrating aortic ulcer have advanced atherosclerotic disease in other locations, including coronary artery disease, peripheral arterial occlusive disease, and cerebrovascular disease. An increased association of penetrating aortic ulcer and abdominal aortic aneurysm, and aneurysms in other locations, has also been reported.^{118,120}

Clinical Features

The clinical presentation of penetrating aortic ulcer and acute aortic dissection are similar, the most common presentation being an elderly patient with systemic hypertension and

the sudden onset of severe pain in the chest, back, and, less commonly, epigastrium. Unlike aortic dissection, the pain is rarely migratory. Since the most common site of penetrating aortic ulcer is in the descending thoracic aorta, a murmur of aortic regurgitation, pericardial friction rub, and peripheral pulse deficits are not seen. In addition, visceral vessel involvement has not been reported. Neurologic deficits are very rare, but acute lower-extremity paraplegia has been reported.¹¹⁸ In a patient with a history compatible with aortic dissection, it is the *absence* of physical findings that suggests the diagnosis of penetrating aortic ulcer. Asymptomatic penetrating aortic ulcer does occur and is usually incidentally discovered as enlargement of the descending thoracic aorta or a hilar mass on routine chest radiography or on CT done for another indication.^{118,120}

Laboratory Findings

Routine laboratory studies are nonspecific with penetrating aortic ulcer. The chest roentgenogram is the most helpful of the routine laboratory tests because it is often abnormal. It may demonstrate mediastinal widening, focal or diffuse enlargement of the descending thoracic aorta, a hilar mass, left apical mass, bilateral pleural effusion, or isolated left pleural effusion.^{116,117} However, normal chest radiographic findings do not exclude penetrating aortic ulcer. The most common electrocardiographic abnormality is left ventricular hypertrophy from chronic systemic hypertension.

Diagnosis

The findings on CT, MRI, TEE, and aortography in patients with penetrating aortic ulcer are characteristic, allowing for differentiation of penetrating aortic ulcer from classic aortic

dissection. In contrast to aortic dissection, an undulating flap or false lumen are not present and TEE will usually demonstrate significant, often advanced atherosclerotic disease of the aorta, most commonly the descending thoracic aorta. An echolucent intramural hematoma with overlying advanced atherosclerotic disease is the most common TEE finding in patients with acute penetrating aortic ulcer. A careful evaluation may demonstrate a crater-like ulceration with surrounding atheroma. When the intramural hematoma undergoes thrombosis it becomes echogenic, creating the appearance of an increase in aortic wall thickness. The intramural hematoma may extend proximally or distally for a variable distance from the entry site. Additional findings in patients with penetrating aortic ulcer may be an aortic pseudoaneurysm or saccular aneurysm. Using CT, penetrating atherosclerotic ulcer manifests as focal involvement with adjacent subintimal hematoma and is often associated with aortic wall thickening or enhancement. Magnetic resonance imaging is superior to conventional CT in differentiating acute intramural hematoma from atherosclerotic plaque and chronic intraluminal thrombus and allows unenhanced multiplanar imaging (Fig. 29-10). Spiral CT involves shorter examination times and allows high-quality two- and three-dimensional image reconstruction. CT angiography can demonstrate complex spatial relationships, mural abnormalities, and extraluminal pathologic conditions. It should be noted that penetrating aortic ulcer is strongly associated with abdominal aortic aneurysm, which is seen concomitantly in 42% of patients; therefore imaging of the abdominal aorta should be included in the initial evaluation.¹¹⁹

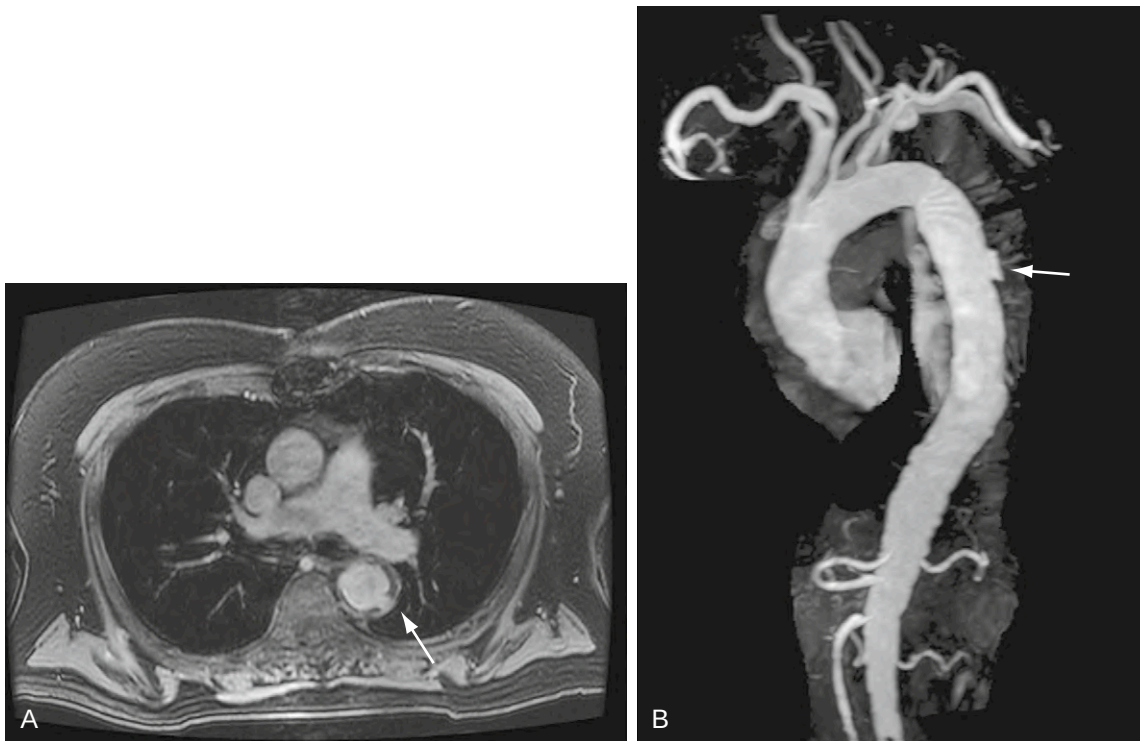


Figure 29-10. MRI in a patient with multiple penetrating aortic ulcers. **A**, Transverse imaging plane shows a penetrating aortic ulcer in the proximal descending thoracic aorta (arrow). **B**, MR angiogram with gadolinium enhancement shows severe atherosclerotic changes of the descending thoracic aorta and a penetrating aortic ulcer in the proximal descending thoracic aorta (arrow).

Management

The optimal treatment for penetrating aortic ulcer is not well-defined. Treatment is individualized as the natural history of penetrating aortic ulcer and indications for surgery are evolving. Although careful follow-up is necessary, many penetrating aortic ulcers involving the descending thoracic aorta can be managed nonoperatively in the acute setting. The natural history of an intramural hematoma involving the descending thoracic aorta has been shown by serial noninvasive imaging studies to follow a course of resorption of the hematoma and compensatory aortic dilation in the region of the involved aorta in 85% of patients over 1 year.^{117,118} Patients with an intramural hematoma should be treated medically initially, with special emphasis placed on control of blood pressure, preferably with a β -adrenergic blocking agent.¹²⁰ Ascending aortic involvement, progressive aortic dilation, persistent symptoms, or difficult to control hypertension are indications for surgery. When saccular or pseudoaneurysm is the result of a penetrating atherosclerotic ulcer of the aorta, surgery is also recommended. Thoracic endograft technology is being applied to patients with penetrating aortic ulcer involving the descending thoracic aorta with high procedural success and a low perioperative morbidity and mortality.¹²²⁻¹²⁵

Aortic Intramural Hematoma

Aortic intramural hematoma (IMH) is an acute, potentially lethal disorder that is similar to but pathologically distinct from acute aortic dissection. Although hemorrhage into the aortic media occurs in both disorders, an intimal tear with resultant false lumen is not present in IMH. The prevalence of IMH among patients with acute aortic syndromes has been reported to be 5.7%.¹²⁶ The clinical presentation and noninvasive diagnosis of IMH are similar to aortic dissection, as are the classification scheme and general principles of management.

Pathogenesis

Although hemorrhage into the aortic media occurs in both acute aortic dissection and IMH, an intimal tear with resultant false lumen is not present in IMH. Instead, hemorrhage occurs within the aortic wall either because of rupture of the vasa vasorum or, less commonly, because of an atherosclerotic penetrating aortic ulcer.¹²⁷ IMH evolves very dynamically in the short term to regression, dissection, or aortic rupture.¹²⁸ The most frequent long-term outcome of IMH is the development of aortic aneurysm or pseudoaneurysm. Lesions of the ascending aorta appear to represent the early stage of a classic dissection in some patients.¹²⁹ Complete regression without changes in aortic size is observed in one third of cases, and progression to classical dissection is less common. A normal aortic diameter in the acute phase is the best predictor of IMH regression without complications, and absence of echolucent areas and atherosclerotic ulcerated plaque are associated with evolution to aortic aneurysm.¹²⁸ IMH is most often associated with long-standing hypertension (50% to 84% of patients), but has also been reported in association with trauma (e.g., auto accident or iatrogenic) in 6% of cases in a meta-analysis.^{126,130,131}

Classification

The classification scheme for IMH is the same as is used for classic aortic dissection (please see section on aortic dissection above). Patients with IMH are more likely to have type B

lesions than in those with classic aortic dissection (e.g., 60% versus 35%).¹²⁶

Clinical Features

Clinically, patients with acute IMH have a similar presentation to those with acute aortic dissection. Sudden, severe chest and/or back pain, as occur in classic aortic dissection, are common in IMH.¹³⁰ Although not specific, anterior chest pain is more common with ascending (type A) lesions, whereas interscapular back pain is more common with descending (type B) lesions.¹³² In contrast to aortic dissection, manifestations associated with aortic branch vessel disease (e.g., myocardial infarction, stroke, aortic regurgitation, visceral vessel compromise, and paraplegia) are relatively uncommon with type A IMH.

Diagnosis

The noninvasive imaging methods used to diagnose IMH are the same as those used in the diagnosis of acute aortic dissection (TEE, CT, MRI). Exclusion of a dissecting intimal flap is a prerequisite for the diagnosis of IMH. Specific findings on TEE for IMH include: crescentic or circumferential regional thickening of the aortic wall exceeding 7 mm, echolucent areas within the involved aortic wall, displaced intimal Ca^{2+} , and absence of an intimal flap. CT and MRI will typically demonstrate a crescentic or circular high attenuation area along the aortic wall that does not enhance with contrast,¹³³ (Fig. 29-11).

Management

In general, the acute management of IMH and acute aortic dissection are similar. Initial treatment places emphasis on reduction of systolic blood pressure to the lowest level compatible with adequate cerebral and renal perfusion (please see section on initial management of acute aortic dissection). Beta-blockade is indicated in all patients without absolute contraindications to their use and presumably exert their beneficial effect by reducing both systolic blood pressure and decreasing aortic wall stress. Patients with ascending aortic involvement have a reduction in early mortality with surgical intervention as compared with medical management (14% versus 36%).¹³⁰ Patients

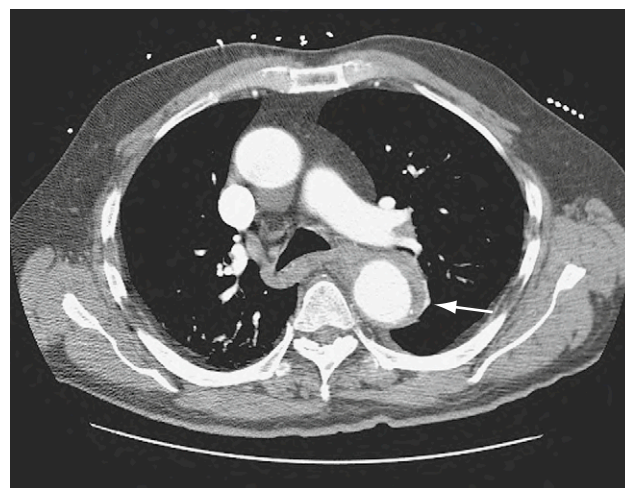


Figure 29-11. CT scan with contrast enhancement in a patient with sudden and severe chest pain shows a circumferential intramural hematoma involving the mid-descending thoracic aorta (arrow).

with type B lesions have a similar mortality with medical or surgical management (14% versus 20%). Therefore surgical intervention is usually recommended in patients with type A (ascending aortic) IMH, whereas aggressive medical therapy is the most common course for patients with type B (descending aortic) IMH.

Progression of disease in patients who are managed medically and survive the acute phase of the illness often occurs, although the rate of progression can be reduced in patients treated with beta-blocker therapy acutely.¹³² Aortic diameter at the time of initial presentation may also predict which patients are most likely to have disease progression (aortic diameter >5 cm predicting progression), potentially identifying a high-risk group that would benefit from early surgical intervention. Interestingly, in patients with ascending aortic IMH managed medically (due to advanced age and comorbid medical conditions), the mortality rate is much lower as compared with patients with classic ascending aortic dissection who do not undergo surgery.¹²⁹

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Introduction

Pericardial disease is encountered much less often in cardiac intensive care units (CICUs) than in cardiology clinics and inpatient services. Acute pericarditis is nevertheless an entity that sometimes must be considered in the population of patients hospitalized in a CICU. Patients who in reality do not have, or are unlikely to have, myocardial ischemic pain may be wrongly treated as though they were having a myocardial infarction or another acute coronary syndrome. Only after they have endured discomfort and have been exposed to the slight risk of harm, and after considerable expense, is the diagnosis of pericardial disease recognized and appropriate treatment begun whereas, in reality, many of these patients did not require hospitalization, still less admission to a CICU.

The possibility of acute pericarditis should be remembered by physicians who receive requests for admission of patients to the unit when the cause of chest pain has not been established.

Similarly, cardiac tamponade rather than massive myocardial infarction may be the true cause of apparent cardiogenic shock. Treatment aimed at the supposed myocardial infarction, instead of relieving pericardial pressure, is harmful and can easily prove fatal under these circumstances. Cardiac tamponade should always be included in the differential diagnosis of patients who develop unexplained significant hemodynamic deterioration following an invasive cardiac procedure, especially an interventional one.

The clinical picture of constrictive pericarditis is the same as that of right heart failure. Constrictive pericarditis and right heart failure of other etiology share some hemodynamic abnormalities, such as peripheral edema, pleural effusion and ascites, increased left and especially right ventricular diastolic pressure, and reduced cardiac output.

This chapter will focus on the issues outlined above. References that are to review papers are indicated as such in the text or citations. Physicians in charge of patients in a CICU must be aware of disorders of the pericardium because pericardial disease may simulate disease of the heart itself and lead to incorrect diagnosis and treatment. In the most extreme cases, this error may have fatal consequences. It remains as true today as when Osler¹ first made the observation that pericardial disease is a frequently missed diagnosis. Especially in a CICU, pericardial disease is much less common than myocardial disease; therefore the best way to recognize pericardial disease is to maintain

a high index of suspicion for this possibility when the cause of right heart failure or precordial pain is not readily apparent. The principal manifestations of pericardial disease simulating ischemic heart disease are listed in [Table 30-1](#).

Pericardial Syndromes in Ischemic Heart Disease

Chest Pain

A significant proportion of patients experience some type of chest pain in the first day or so after acute myocardial infarction. The most important cause of recurring chest pain in patients in the CICU with a documented acute myocardial infarction is myocardial ischemia, which often demands therapeutic action; however, not all chest pain occurring under these circumstances is so ominous. Many episodes of such pain elude diagnosis, especially those that are the result of the patients' natural apprehension and the understandable way in which they become sensitized to any abnormal sensations in the chest. Pulmonary infarction, embolism, or other conditions associated with pleuritic or substernal pain are included in the differential diagnosis. The cause of pleuritic chest pain can often be established from the clinical examination and the chest radiogram, but pleuritic pain may be a symptom of post-myocardial infarction pericarditis. Unfortunately, the pain of pericarditis is not always pleuritic in nature, but may simulate or be indistinguishable from pain of myocardial origin. The symptom may also have characteristics

Table 30-1. Major Ways in Which Pericardial Disease May Simulate Ischemic Syndromes

Pericardial pain simulating ischemic pain
ST segment deviation suggesting myocardial ischemia
Dressler syndrome mistaken for reinfarction
Cardiac tamponade misinterpreted as heart failure
Severe tamponade mistaken for cardiogenic shock
Friction rub mistaken for murmur of acute mitral regurgitation
Friction rub mistaken for murmur of rupture of the ventricular septum

of both myocardial and pericardial pain; for instance, it may be a crushing sensation, yet be aggravated by inspiration, influenced by posture, or be referred to the trapezius ridge. It would be desirable to be able to rely on the electrocardiogram to distinguish with certainty between pericardial and myocardial pain, but the typical changes of acute pericarditis often are not recognizable against a background of the changes associated with acute myocardial infarction or active ischemia.²

Acute Pericarditis

A number of comprehensive reviews of this subject have been published in recent years.³⁻⁹ Acute pericarditis most commonly is an acute infection of the pericardium and superficial myocardium (epicardium) that is adherent to the visceral pericardium. Acute viral pericarditis is a self-limiting relatively short disease that responds rapidly to anti-inflammatory treatment and therefore is classified as low risk for an early complication, most importantly cardiac tamponade, although tamponade does complicate about 1% to 2% and requires drainage to prevent a fatal outcome. In striking contrast is acute pericarditis of other etiologies, including infection with any living organism. Of special relevance to this chapter are pyogenic and tuberculous infection and acute pericardial injury of etiology other than that caused by viral infection. Examples include trauma including surgical or percutaneous intervention. The only common *late* complication is unpredictable recurrence that occurs at various intervals repeated over a highly variable period of time in 15% to 30% of patients (recent review papers).^{8,9}

Almost all patients complain chiefly of chest pain, but they may have few if any risk factors for coronary disease. They are often quite young and report a prodrome described as very like the flu. This prodromal event is febrile and very different from the feeling of general malaise that may precede acute myocardial infarction. Once the receiving physician considers it likely that a patient has acute pericarditis, evaluation and initial management should be done in a same-day unit,¹⁰ otherwise, hospital admission is necessary. The initial assessment can be completed in 24 hours and comprises enquiry about the details of the chief complaint (chest pain), any other symptoms, past medical history, standard biochemical laboratory tests, including C-reactive protein, and the erythrocyte sedimentation rate, and markers indicating myocardial inflammation.

Biomarkers

Acute pericarditis is associated with increased levels of serum biomarkers for myocardial injury, including modest elevations of creatine kinase (CK-MB) and serum cardiac troponin I (cTnI).¹¹⁻¹³ Serum cTnI is detectable in 32% to 49% of patients and exceeds the threshold value of 1.5 ng/mL in 8% to 22%. Mild increases in cTnI often occur in the absence of elevations in CK-MB. The rise in serum cTnI in acute pericarditis is roughly related to the extent of concurrent myocardial inflammation and is transient, resolving within 1 week. Persistent cTnI elevation suggests ongoing epicardial inflammation. Patients with a rise in cTnI do not, however, have a higher incidence of complications. Laboratory signs of inflammation are diagnostic criteria for acute pericarditis. These include the elevated white blood cell count erythrocyte sedimentation rate and, most important, serum C-reactive protein concentration.

I believe that the initial evaluation, in addition to an ECG and chest radiogram, should include an echocardiogram, but

some authorities state that echocardiography is not needed in straightforward cases. At the conclusion of this evaluation, most patients can be classified as either low or high risk for an early complication. Continued care of patients at low risk can be provided in an outpatient clinic. Patients considered to be at high risk or in whom the risk remains in doubt, should be admitted to the CICU or a medical ward, whichever is appropriate in individual cases, to determine the cause of the acute pericarditis, treat the cause and the pericarditis itself, a complication such as cardiac tamponade, or a large, slowly resolving pericardial effusion, if present.

Features suggesting high risk for an early complication are:

- Insidious rather than the customary acute onset
- Failure to respond promptly to NSAID therapy, suggesting a nonviral etiology
- Evidence of cardiac tamponade
- Neoplastic pericarditis, because it often causes tamponade, and may be the presenting feature
- Patient receiving anticoagulant or immunosuppressive treatment
- High fever, shaking chills, and leukocytosis suggesting pyogenic pericarditis

Viral, idiopathic, or acute pericarditis of various other causes is seldom an indication for admission to the CICU. Therefore most pericarditis encountered in the CICU is related to myocardial infarction and, less commonly, a cardiac or coronary intervention. Patients with acute pericarditis unrelated to ischemic heart disease may, however, also be placed in the CICU. When receiving physicians are unsure of the nature of the patients' pain and/or suspect cardiac tamponade, they should admit them to the CICU. Rarely, acute pericarditis presents as severe cardiac tamponade. Patients with this presentation, or those who are clinically unstable for another reason, may also become CICU patients.

Two pericardiopathies may occur after an acute myocardial infarction. The more frequent but less ominous is acute pericarditis with or without a benign small effusion. This acute pericarditis occurs early in the course, the peak incidence being at 3 days. This is a manifestation of contiguous pericardial inflammation over the region of the infarction and is thus more a feature of Q-wave than non-Q-wave infarctions. Using clinical criteria, a pericardial friction rub used to be reported in about 10% of patients after acute myocardial infarction² but is considerably more common in autopsy series. Pericardial friction rubs are most commonly detectable on the third day after the onset of infarction but sometimes are heard as early as the first day postinfarction. The rub has a tendency to be evanescent; therefore, if it is to be detected reliably, frequent careful auscultation focused on its detection is necessary.

The second pericardiopathy associated with acute myocardial infarction usually occurs considerably later. It is not caused by pericardial inflammation over the contiguous infarction, but is an autoimmune response to prior myocardial injury. The CICU is not the ideal milieu for auscultation, which doubtless is a reason for the underrecognition of pericardial friction rub. Rubs that first appear later than 1 week after an infarction suggest the onset of post-myocardial infarction syndrome, a subset of the pericardial injury syndrome and formerly known as Dressler syndrome.

Pericarditis may exaggerate the degree of ST segment elevation in acute myocardial infarction.^{14,15} ST segment elevation

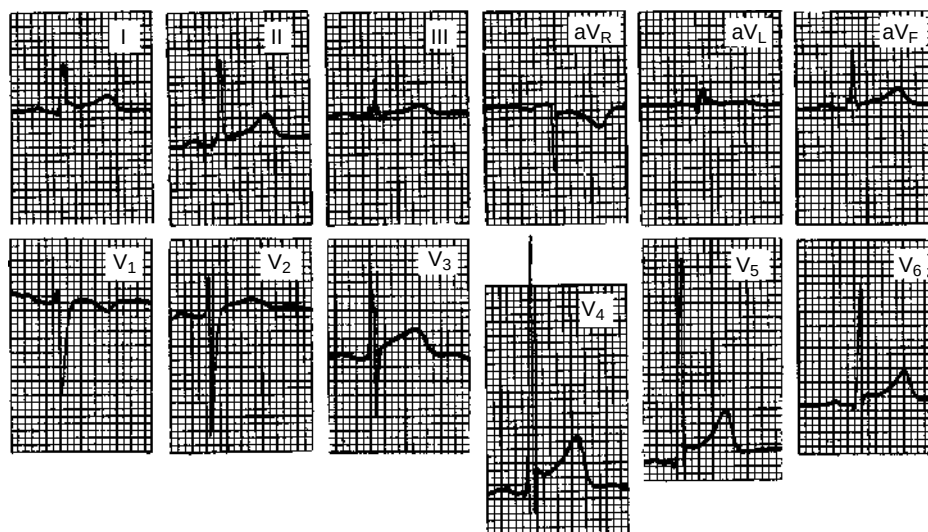


Figure 30-1. ECG of a patient with acute viral pericarditis. Characteristic features include ST segments elevated concave upward and not localized. T waves are upright in leads with ST segment elevation. Reciprocal repolarization changes are seen in aV_R and V_1 . PR segments are depressed.

in leads in which reciprocal depression would be anticipated is suggestive of complicating generalized pericarditis;¹⁶ thus ST elevation is concordant (Fig. 30-1). When pericarditis, with or without effusion, complicates myocardial infarction, evolution of the T-wave changes may be atypical, with the T wave remaining or becoming positive when T-wave inversion would be anticipated in an uncomplicated infarction.¹⁷

The standard treatment for acute pericarditis is administration of an anti-inflammatory agent, preferably nonsteroidal; corticosteroid treatment should be avoided, if at all possible. In the setting of acute myocardial infarction, however, the clinician should be aware that anti-inflammatory treatment, by inhibiting the normal healing process, may increase the risk of myocardial rupture.

Pericardial Effusion

Pericardial effusion after myocardial infarction, when specifically sought by serial echocardiography, is surprisingly common,¹⁸ occurring in about one fourth of the patients. Another unexpected feature of pericardial effusion as a sequel of myocardial infarction is that it persists for several weeks and bears no relation to pericardial friction rub. Pericarditis and pericardial effusion are associated with a worse prognosis, probably because they are more common after large infarctions, which tend to be anterior, and usually transmural.¹⁸⁻²⁰ It is accepted practice to avoid administering anticoagulants or thrombolytic agents to patients with active or recent inflammatory pericarditis,²¹ but both the Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardio (GISSI)^{20,21} and the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) trials²² have shown that thrombolytic therapy for myocardial infarction reduces rather than increases the incidence of pericardial effusion, presumably as a secondary consequence of its ability to reduce infarct size. Delayed pericardial effusion is an example of postinfarction pericardial injury. This autoimmune syndrome tends to be recurrent; therefore patients may be readmitted to the CICU with a diagnosis of a myocardial ischemic syndrome when the diagnosis is actually postinfarction autoimmune

pericardial effusion, formally known as Dressler syndrome.^{23,24} The correct diagnosis can be established when the physician keeps this diagnostic possibility in mind and seeks the characteristic features that include fever, leukocytosis, and chest pain that is usually somewhat pleuritic in nature. The chest radiogram discloses new apparent cardiomegaly and pleural effusion, which is often bilateral. Pulmonary infiltrates are less common. The correct diagnosis can usually be confirmed by echocardiography because a large pericardial effusion is a common manifestation of this condition. A review of post-myocardial infarction syndrome was published quite recently.²⁵

The evidence that the syndrome is an autoimmune phenomenon includes its association with antibodies against myocardium, but immunologic studies are not part of standard clinical care. The syndrome is considerably less common today than in the decades following its first description. The reason for this decreased incidence is not known, but it is speculated that it may be associated with decreased use of anticoagulant therapy after myocardial infarction.

Treatment is with an NSAID, but prednisone may be required in refractory cases. Relapses may occur for several months or longer and require the same treatment. In these cases, the patient's prior history is of great help in making the diagnosis. Anticoagulant or thrombolytic therapy is contraindicated because of the likelihood of hemorrhagic cardiac tamponade. This contraindication does not apply to early postinfarction pericarditis.

Cardiac Tamponade

Physiology

Cardiac tamponade is the syndrome that develops when fluid accumulates in the pericardial space faster than it is absorbed. After the small physiologic reserve volume has been reached, further influx of fluid therefore must elevate pericardial pressure, because after its reserve volume has been used up, the pericardium is virtually inextensible because its stress-strain relation is J shaped. Total cardiac volume consequently cannot

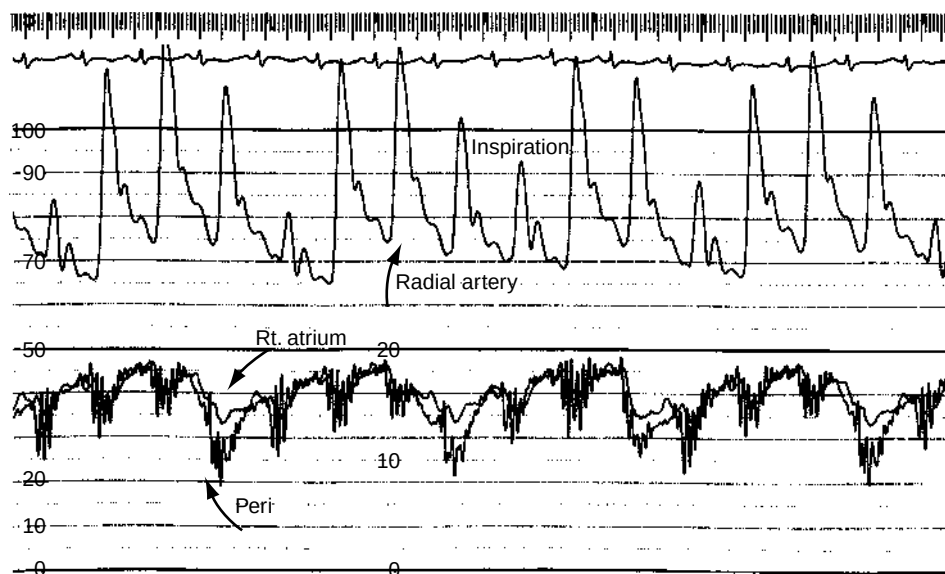


Figure 30-2. Hyperacute cardiac tamponade caused by penetration of a saphenous vein graft during angioplasty of the graft. The radial arterial tracing shows tachycardia and extreme pulsus paradoxus. The right atrial and pericardial pressures are equilibrated at a very high level. The volume of blood in the pericardium was small.

vary; therefore, an increase in right heart volume must cause decreased left heart volume and vice versa. This interdependence or interaction between the left and right sides of the heart is the principal mechanism underlying many of the clinical and imaging abnormalities characteristic of cardiac tamponade. These include pulsus paradoxus and greatly increased respiratory variation of transmitral and transtricuspid filling velocities, and stroke output and input. Pulsus paradoxus is detected by bedside examination and imaging that shows inspiratory decrease in stroke volume far greater than in normal subjects. The latter is shown and quantified by echo Doppler. Cardiac catheterization quantifies pulsus paradoxus and documents that systolic and pulse pressures in the systemic circulation are maximum at the time of peak expiration, but in the pulmonary circulation they are maximum at peak inspiration. This 90 degree out-of-phase relationship is another manifestation of chamber interdependence.

Common Causes of Tamponade in the CICU

Cardiac tamponade may complicate both early postinfarction pericarditis and late autoimmune pericardial effusion (Dressler syndrome). Cardiac tamponade is most often immediately life-threatening when it occurs as a result of the rupture of an infarcted myocardium or the aorta. Many cases of myocardial rupture are immediately fatal but, less frequently, the pericardial hemorrhage is sufficient to cause tamponade but insufficient to kill the patient rapidly. This condition is called pseudoaneurysm and usually requires later elective surgical treatment. Management of mechanical complications of myocardial infarction. Victims of this catastrophe will not survive if the diagnosis is missed or significantly delayed. Cardiac tamponade is thus a condition that the CICU physician must be able to recognize and be competent to treat, sometimes as an emergency. When the cause is rupture in the area of infarcted myocardium, the resulting tamponade is almost always hyperacute because the pericardium is stiff and stretches only minimally when the

increase in volume load is virtually instantaneous or rapid. The characteristics, therefore, are a relatively small volume of pericardial hemorrhage, but an excessively elevated pericardial pressure that causes stroke volume and arterial systolic pressure to fall dramatically and pulsus paradoxus to be severe (Fig. 30-2). A CAT scan or MRI provide optimal images, but in most cases, the patient is too ill to wait and be transferred to the imaging facility for these procedures, therefore echocardiography is used instead. The images will show the intrapericardial blood and flow from a ventricular cavity to the pericardial space, and will exclude the differential diagnosis of rupture of the chordae causing severe acute mitral regurgitation.

In summary, a high index of suspicion for cardiac tamponade must be maintained. Thus, sudden unexpected hemodynamic collapse that is not otherwise readily explained must always trigger a differential diagnosis that includes cardiac tamponade. An emergency echocardiogram should be obtained as quickly as possible.

Recognizing Cardiac Tamponade

Cardiac tamponade must be considered in any patient with a condition that commonly affects the pericardium. Myocardial infarction and its sequelae have been discussed, but today's CICU is not the coronary care unit of yesteryear. Because of the expanded role of the CICU, cases of cardiac tamponade of various causes may be admitted for monitoring and treatment.

Diagnosis

Diagnosis is facilitated as described previously by considering the possibility of cardiac tamponade in any unexplained hemodynamically compromised patient. The symptoms depend on the severity of cardiac tamponade, which clinicians should not consider as an all-or-none phenomenon but rather as one that ranges from mild to severe.²⁶ Mild cases are usually asymptomatic, but with increasing severity comes dyspnea, oliguria, and impending syncope, and ultimately death.

Tamponade, when a complication of a noncardiac systemic illness, is often accompanied by symptoms and signs of the systemic illness in addition to physical signs that are more commonly associated with right heart failure, but these patients lack any apparent cardiac abnormality to explain why the heart is failing. These findings are more difficult to interpret in patients with recent or past myocardial infarction or in those receiving hemodialysis, in whom the index of suspicion must be raised.

The venous pressure is elevated in all except the mildest cases of tamponade and those in whom there is a complicating cause of hypovolemia (low pressure tamponade). Careful inspection of the jugular venous pressure is critical in patients who have not received a central venous catheter. In those who are catheterized, the magnitude of the venous pressure and a detailed analysis of its waveform are easily obtained from the superior vena cava or right atrial pressure tracing. A central venous pressure less than 7 mm Hg is consistent with mild tamponade. Moderate tamponade is usually associated with a pressure of approximately 10 to 15 mm Hg, and severe tamponade is associated with higher pressure, sometimes up to 30 mm Hg.

When the jugular pressure cannot be determined by inspection and the patient does not have a central venous catheter in place, it can be assessed from the dimension of the inferior vena cava and its change or lack of change during the respiratory cycle (Table 30-2). Evaluation of the inferior vena cava is an essential component of the echocardiographic assessment for cardiac tamponade.

In patients with heart disease, it is important to evaluate how much of the pressure elevation in the central venous circulation is pre-existing and the result of heart disease and how much is a manifestation of tamponade. The venous pressure in uncomplicated cardiac tamponade, even when greatly elevated, declines during inspiration; thus Kussmaul sign is not a feature of tamponade.^{27,28} The other important diagnostic feature of the contour of the venous pressure tracing is attenuation or absence of the y descent (Fig. 30-3). The most likely explanation for this phenomenon is that early rapid ventricular filling is increased by enhanced recoil, but later filling is absent because cardiac volume, and therefore tamponade, are maximal at end-diastole. These features of the venous pulse can often be observed at the bedside. The x descent is synchronous with the carotid pulse and is prominent in tamponade.

In patients with severe tamponade manifested by tachycardia and respiratory distress, respiratory variation and the waveform of the jugular venous pulse become difficult or impossible to detect by simple inspection.

Table 30-2. Using the Dimension of the Inferior Vena Cava and Its Decrease with Inspiration to Estimate Central Venous Pressure

Inferior Vena Cava	Decrease with Inspiration	Right Atrial Pressure
Small: <1.5 cm	Collapse	0-5 mm Hg
Normal: 1.5-2.5 cm	<50%	5-10 mm Hg
High normal: 2.5 cm	< or >50%	11-15 mm Hg
Dilated: >2.5 cm	50%	16-20 mm Hg
Dilated: >2.5 cm	Zero change	20 mm Hg

When the clinician suspects cardiac tamponade, two other diagnostic tools are called into play: echocardiography and simultaneous recording of the central venous and pulmonary wedge pressures. Which of these to perform first depends on the circumstances. The echocardiogram provides definitive information in that if it shows that there is no pericardial effusion, the patient cannot be suffering from cardiac tamponade. Much other important diagnostic information is provided by the echocardiogram²⁹ (Fig. 30-4). Compression of the right atrium (Fig. 30-5) or right ventricular diastolic collapse³⁰ are both highly sensitive and reasonably specific signs of cardiac tamponade. Cardiac chamber collapse is caused by transient reversal of the normal ratio of right atrial to pericardial pressure.³¹

Doppler examination of ventricular inflow shows exaggerated respiratory variation.³¹ Additional information can be gathered from evaluation of cardiac chamber size and function. In

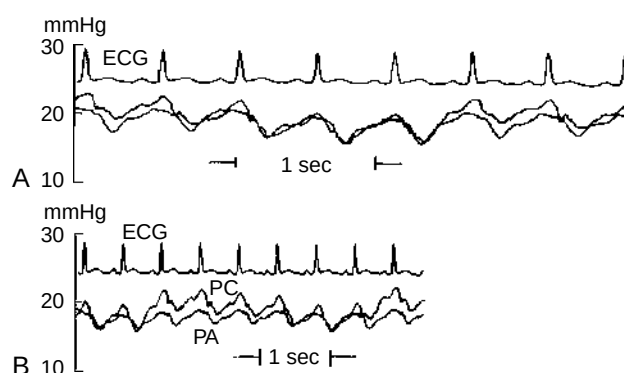


Figure 30-3. Equilibration of pressures in cardiac tamponade. The patient had severe cardiac tamponade. **A**, Right atrial and pericardial pressures are elevated to 20 mm Hg. Both pressure contours are monophasic with a prominent x but no y descent. **B**, Right atrial and pulmonary wedge pressures are also 20 mm Hg, and their contours are similar. (From Shabetai R: *Pericardial disease*. In Brown DL [ed]: *Cardiac Intensive Care*. Philadelphia, Saunders, 1988, pp 469-475.)

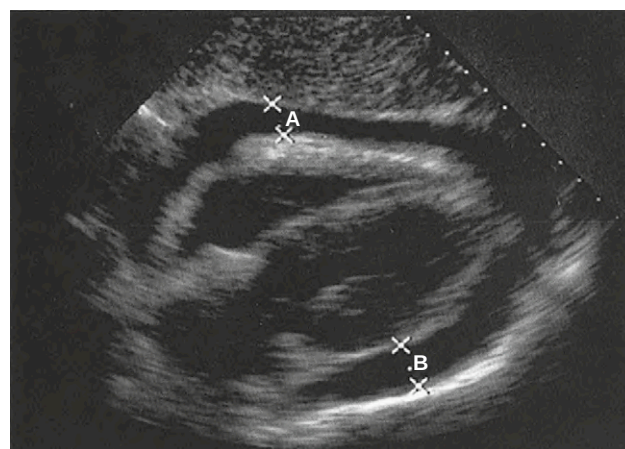


Figure 30-4. Echocardiogram showing a large circumferential pericardial effusion. Anterior (A) and posterior (B) aspects of the effusions are shown. (From Shabetai R: *Pericardial disease*. In Brown DL [ed]: *Cardiac Intensive Care*. Philadelphia, Saunders, 1988, pp 469-475.)

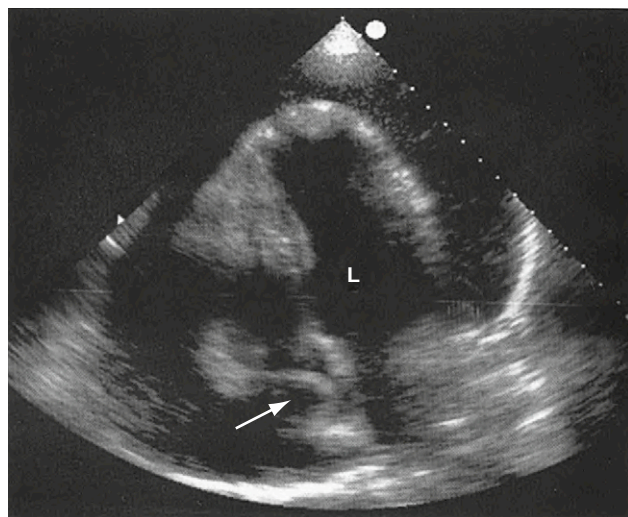


Figure 30-5. Echocardiogram showing severe right atrial compression (arrow) in a patient whose pericardial effusion had caused cardiac tamponade. (From Shabetai R: *Pericardial disease*. In Brown DL [ed]: *Cardiac Intensive Care*. Philadelphia, Saunders, 1988, pp 469-475.)

uncomplicated cardiac tamponade, the ventricles are of normal size, and their systolic function is normal.³² Demonstration of ventricular enlargement or systolic dysfunction calls for judgment regarding whether hemodynamic abnormalities are cardiogenic or manifestations of tamponade.

When cardiac tamponade is severe, pulsus paradoxus and, in more extreme cases, hypotension appear, at which stage tamponade is considered to be decompensated and is treated as an emergency. Right ventricular diastolic collapse develops earlier than pulsus paradoxus in the course of tamponade.³³

If a Swan-Ganz catheter is not already in place, one should be inserted to complete documentation and assessment of tamponade. The central venous pressure is measured at the proximal port and the wedge pressure is measured at the distal port. The two pressures are recorded simultaneously at precisely identical sensitivities and, if the apparatus permits, from a common baseline. In uncomplicated tamponade, the wedge and right atrial pressures are equal, so the tracings will be superimposed. This equilibration of right and left atrial pressures is a characteristic finding in tamponade. Records should be made during normal respiration and at expiration and with respiration arrested at end-tidal volume. The mean pressures should not differ by more than 2 or 3 mm Hg if scrupulous attention is paid to the recording technique (see Fig. 30-3).

Pulsus Paradoxus

Pulsus paradoxus develops when tamponade becomes moderately severe and is easily quantified if a systemic arterial line has been placed. Pulsus paradoxus is considered present when systemic arterial pressure drops 10 mm Hg or more during a normal inspiration (Figs. 30-2 and 30-6). The pulse pressure also falls during normal inspiration, reflecting decreased stroke volume. Respiration affects hemodynamics via a number of mechanisms, all of which contribute to pulsus paradoxus, but the most important is ventricular interaction.³⁵ In the absence of direct arterial monitoring, pulsus paradoxus can be estimated by

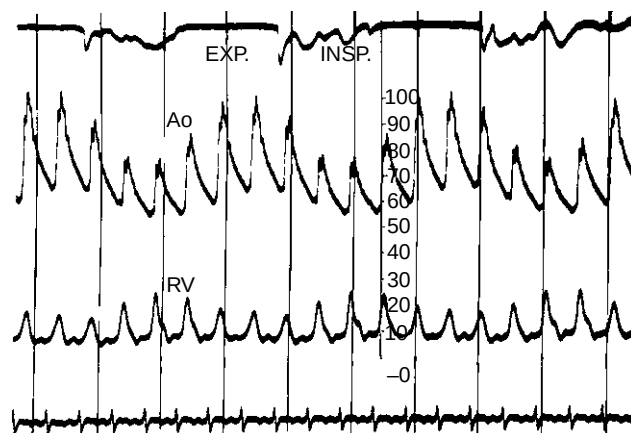


Figure 30-6. Low-pressure cardiac tamponade. The right ventricular pressure was only 10 mm Hg, but otherwise the characteristic hemodynamic abnormalities of severe tamponade were present, including pulsus paradoxus, which was out of phase between the right ventricle (RV) and the aorta (Ao), and absence of an early diastolic dip. (From Shabetai R: *Cardiac tamponade*. In Shabetai R [ed]: *The Pericardium*. Kluwer Academic Press Norwell, Massachusetts, 2003, pp 122-166.)

sphygmomanometry; the first blood pressure sound is initially heard only during expiration but, as cuff pressure is lowered, becomes audible consistently. Pulsus paradoxus is estimated as the difference in pressure between the levels at which the first heart sound is heard only in expiration and heard all the time. It is important when quantifying pulsus paradoxus to avoid requesting the patient to breathe deeply to bring out pulsus paradoxus because serial measurement of pulsus paradoxus is useful in monitoring the progress of patients monitored for tamponade.

The degree of pulmonary hypertension depends on the severity of tamponade. In mild cases, pulmonary arterial pressure is normal and, in the severe cases, pulmonary arterial systolic pressure is usually in the range of 40 mm Hg. In hyperacute cases, in which pulmonary diastolic pressure may be 50 to 60 mm Hg, pulmonary systolic pressure may be 70 to 80 mm Hg. Otherwise, pulmonary hypertension of substantially more than 40 mm Hg indicates that either the diagnosis is wrong or tamponade is superimposed on another cause of pulmonary hypertension. The right ventricular diastolic pressure does not show a dip-and-plateau configuration in tamponade, just as there is no γ descent of right atrial pressure. The dip-and-plateau configuration of ventricular diastolic pressure is a feature of constrictive pericarditis and restrictive cardiomyopathy in which early diastolic filling is abnormally rapid. In cardiac tamponade, filling in late diastole is attenuated or absent.

In a typical case of moderate-to-severe tamponade, all filling pressures are determined by the elevated pericardial pressure; thus right atrial, right ventricular diastolic, pulmonary wedge, and pulmonary arterial diastolic pressures are equal (see Fig. 30-3).

Exceptions to the classic findings of tamponade occur and are more common in CICU patients because these exceptions are manifestations of pre-existing heart disease. The mechanism of pulsus paradoxus is related to competition between the two sides of the heart for severely restricted intrapericardial space (ventricular interdependence) so that the inspiratory expansion

of right heart volume must impair left heart stroke volume during inspiration.³⁵ This mechanism implies that the external pericardial force, by rendering left and right ventricular pressures equal, equalizes left and right ventricular diastolic compliance. In patients who have heart disease with elevated left or right ventricular diastolic pressure, pericardial pressure can be lower than that in which whichever ventricle diastolic pressure is elevated by pre-existing heart disease, even when tamponade is severe. In that circumstance, ventricular diastolic compliance ceases to be equal on the two sides, and pulsus paradoxus is not present. Likewise, pulmonary hypertension or right heart failure can prevent the occurrence of echocardiographic right heart compression. Systemic arterial pressure should be monitored throughout pericardiocentesis, preferably by cannulation of an artery.

Low Pressure Cardiac Tamponade

Low pressure cardiac tamponade describes the condition in which cardiac tamponade is present without the characteristic elevation of central venous pressure.³⁶ Sometimes this phenomenon occurs simply because tamponade is mild. In these cases, hypotension, tachycardia, pulsus paradoxus and echocardiographic chamber compression and collapse are absent. The CCU staff should note it in the discharge summary, but no other immediate action is required. Low pressure cardiac tamponade may, however, be associated with hypovolemia, secondary to dialysis or ultrafiltration, highly aggressive diuresis, or acute hemorrhage as in cardiac tamponade caused by thoracic trauma. In these cases, chamber collapse, pulsus paradoxus (see Fig. 30-6) and hemodynamic compromise are very much in evidence. Treatment comprises pericardiocentesis and intravenous fluid replacement monitored by hemodynamics. Replacement should commence before a significant volume of fluid has been removed and be continued during pericardiocentesis.

Treatment

Cardiac tamponade is generally an indication for pericardiocentesis. Whenever possible, pericardiocentesis should be carried out in a cardiac catheterization or echocardiographic laboratory rather than in the CICU. In the catheterization laboratory, the physiologic recorder probably has considerably larger capacity and flexibility, and the technicians are usually more skilled at precise pressure recording than are their counterparts in the CICU. Likewise, the radiologic facility is apt to have far greater capability than the portable x-ray equipment available in the CICU. In the cardiac catheterization and echocardiographic laboratories, the inventory of catheters, guide wires, and cannulae immediately available to the operator is much larger. Contrast injection, be it with agitated saline or radio-opaque contrast agent, is a useful means of ensuring the proper position of a needle or catheter in the pericardial space and is more readily available in the catheterization or echocardiographic laboratory. An echocardiogram should be in the laboratory, and the machine should be available to give the operator the option of using echocardiographic guidance.

Pericardial pressure should always be measured, and simultaneous measurements of pericardial, right atrial, and pulmonary wedge pressures should be obtained at the outset to confirm the diagnosis, and serially during the procedure, or at its end, to monitor the hemodynamic response. By the time pericardiocentesis nears completion, pericardial pressure should have fallen to subatmospheric levels, at least during inspiration, and be

consistently below right atrial and pulmonary wedge pressures. When right atrial pressure remains elevated, consideration must be given to effusive-constrictive pericarditis, right heart failure, or tricuspid valve disease. Persistent elevation of the pulmonary wedge pressure, but normalization of the pericardial and right atrial pressures implies left heart failure or mitral valve disease. Systemic arterial pressure should be monitored throughout the procedure, preferably by cannulation of an artery.

Constrictive Pericarditis

Constrictive pericarditis is seldom an indication for admission to a CICU and therefore is not discussed in detail here. When patients with late stage disease are admitted, they have severe anasarca that should be ameliorated in a manner similar to that for patients with severe congestive heart failure, except that no attempt should be made to achieve a normal central venous pressure. This precaution is necessary because overly vigorous diuresis causes hypotension and low cardiac output and may lead to the patient's death, but enough fluid should be removed to make the patient comfortable and improve renal and hepatic function and protein-losing enteropathy. Patients not previously known by the CICU staff may be admitted for acute decompensated heart failure when the correct diagnosis is ultimately found to be constrictive pericarditis. A clue to the diagnosis of constrictive pericarditis is a patient who presents the findings usually associated with right heart failure but in whom there is no discernible cause or evidence of heart disease. Another clue is that the BNP level is significantly lower than expected. Suspicion that a patient has constrictive pericarditis rather than heart failure should lead to echo-Doppler evaluation, which would show elevated central venous pressure with absent respiratory variation, except for the y descent. As in cardiac tamponade, enhanced ventricular interaction is the cause of greatly increased respiratory variation of transmitral and transtricuspid velocity.

Imaging is very helpful in distinguishing heart failure, particularly when it is a manifestation of restrictive cardiomyopathy. Whereas the profile of mitral inflow velocity shows a severe restrictive pattern in both, the tissue Doppler findings in each are very different. Details are beyond the scope of this chapter, but are summarized in a review paper.³⁷

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Acute Respiratory Failure

Marc Chalaby, Jay I. Peters

CHAPTER 31

Physiology of Gas Exchange Pathophysiology of Acute Respiratory Failure

Conclusion

RESPIRATORY FAILURE is defined as the inability to maintain either the normal delivery of oxygen to tissues or the normal removal of carbon dioxide from the tissues. From a physiologic perspective, respiratory failure can be caused by diffuse pulmonary dysfunction (ventilation/perfusion [$\dot{V}/\dot{Q}$] mismatch or pulmonary shunt), neurologic dysfunction (depression of the respiratory drive), cardiac dysfunction (low cardiac output or pulmonary edema), or a lack of hemoglobin to transport gases. Clinically this is seen as arterial hypoxemia leading to tissue hypoxia and/or arterial hypercapnia. Acute respiratory failure (ARF) may evolve over a period of minutes or hours to days depending on the clinical situation. ARF, therefore, is a generic term that encompasses a heterogeneous spectrum of diseases that eventually end with the same pathophysiologic outcomes, namely, arterial hypoxemia (usually with P_{aO_2} of less than 60 mm Hg) or hypercapnia (P_{aCO_2} of >45 to 50 mm Hg).

Physiology of Gas Exchange

In the lung, gas exchange occurs at the capillary-alveolar interface. Close examination of septal capillaries reveals that they are significantly thinner on the side that bulges into the air space. This conformation enhances the diffusion of oxygen from the air space into the blood and the elimination of carbon dioxide from the blood into the air space. Equilibration of partial pressures of gases between the two compartments occurs rapidly. Oxygen in the blood is carried by hemoglobin. Only a small percentage is transported as dissolved gas. The following equation describes the arterial oxygen content (CaO_2):

$$CaO_2 = (1.36 \times Hgb \times SaO_2) + (0.003 \times PaO_2)$$

where CaO_2 is the oxygen content of arterial blood in milliliters of O_2 per deciliter of blood; Hgb is the hemoglobin concentration in grams per deciliter of blood; SaO_2 is the fraction of hemoglobin sites bound by oxygen; and PaO_2 is the arterial partial pressure of oxygen.

Because the amount of dissolved oxygen is small in comparison to the amount transported by hemoglobin, in most clinical situations, CaO_2 depends primarily on the hemoglobin concentration and the oxygen saturation of the arterial blood, not on PaO_2 . Even in severe anemia, the contribution of dissolved oxygen in the overall CaO_2 is negligible despite very high PaO_2 . This principle is important clinically in patients with ARF for whom increasing CaO_2 can be accomplished by increasing hemoglobin

concentration and SaO_2 , but not necessarily by increasing PaO_2 . This follows from the sigmoid shape of the oxygen-hemoglobin dissociation curve, in which significantly higher PaO_2 is needed to increase the SaO_2 beyond 90% as the curve plateaus.

Carbon dioxide is transported in the blood mostly in the form of carbonic acid. Only approximately 5% is transported by binding with hemoglobin. Ten percent is transported as dissolved gas.¹ As the tissues extract more and more oxygen from the blood, the deoxygenated hemoglobin increases its ability to carry carbon dioxide (Haldane effect). Similarly, as more and more oxygen becomes available in the arterial and venous blood, less carbon dioxide may be carried by the oxidized hemoglobin. This effect has been implicated in the pathogenesis of worsening hypercapnia after oxygen supplementation in patients with baseline hypercapnia.

To achieve optimal gas exchange, local matching of ventilation and perfusion has to occur. The interrelationships between ventilation and blood flow are shown schematically in Figure 31-1 where imbalance (B) is typified by bronchospasm, shunt (C) is typified by dense pneumonia or severe acute respiratory distress syndrome (ARDS), and dead space (D) is typified by digestion of the capillaries in emphysema.

Normally, both ventilation and perfusion exhibit a gradient from the top to the bottom of the lung. However, the gradient is more pronounced in blood flow than in ventilation, such that in the upper portions of the lung there are predominantly high $\dot{V}/\dot{Q}$ areas and in the lower portions of the lung, low $\dot{V}/\dot{Q}$ areas. The overall $\dot{V}/\dot{Q}$ ratio of the normal lung is 0.8.²

The overall efficiency of gas exchange can be assessed in terms of maintenance of normal PaO_2 and $PaCO_2$. The assessment can be performed by calculating the alveolar-arterial partial pressure oxygen difference ($PAO_2 - PaO_2$), which is also known as the A-a gradient. The mean alveolar oxygen tension (PAO_2) is calculated by using the alveolar gas equation as follows:

$$PAO_2 = (P_B - PH_2O) \times FiO_2 - \frac{PaCO_2}{R}$$

where P_B is the barometric pressure of the atmosphere, which changes with altitude; FiO_2 is the fraction of inspired oxygen (approximately 0.21 in room air); $PaCO_2$ is the partial pressure of arterial carbon dioxide; and R is the respiratory quotient.

This equation gives an estimation of PAO_2 , which changes with altitude (P_B), with inspired oxygen concentration, and with $PaCO_2$. PaO_2 not only changes with changes in PAO_2 but also decreases

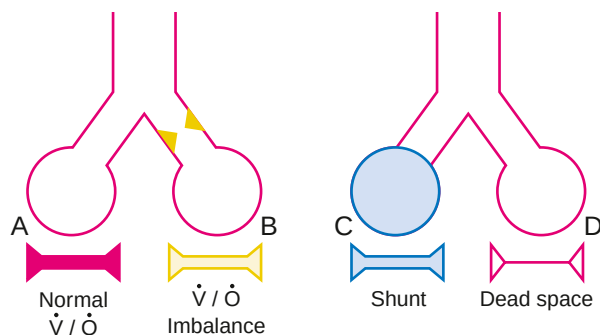


Figure 31-1. Schematic representation of various patterns of ventilation ($\dot{V}$) and perfusion ($\dot{Q}$). **A**, Normal $\dot{V}/\dot{Q}$ ratio in which the $P\dot{V}O_2 = 40$ mm Hg and $P\dot{C}O_2 = 46$ mm Hg. After equilibration, the capillary $PO_2 = 101$ mm Hg, $PCO_2 = 40$ mm Hg, and $P(A - a)O_2 = 0$ mm Hg. **B**, $\dot{V}/\dot{Q}$ imbalance caused by airway obstruction would decrease the PO_2 . This could be corrected with supplemental oxygen. **C**, A shunt allows mixed venous blood to traverse the capillary without any gas transfer. **D**, Dead space, the ventilated area of the lung that does not participate in gas exchange. (From Greene KE, Peters JI: Pathophysiology of acute respiratory failure. *Clin Chest Med* 1994;15:1-11.)

with age in normal individuals. Therefore $PAO_2 - PaO_2$ increases with age and can be estimated in most adults breathing room air to be approximately 4 mm Hg for each decade of life until the maximum of the seventh decade. This estimation is not valid for patients receiving oxygen supplementation. For these patients, assessment of efficiency of gas exchange can be obtained using the ratio of PaO_2 to FiO_2 (PaO_2/FiO_2 ratio normally is above 400 mm Hg). Although it is not as accurate as the $PAO_2 - PaO_2$ difference, it is useful clinically because most patients with ARF receive supplemental oxygen at the time blood gas analysis is performed. This ratio also forms one of the newer basic criteria for the diagnosis of acute lung injury or ARDS. By consensus acute lung injury is defined as noncardiogenic pulmonary edema with a PaO_2/FiO_2 ratio of less than or equal to 300 mm Hg; ARDS is diagnosed in the presence of a ratio of less than or equal to 200 mm Hg.³ This ratio is most helpful when used serially or when the ratio changes significantly with a therapeutic maneuver.

Pathophysiology of Acute Respiratory Failure

The three most important pathophysiologic mechanisms that cause ARF are hypoventilation, $\dot{V}/\dot{Q}$ mismatch, and shunt. Diffusion abnormalities, which occur with mild pulmonary edema or early interstitial lung disease, may cause exercise-induced hypoxemia but rarely cause clinically significant hypoxemia. Reduction of inspired PO_2 and venous admixture are other potential but less common causes of hypoxemia.

Hypoventilation can be defined as the inadequate movement of fresh alveolar gas necessary for maintaining a normal $P\dot{C}O_2$. Pure hypoventilation is a relatively uncommon clinical event. In most cases, hypoventilation occurs along with other causes of hypoxemia.

When pure hypoventilation does occur, it is usually caused by depression of the respiratory center by sedative-hypnotic drugs or by neuromuscular diseases that affect the respiratory muscles.

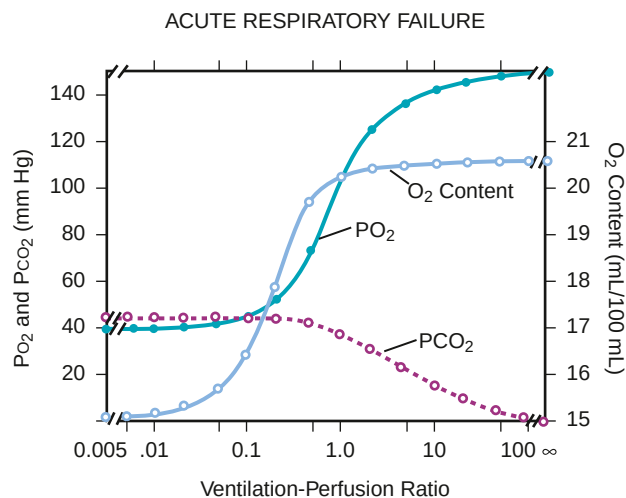


Figure 31-2. Variations in PO_2 , PCO_2 , and O_2 content in a gas exchange lung unit as its ventilation-perfusion ratio is progressively increased. This lung is assumed to be breathing air, and the mixed venous blood PO_2 and PCO_2 are 40 mm Hg and 45 mm Hg. (From West JB: Ventilation-perfusion relationships. *Am Rev Respir Dis* 1977;116:919-943.)

The increase in $P\dot{C}O_2$ that accompanies pure alveolar hypoventilation invariably affects PAO_2 as predicted in the alveolar gas equation, causing a decrease in PAO_2 . This results in hypoxemia with a normal $PAO_2 - PaO_2$ gradient. In patients on room air, the PaO_2 will fall 5 mm Hg for every 3 mm Hg rise in $P\dot{C}O_2$. If the $PAO_2 - PaO_2$ gradient is abnormally increased, then other mechanisms may also be involved in the pathogenesis of hypoxemia. Hypoxemia resulting from pure alveolar hypoventilation usually responds adequately to increasing FiO_2 .

By far the most common cause of clinically important hypoxemia is $\dot{V}/\dot{Q}$ mismatching. $\dot{V}/\dot{Q}$ mismatching is present as a continuum from pure shunt $\dot{Q}$ without $\dot{V}$ to pure dead space ventilation $\dot{V}$ without $\dot{Q}$, with unlimited patterns of $\dot{V}/\dot{Q}$ mismatching in between. In young normal individuals, $\dot{V}/\dot{Q}$ ratios range from 0.6 to 3.0 and usually center around 1.0.⁴ Low $\dot{V}/\dot{Q}$ lung units can result from compromised ventilation such as obstructed airways or from partial alveolar filling with pneumonia or pulmonary edema. High $\dot{V}/\dot{Q}$ lung units most often occur with obstruction of blood flow due to pulmonary vascular disease or from a lack of capillaries due to lung parenchymal destruction such as that seen in emphysema.

$\dot{V}/\dot{Q}$ mismatching causes hypoxemia and hypercapnia. However, in most cases, an increase in minute ventilation stimulated by hypercapnia results in normalization of $P\dot{C}O_2$ with persistent hypoxemia. This is possible because the CO_2 dissociation curve is linear, allowing well-ventilated areas to compensate. The O_2 dissociation curve is sigmoid-shaped; therefore the increase in minute ventilation, despite producing higher end-capillary PO_2 , results in very modest changes in oxygen saturation, which in most cases is inadequate to reverse the hypoxemia (Figure 31-2). Hypoxemia due to $\dot{V}/\dot{Q}$ mismatching is usually correctable with increasing the FiO_2 . Local hypoxia in low $\dot{V}/\dot{Q}$ areas triggers reflex hypoxic pulmonary vasoconstriction in an attempt to correct the $\dot{V}/\dot{Q}$ imbalance. This reflex vasoconstriction can be abolished by a number of vasodilators, including nitroprusside, nitroglycerin, calcium channel blockers, and inhalational anesthetics. When

compensatory mechanisms fail in a patient with severe lung disease, the body may set a new steady state PaCO_2 and pH as an adaptive response to conserve the work of breathing.

Right-to-left shunt occurs when there is no ventilation into a lung unit while perfusion is preserved. It is one of the extreme ends in the spectrum of $\dot{V}/\dot{Q}$ mismatches. In a normal lung, the amount of shunt present is less than 5%. Shunt in the lung results from atelectasis, severe pulmonary edema, and air space consolidation such as pneumonia. In addition, right-to-left shunt can also occur as a consequence of arteriovenous malformation and intracardiac shunts from a patent foramen ovale, patent ductus arteriosus, or ventricular septal defect. Shunt causes significant hypoxemia due to the mixture of oxygenated blood with shunted, poorly oxygenated venous blood. Hypercapnia is usually not present until the shunt is greater than 50%. In contrast to other mechanisms of respiratory failure, hypoxemia due to shunting is not responsive to increases in FiO_2 . This feature of shunt can be conveniently used to separate it from other causes of hypoxemia. Calculation of shunt ($\dot{Q}_s/\dot{Q}_t$) is easily done by administering 100% oxygen for 15 minutes and then analyzing arterial blood gases. Percent shunt can be estimated using a nomogram or by using the following formula:

$$\dot{Q}_s/\dot{Q}_t = \frac{(C_{\text{CO}_2} - C_{\text{aO}_2})}{(C_{\text{CO}_2} - C_{\text{vO}_2})} \times 100$$

In this equation, C denotes content, and the lower case letters c , a , and v denote end-capillary, arterial, and venous blood, respectively. A simplified shunt equation assumes that the C_{vO_2} is normal and that the shunt is less than 25%. This simplified shunt equation states

$$\dot{Q}_s/\dot{Q}_t = \frac{\text{PAO}_2 - \text{PaO}_2}{20}$$

When the FiO_2 used is less than 1.0, the resulting calculation is called venous admixture instead of shunt. This reflects the contribution of severe $\dot{V}/\dot{Q}$ mismatching, including very low $\dot{V}/\dot{Q}$ ratios that approach zero, which may act like shunts when alveoli are not ventilated with 100% oxygen.

The hypoxemia of shunt is remarkably resistant to correction by increasing the FiO_2 . Patients with significant shunts may have the same arterial oxygen saturation when maintained on a relatively toxic FiO_2 (near 1.0) or when titrated down to relatively safe FiO_2 (0.6 to 0.7).

Clinical Assessment

Patients with ARF commonly have dyspnea. For those with underlying lung disease, dyspnea may be present chronically. Therefore mild changes in the degree of dyspnea may or may not be perceived. In the presence of significant hypoxemia and acidosis, patients may have symptoms of central nervous system depression ranging from irritability to coma. Patients may also have evidence of the effects of hypoxemia or acidosis on the cardiovascular system, such as arrhythmias, angina, or infarction. Depending on the underlying disease, other symptoms may also be present. Although they may be important and helpful in evaluating the underlying process causing the respiratory failure, they are not that helpful in evaluating the degree of respiratory dysfunction. For example, the additional symptoms of cough, sputum production, and fever may suggest pneumonia, whereas pleuritic chest pain with certain characteristics may

suggest pneumothorax or pulmonary embolism as the cause of the respiratory distress.

Initial physical examination of patients with ARF should focus on overall appearance, vital signs, and the ABCs (airway, breathing, circulation). In general, patients with ARF have tachypnea, tachycardia, and variable mental status. Assessment of mental status may help by anticipating the cooperation the patient will give in the process of evaluation and management. The degree of alteration of mental status may reflect the severity of the respiratory failure. Confusion or disorientation in the presence of dyspnea and tachypnea may reflect profound hypoxemia or hypercapnia with its attendant respiratory acidosis. Pulsus paradoxus, a decrease in arterial systolic pressure of greater than 10 mm Hg with inspiration, also suggests severe airway obstruction associated with significant negative intrathoracic pressures. Patients with severe respiratory distress are usually unable to speak in full sentences. Likewise, the presence or absence of adventitious breath sounds may assist the clinician in evaluating the degree and acuity of the respiratory distress. Crackles suggest alveolar flooding or early bronchopneumonia, whereas rhonchi often herald an increase in mucus production or an inability to clear secretions. Wheezing suggests airway obstruction, whereas wheezes located over the neck suggest upper airway stridor that may be associated with respiratory collapse. Decrease in breath sounds may be seen in patients with chronic obstructive pulmonary disease (COPD) or those with severe airway obstruction. The absence of wheezing and breath sounds in a patient with underlying obstructive lung disease and respiratory distress may suggest impending respiratory collapse as a result of very limited air movement. Absence of breath sounds may also be associated with pneumothorax. Subcutaneous emphysema usually indicates pneumomediastinum with or without accompanying pneumothorax.

Despite advances in noninvasive technologies in oxygenation assessment, arterial blood gas analysis remains the best and most accurate test in the initial assessment of patients with ARF. Pulse oximetry is acceptable as a method for following oxygenation once it has been calibrated to true blood gas co-oximetry saturation and the arterial PaO_2 is known. Pulse oximetry (SpO_2) carries $\pm 4\%$ error in measuring oxygen saturation. In patients with carbon monoxide poisoning, SpO_2 does not reflect true PaO_2 , and profound hypoxemia may be missed. With methemoglobinemia, the SpO_2 may falsely read the oxygen saturation at around 85%, irrespective of the true saturation. Furthermore, pulse oximetry does not give information on PaCO_2 and pH, which may be crucial in the differential diagnosis and management of the patient with ARF. The presence of hypercapnia is a marker of the severity of disease. Hypercapnia is more likely to complicate hypoxemic failure when the disease is superimposed on significant underlying lung or neuromuscular disease.

The presence of hypoxemia, hypercapnia, and respiratory acidosis can be used to define ARF, but it is difficult to set specific levels of PaO_2 or PaCO_2 because patients with underlying lung disease may have markedly abnormal baselines. Given these qualifications, generally patients with ARF have a PaO_2 less than 55 mm Hg or a PaCO_2 more than 50 mm Hg. The pH is very helpful in assessing the acuity of the hypoventilation. In cases of subacute or chronic hypoventilation, the patient usually has an elevated serum bicarbonate level and a mild depression of the pH. In acute respiratory acidosis without renal compensation, the pH drops by 0.08 for each 10-mm Hg rise in PaCO_2 .

Table 31–1. Radiographic Approach to Acute Respiratory Failure

Radiograph	Clinical Characteristics	Responses to Oxygen*
“White” Chest Radiograph		
Pneumonia	Fever, leukocytosis, sputum production	+ to + + +
Adult respiratory distress syndrome	Predisposing risk factors, wedge $\leq$ 18 mm Hg	+ to + +
Cardiogenic edema	Paroxysmal nocturnal dyspnea, orthopnea, edema	+ + + to + + + +
Interstitial lung disease	Prior chest radiographic abnormalities	+ + + to + + + +
“Black” Chest Radiograph		
Chronic obstructive pulmonary disease/asthma	Reduced flow on bedside spirometry	+ + to + + + +
Pulmonary emboli	Acute dyspnea, pleuritic pain	+ + + to + + + +
Right-to-left shunt	History and physical examination consistent with pulmonary hypertension	+
Microatelectasis	Postoperative or rib fracture, bronchial breath sounds	+ + to + + +

*Range from +, which is shuntlike (Po_2 increases 1 mm Hg for 1% rise in FiO_2), to + + + +, which is $\dot{V}/\dot{Q}$ imbalance (Po_2 increases 5 mm Hg for 1% rise in FiO_2)

Compensatory bicarbonate retention or wasting by the kidneys to buffer the pH changes usually takes 2 to 3 days to occur. After renal compensation, a change of 10 mm Hg of PaCO_2 will produce 0.03 change in pH in the opposite direction.

The chest radiograph is useful in sorting out the differential diagnosis of ARF during the initial presentation. The causes of hypoxemia can be classified based on radiographic appearance. Table 31-1 shows examples of diseases associated with “white” chest radiographs showing diffuse or patchy infiltrates and diseases associated with “black” chest radiographs showing normal or clear lung fields.

Differential Diagnosis

The clinical classification of ARF based on chest radiographic appearance provides a convenient algorithm in evaluating hypoxemic patients. PA and lateral films or CT of the chest provide better quality than portable films and can help visualize the retrocardiac space. Patients having a “white” chest radiograph usually have pneumonia, ARDS, cardiogenic pulmonary edema, or progressive interstitial lung disease. Patients having a “black” chest radiograph usually have obstructive lung disease, pulmonary emboli, a right-to-left shunt, or microatelectasis. Most patients with hypoxemic respiratory failure have radiographic infiltrates. The presence of additional compatible history and physical examination findings often allows the clinician to narrow the differential diagnosis. With fever, cough, sputum production, and lobar or patchy infiltrate, pneumonia is a likely possibility. Pneumonia often presents in an atypical fashion in older patients (those older than 65 years old).⁵ Up to 50% of older patients do not have a fever or specific respiratory complaints, and confusion or mild hypotension may be the primary findings on examination. Cardiogenic pulmonary edema superimposed on abnormal lung parenchyma such as in emphysema will often give bilateral patchy radiographic infiltrates and not necessarily the classic central batwing distribution. In such cases, a history of underlying heart disease and compatible physical examination may aid in arriving at the presumptive diagnosis of congestive heart failure. In recent

years, an increase in the use of brain natriuretic peptide levels (BNP) have been used to support the diagnosis of heart failure. A recent review by Korenstein pooled over 3000 patients and determined that BNP of less than 100 pg/mL essentially rules out the diagnosis of heart failure, whereas a BNP greater than 400 pg/mL has a sensitivity and specificity of 81% and 90%, respectively.⁶ Elevated levels do not distinguish between right and left ventricular failure and may be seen in patients having pulmonary emboli and cor pulmonale. BNP levels have also been noted to be elevated in patients with septic shock without evidence of clinical heart failure.

The most helpful feature in separating these disorders is the radiographic response to therapy. Radiographically, pneumonia resolves over 3 to 12 weeks, whereas cardiogenic pulmonary edema may clear over days. In the absence of supportive clinical evidence for left ventricular failure, diffuse infiltrates may represent noncardiogenic pulmonary edema, pulmonary hemorrhage, or interstitial pneumonitis. Noncardiogenic pulmonary edema (ARDS) most often occurs in hospitalized patients. If a patient presents to the hospital with ARDS, a diagnosis of severe bilateral pneumonia should strongly be considered. Most patients with ARDS have one of the common precipitating factors leading to this disorder. The common predisposing events include sepsis, hypotension, massive aspiration, severe pneumonia, and massive trauma or transfusions. Less common precipitating events include pancreatitis, drug overdose, and postcardiopulmonary bypass surgery. Revised criteria for ARDS are listed in Table 31-2.³ Low tidal volumes of 6 to 8 mL/kg of ideal body weight and plateau pressures less than 30 to 32 cm/H₂O have been shown to significantly reduce mortality in patients with ARDS.⁷ Comprehensive reviews of ARDS have been published⁸ and therapeutic trials and protocols are maintained on the ARDS-net website (www.AARDSnet.org). In a patient with a history of joint complaints, an undiagnosed rash, or unexplained renal insufficiency, a diagnosis of vasculitis or collagen vascular disease should be considered. In the presence of an acute drop in hematocrit, pulmonary hemorrhage syndrome may

Table 31–2. The American-European Consensus Criteria of Acute Lung Injury and Acute Respiratory Distress Syndrome.

Shared Criteria	
• Acute onset • Bilateral infiltrates on frontal chest radiograph • Pulmonary artery occlusion pressure ≤ 18 mm Hg or no clinical evidence of left atrial hypertension	
Specific Criteria	
• Acute lung injury: $P_{aO_2}/F_{iO_2} \leq 300$ mm Hg • Acute respiratory distress syndrome: $P_{aO_2}/F_{iO_2} \leq 200$ mm Hg	

be entertained, in which case, a definitive diagnosis including lung biopsy may be essential to allow proper treatment and management. In some cases, pulmonary hemorrhage is not accompanied by hemoptysis. The Infectious Diseases Society in conjunction with the American Thoracic Society has recently published consensus guidelines on the management of community-acquired pneumonia in adults. The antibiotics regimen chosen by the IDSA/ATS mainly relies on macrolides (with or without a β -lactam), or respiratory fluoroquinolones (e.g., levofloxacin or moxifloxacin), for outpatient therapy. They recommend respiratory fluoroquinolones or cephalosporins plus macrolides for hospitalized patients. In 2005, the IDSA/ATS also published evidence-based guidelines for hospital-acquired pneumonia (HAP), including health care-associated pneumonia (HCAP) and ventilator-associated pneumonia (VAP) that were again updated in 2007. The major goals of this evidence-based guideline for the management of HAP, VAP, and HCAP emphasize early, appropriate antibiotics in adequate doses, while avoiding excessive antibiotics by de-escalation of initial antibiotic therapy based on microbiologic cultures and the clinical response. If patients receive an initially appropriate antibiotic regimen, efforts should be made to shorten the duration of therapy from the traditional 14 to 21 days to periods as short as 7 days if the patient has a good clinical response with resolution of clinical features of infection and the etiologic pathogen is not *Pseudomonas aeruginosa*.^{9–10}

Pneumonia may be difficult to distinguish from atelectasis presenting as a localized infiltrate. Atelectasis can be seen with pulmonary embolism (PE), diaphragmatic dysfunction with volume loss, splinting from rib fracture or pleuritis, and in mechanically ventilated patients. Unfortunately, the presenting signs and symptoms may overlap in many instances, including dyspnea, chest pain, fever, and leukocytosis. High clinical suspicion is needed not to miss PE. Mortality of untreated PE has been reported to be about 30%, and with treatment approximately 8%.¹¹ High probability $\dot{V}/\dot{Q}$ scan carries a positive predictive value for PE of 88%.¹² With the addition of strong clinical suspicion, the positive predictive value is as high as 96%. About 12% of patients with low probability $\dot{V}/\dot{Q}$ scan may have angiographically proven PE. Therefore, if PE is clinically suspected, further evaluation after a low probability scan is needed. Evaluation of the lower extremities for deep venous thrombosis with Doppler ultrasonography is noninvasive and, if positive, obviates the necessity to perform pulmonary angiography. If the patient

does not have a high pretest probability of PE, some advocate repeating the Dopplers after 72 hours. If both Doppler studies are negative, there is a very low probability of significant PE. Pulmonary angiography has been shown to be safe in 755 patients enrolled in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study. The diagnostic utility of $\dot{V}/\dot{Q}$ scans for acute PE persists even in the presence of preexisting cardiac or pulmonary disease.^{13–14} In recent years there has been an increased use of D-dimer in patients presenting to the emergency department. D-dimer is formed from the degradation products of cross-linked fibrin by plasmin. It is very sensitive but nonspecific (elevated in almost all patients with carcinoma and most seriously ill hospitalized patients) for either DVT or PE. A negative D-dimer using enzyme-linked immunosorbent assays (ELISA) has a negative predictive value of 95%.¹⁵

Righini and colleagues showed that a diagnostic strategy including clinical probability, D-dimer, Doppler ultrasonography, and helical CT was highly cost-effective. A negative D-dimer in the setting of a negative Doppler ultrasound may obviate the need for further testing.¹⁶ Helical CT with a PE protocol has virtually replaced pulmonary angiography. The great benefit of CT is in providing an additional diagnosis to explain the patient's symptoms; its sensitivity and specificity ranges from 78% to 100%; its accuracy drops in the areas of atelectasis and segmental or subsegmental vessels. Multidetector scanning increases the sensitivity to 89% and can visualize thrombi up to the sixth pulmonary artery branch. The PISA-PED investigators recently published diagnostic algorithms based on their 40 years of experience that relies heavily on ventilation/perfusion lung scanning and only used multidetector scanning in 16% of the cases when there was discordance between pretest probability and lung scanning. This option may be very useful in patients who cannot tolerate IV dye secondary to renal insufficiency.¹⁷

Exacerbation of underlying obstructive lung disease is the most common cause of hypoxemic respiratory failure in patients who do not have infiltrates on chest radiography. The most important precipitants of ARF in patients with COPD are airway infection, congestive heart failure, anatomic interference with chest wall function (e.g., pleural effusion, pneumothorax, or rib fracture), and medication noncompliance.¹⁸ Additionally, PE and oversedation can also precipitate respiratory distress. The most common bacteria isolated from the airway and lungs of patients with COPD are *Haemophilus influenzae* and *Streptococcus pneumoniae*¹⁹ (and *Moraxella catarrhalis*). Antibiotics have been shown to be beneficial in patients having at least two of the following: dyspnea, increased sputum production, and sputum purulence.²⁰ Therefore a β -lactam antibiotic (e.g., amoxicillin, oral cephalosporin) or trimethoprim-sulfamethoxazole are frequently given during exacerbations of COPD. Recent studies have documented the benefit of oral corticosteroids in acute exacerbations of COPD. A large randomized controlled study of 271 patients with COPD exacerbation who were randomly assigned to receive either systemic corticosteroids or placebo for up to 2 weeks demonstrated that systemic corticosteroids reduced the 30-day treatment failure rate (23% versus 33%), the 90-day treatment failure rate (37% versus 48%), and hospital stay (8 versus 10 days), while improving lung function. Standard practice is to now treat all significant exacerbations with 7 to 10 days of oral corticosteroids.²¹

Another cause of respiratory failure with a normal chest radiograph is a right-to-left shunt. The presence of a significant shunt can be suspected when arterial hypoxemia is resistant to improvements with higher FiO_2 . An acute rise in right-sided cardiac pressures from PE or from right ventricular infarction may acutely open the foramen ovale and cause a right-to-left shunt. An echocardiogram with a bubble study may be used to detect a cardiac shunt. Finding radio-macroaggregated albumin in the brain or kidney after a lung perfusion scan is a sensitive and specific way of identifying the presence of a pulmonary or cardiac right-to-left shunt.

Microatelectasis is another cause of respiratory failure with a normal chest radiograph. This disorder almost always occurs in the setting of inadequate ventilation, usually seen in postoperative patients or in the setting of splinting secondary to chest wall pain. Diffuse alveolar collapse leads to bronchial breath sounds at the base of the lung without the infiltrate that is seen with obstructive atelectasis. The use of analgesics for pain, incentive spirometry, and the addition of positive pressure to the airway leads to resolution of this process. In hospitalized patients, inspiratory positive pressure breathing devices with nebulized therapy is often beneficial, especially in postoperative patients.

Hypercapnia may develop in patients with either a “black” (normal) chest radiograph or “white” (infiltrative) chest radiograph. Hypercapnic respiratory failure results usually from alveolar hypoventilation or severe $\dot{V}/\dot{Q}$ mismatching or a combination of the two. In patients with normal lungs, it generally occurs in the setting of reduction in central nervous system respiratory drive or acute neuromuscular weakness. In both cases, alveolar hypoventilation is the predominant mechanism. In patients with preexisting lung disease, hypercapnic respiratory failure usually occurs in the setting of severe lung disease and $\dot{V}/\dot{Q}$ mismatching. Whatever the triggering event may be, the patient is generally incapable of increasing the minute ventilation needed to compensate for the increased ventilatory workload requirements.

Reduction in central nervous system respiratory drive may be caused by sedative-hypnotic medications or depressed mental status from organic and metabolic or hypoxic encephalopathy. Although patients with stroke or brain hematoma rarely have clinically significant depression of respiratory drive, hypercapnia may still occur if the breaths are shallow with small tidal volumes, increasing dead space ventilation and resulting in alveolar hypoventilation. Acute hypoxemia that results in global brain hypoxia may also lead to depression of mental status and alveolar hypoventilation.

Neuromuscular weakness is a less common cause of clinically significant alveolar hypoventilation. Typically the tidal volume is reduced secondary to shallow breathing, with increased respiratory rate, in an attempt to restore minute ventilation. This type of shallow and rapid breathing increases dead space ventilation, and given the same minute ventilation, alveolar ventilation will be reduced. Amyotrophic lateral sclerosis, high cervical spinal cord injury, Guillain-Barré syndrome, myasthenia gravis, phrenic nerve paralysis, and muscular dystrophy may result in both hypercapnic and hypoxemic respiratory failure. Hypercapnia may also result from respiratory muscle fatigue after a period of sustained rapid breathing, such as seen in the later stages of acute exacerbations of asthma or COPD.

Hypercapnic respiratory failure that occurs in the absence of respiratory drive depression or neuromuscular weakness is usually caused by severe $\dot{V}/\dot{Q}$ mismatching and often associated with conditions that increase CO_2 production $\dot{V}/\dot{Q}$. Fever increases $\dot{V}\text{CO}_2$ by 13% for each degree Celsius.²² Patients with severe preexisting $\dot{V}/\dot{Q}$ abnormality, in particular those with large low $\dot{V}/\dot{Q}$ areas, may not be able to compensate for the increased workload. Therefore when compensatory efforts fail in a COPD patient with pneumonia and fever, hypercapnia ensues. Patients with severe lung disease, baseline hypoxemia, and hypercapnia are also at risk of worsening the hypercapnia when they receive oxygen supplementation. When these patients require oxygen therapy for hypoxemic exacerbation, extreme caution must be exercised to prevent too much oxygen. Low flow oxygen (1 to 2 L/min nasal cannula or 24% to 28% FiO_2 by mask) should be started and titrated up until the saturation is approximately 90%. If acute severe hypercapnia occurs, assisted ventilation is the treatment of choice. The pathophysiology of this process is still being debated and may involve three mechanisms.²³⁻²⁵ Worsening of $\dot{V}/\dot{Q}$ mismatching is believed by many to be the major mechanism. Additionally, displacement of CO_2 molecules from hemoglobin (known as the Haldane effect) has been proposed but probably plays only a small role. Finally, suppression of hypoxic ventilatory drive has long been debated and remains controversial.

Management

The initial approach to managing patients in acute respiratory failure is supportive. The essential first step remains assessment of airway patency, presence of breathing, and adequacy of circulatory function. Once this is ensured, specific treatments must be directed at the underlying disease that initiated respiratory failure. Specific therapy for each of these disorders is beyond the scope of this chapter but has been reviewed.²⁶

In most cases, administration of supplemental oxygen is required. The ultimate goal of oxygen therapy is to provide adequate oxygen to the tissues, thereby preserving tissue and organ function. Because there is no clinically useful measure of cellular oxygen tension, tissue hypoxia can only be indirectly predicted from overall organ function and oxygen transport. The critical level of hypoxemia that compromises organ function varies depending on the organ system and local factors. Clinical studies in patients without adaptive mechanisms suggest that short-term memory is adversely affected at PaO_2 less than 55 mm Hg.²⁷ Generally, PaO_2 of about 60 mm Hg, usually corresponding to SaO_2 of about 90%, is considered as an adequate target. Further increase in PaO_2 offers little additional benefits because of the shape of the oxygen-hemoglobin dissociation curve and determinants of arterial oxygen content and may potentially increase the risk of hypercapnia in some patients. Therefore hypoxemic patients with severe lung disease, especially those with baseline hypercapnia, must be monitored closely with serial blood gases for correction of hypoxemia and prevention of worsening hypercapnia. The use of pulse oximetry to follow the adequacy of oxygenation may be appropriate if the pulse oximetry saturation (SpO_2) has been properly calibrated to accurately reflect co-oximetry saturation (SaO_2) of the patient when hypercapnia is not a concern.

Once the decision for oxygen supplementation has been made, the next step is to choose the method of delivery. In patients who are intubated, delivery of oxygen can be accomplished through a ventilator or through a T-piece, the latter if

mechanical breaths are not needed. For patients who are not intubated, there are several choices of oxygen delivery systems.

Nasal cannula is the most commonly used low-flow system. It delivers pure (100%) oxygen at various rates up to 5 to 6 L/min. Rates beyond this are associated with nasal mucosal and septal complications. This system is simple to use and comfortable, allowing the patient to speak, eat, and drink without much interference. As is true with all low-flow systems, the FiO_2 is not accurate, depending on several factors, including total minute ventilation. Investigators have measured an FiO_2 of 48% with 6 L/min and high-flow heat humidified nasal cannulas may go up to 15 L and achieve FiO_2 in the 75% range.²⁸⁻²⁹ A simple face mask also delivers low-flow oxygen with a somewhat higher FiO_2 than a nasal cannula because of the presence of 100 to 200 mL of reservoir space between the mask and the patient's face. It must be removed transiently when the patient eats or drinks. Face masks with reservoir bags come in two varieties. A partial rebreather mask has a reservoir that is filled with pure oxygen mixed with a small amount of early exhaled gas that mainly comes from high oxygen tension dead space. This mask is able to achieve FiO_2 of 0.6 to 0.8. A non-rebreather mask has a reservoir containing pure oxygen and is not mixed with exhaled gas. In addition, there are one-way exhalation valves allowing exhaled gas to leave the mask without inhaling air. This mask allows the achievement of FiO_2 close to 0.9, but not quite 1.0, because of the presence of small amounts of exhaled gas in the space between the mask and the face.

Venturi masks are low-flow masks that use the Bernoulli principle to entrain room air when pure oxygen is delivered through a small orifice, resulting in a large total flow at predictable FiO_2 . The size of the orifice determines the FiO_2 . This oxygen delivery system is useful in patients with ARF who require oxygen supplementation, but in whom there is substantial risk for development or worsening of hypercapnia because the FiO_2 does not fluctuate significantly even with considerable changes in the patient's minute ventilation. Venturi masks or a Venturi device in a humidifier-mixer is accurate only to 40% to 50% FiO_2 ; above this range, many patients overbreathe the system. When a higher FiO_2 is required, a high-flow mask (e.g., Misty-Ox) and a high-flow regulator (that can go up to 30 L/min) is recommended. With all these masks, there is significant deterioration of oxygen delivery as the respiratory rate increases, as when the patient is in respiratory distress. At 30 breaths/min, the FiO_2 delivered by a 15-L oxygen mask can drop from 95% to 60% due to entrainment of ambient air and dilution of the inspired oxygen concentration. In a recent study by Wagstaff, the high levels of inspired oxygen concentration was achieved by a 15-L nasal cannula using a Vapotherm system that humidifies and warms the oxygen-air mix and makes it more tolerable to the patient.²⁸ An alternative is to use a non-rebreather mask where a reservoir bag with a one-way flap is connected to the mask and fills during the patient's expiration.

Aside from the risk of hypercapnia, there are other risks associated with oxygen therapy. High FiO_2 decreases the amount of inert nitrogen that fills and stabilizes peripheral airways and alveoli while oxygen is being rapidly removed from the alveoli, resulting in atelectasis. Absorption atelectasis causes a decrease in vital capacity and an increase in right-to-left shunt, which leads to worsening of hypoxemia. This is more frequently seen at FiO_2 above 0.7. High FiO_2 can also lead to tracheo-bronchitis and acute lung injury with capillary leak syndrome.³⁰ When this happens it is often difficult to distinguish from worsening of the

underlying condition that initially precipitated ARF. In general, FiO_2 of 1.0 can be used for 24 hours and FiO_2 of 0.9 can be used for 72 hours without significant sequelae. FiO_2 of 0.6 or less is usually well tolerated without significant long-term histologic and physiologic changes. If a patient requires very high FiO_2 with the above methods, ventilatory-assist devices should be considered to allow the FiO_2 to be lowered, thereby decreasing the risks of atelectasis and oxygen toxicity. These include non-invasive ventilation using continuous positive airway pressure through nasal or face mask and invasive mechanical ventilation through an endotracheal tube.

Over the past few years there has been a renewed interest in the use of noninvasive ventilation in the management of ARF. Several pilot studies have shown useful applications of these techniques in avoiding intubation in some patients with ARF. Larger clinical trials are needed to further define the role of noninvasive mechanical ventilation in ARF, especially in those patients with advance directives for no intubation and with potentially reversible processes causing ARF.

Although positive airway pressure can be applied to nonintubated patients, these techniques may lead to gastric distention and vomiting. Continuous positive airway pressure is best tolerated at low levels (10 cm H_2O) and for brief periods. Bi-level positive airway pressure allows for the inspiratory pressure to be set at a higher level (e.g., 10 to 20 cm H_2O) than the expiratory pressure (e.g., 0 to 10 cm H_2O). There have now been 14 meta-analyses to date on noninvasive positive pressure ventilation (NPPV), which range from bilevel positive airway pressure machines applied via a full face mask, all the way to a conventional ventilator connected to a mask device that covers the whole face. Its success varies according to the purpose and the diagnosis for which it is used. The best survival data and earliest applications were in exacerbations of COPD and acute cardiogenic pulmonary edema. In COPD, the application of NPPV decreased both mortality and length of hospital stay with a number needed to treat of five. Intubation risk was reduced by 28% in a meta-analysis by Keenan and colleagues. In cardiogenic pulmonary edema, mortality was reduced by 45%.³¹ Other trials proved its effectiveness in acute respiratory failure following lung resection, acute asthma, solid organ transplantation, and in immunocompromised patients. NPPV has also been used in weaning patients from mechanical ventilation and the application of NPPV in one study shortened mechanical ventilation days.³² Other studies, however, have shown increased mortality when NPPV is used in patients requiring vasopressors, lack of improvement of respiratory acidosis, refractory hypoxemia, fatigue, and inability to clear secretions. These clinical parameters should be evaluated after 1 hour of initiation of NPPV, when the first arterial blood gas is obtained. Confalonieri developed a chart predicting the success of NPPV that included APACHE score, acidosis, level of consciousness, and respiratory rate.³³ As can be imagined, patients with a depressed level of consciousness, a pH less than 7.25, and a respiratory rate greater than 35 are more likely to fail and probably benefit from urgent intubation without a trial of NPPV. All studies evaluating NPPV published exclusion criteria that may very well be deemed as contraindications: cardiac or respiratory arrest, hemodynamic instability, the uncooperative patient, patients with facial trauma, copious secretions, or significant risk of aspiration. Those patients should undergo intubation and conventional mechanical ventilation. Intubation facilitates

the delivery of higher tidal volumes and the application of positive end-expiratory pressure needed to avert oxygen toxicity.

Mechanical Ventilation

Mechanical ventilation is a method of supporting intubated patients during illness when spontaneous ventilation is inadequate to sustain life or to achieve a therapeutic target. The clinical objectives are as follows³⁴: (1) to correct hypoxemia; (2) to correct acute respiratory acidosis; (3) to relieve respiratory distress; (4) to prevent or reverse atelectasis; (5) to rest respiratory muscles or prevent fatigue; (6) to allow sedation and neuromuscular blockade; (7) to decrease systemic or myocardial oxygen consumption; (8) to reduce intracranial pressure through controlled hyperventilation; and (9) to stabilize the chest wall.

In general, mechanical ventilators can be divided into two categories: negative pressure ventilators and positive pressure ventilators. The iron lung is the prototype of negative pressure ventilators that gained its popularity during the polio epidemics. Today, newer generations of negative pressure ventilators are still available under different names, such as cuirass, body suit, Porta Lung, pneumobelt, pneumowrap, pneumosuit, and so on. They function by creating a negative pressure outside the chest wall, causing chest wall expansion and subsequent inspiration, simulating physiologic breathing. On release of the negative pressure, exhalation is passively accomplished. In the hospital setting, positive pressure ventilators are the mainstay of mechanical ventilation owing to various features and adjunctive modes that allow for more sophisticated delivery of conditioned gas and assistance in ventilation.

Positive pressure inflation of the lung can be achieved with machines that terminate inspiration according to volume, pressure, or time. The latest generation of positive pressure ventilation allows the physician to select among these options and allows for pressure support (a flow cycled mode of ventilation) and reverse inspiratory to expiratory (I/E) ratio ventilation.

Volume-cycled ventilators deliver preset inspiratory flow to achieve a target volume, regardless of the pressure required. This system guarantees the tidal volume unless the peak pressure during inspiration exceeds the high pressure limit, in which case the resulting volume is less than the preset volume. High pressure delivered to diseased, noncompliant lungs may predispose to barotrauma. Pressure-cycled ventilators deliver preset positive pressure throughout inspiration; however, the resulting tidal volume is variable depending on the compliance of the lungs. A true time-cycled ventilator does not depend on the patient's lung characteristics or even whether the ventilator is attached to the patient to end inspiration; therefore it is important to recognize that a complete ventilatory cycle may occur without generating a tidal volume. Pressure support ventilation can be used either as a ventilatory mode or as an adjunctive mode. As a ventilatory mode, the pressure is set to produce a desired level of tidal volume similar to a pressure-cycled system, whereas in an adjunctive mode the pressure is set just high enough to overcome the tubing and circuit resistance during inspiration such that the level of pressure support does not increase the spontaneous tidal volume of the patient. A pressure support of 5 to 10 cm H₂O is usually adequate for the adjunctive mode.

Volume-cycled ventilators are most commonly used in the intensive care unit. In an assist-control (AC) mode, each patient breath that is recognized by the ventilator is assisted with a preset volume and flow rate in addition to a number of mandatory

breaths per minute. In an intermittent mandatory ventilation (IMV) mode, the patient can take spontaneous unassisted breaths between the mandatory breaths. A synchronized IMV (SIMV) mode synchronizes the machine mandatory breaths to the patient's spontaneous breaths to avoid breath stacking. A pressure support system can be used to augment the spontaneous breaths of patients in the SIMV mode, while at the same time guaranteeing a minimum number of mandatory breaths.

AC mode allows the patient to rest because each recognized spontaneous breath is assisted. Patients with respiratory muscle fatigue should be allowed to rest on this mode. Patients with sepsis and hypotension benefit from this mode by decreasing respiratory muscle work, which accounts for a significant portion of oxygen consumption during hypoperfusion states. Similarly, in patients with cardiogenic pulmonary edema, decreased work of breathing translates to decreased myocardial work demand. However, in patients with abnormal homeostatic mechanisms, such as hepatic encephalopathy, increased central respiratory drive may result in respiratory alkalosis. The SIMV mode is more homeostatic because the patient can determine the tidal volume needed; however, the work of breathing is higher and proportional to the amount of spontaneous ventilation relative to the assisted ventilation. The SIMV mode is primarily used in patients with severe air flow obstruction who tend to air trap when each breath is a relatively large, positive pressure breath. When the mandatory rate is set beyond the patient's spontaneous rate, or if the patient is completely paralyzed, the two modes are practically indistinguishable and the patient will receive only the mandatory breaths. Newer modes of ventilation include airway pressure release ventilation and bilevel modes. The first one allows for continuous positive airway pressure with an intermittent pressure release phase. A P_{high} (high pressure) and P_{low} (low pressure) are set and the patient is allowed spontaneous breathing independently of the ventilator cycle. Rather than continuously distending and deflating the alveoli, the P_{high} keeps them inflated during the entire respiratory cycle and only briefly releases them to P_{low}, thus aiding in ventilation and CO₂ removal. Ventilation can be improved by increasing the T_{high}—the time spent at P_{high}—and reducing the T_{low}. Therefore the APRV mode may result in lower peak airway pressures and less sedation for the patient.³⁵

In addition to ventilator modes, prone positioning has been extensively studied. Most research shows indeed an improvement in oxygenation and P_{aO₂} to F_{IO₂} ratios, but studies fail to show an increase in survival or less ventilator days; however, a French study showed a decreased incidence of ventilator-associated pneumonia in the prone ventilation group. Papazian and colleagues studied a combination of prone ventilation and inhaled nitric oxide, in patients with ARDS. This study demonstrated an additive improvement in the P_{aO₂} to F_{IO₂} (P/F) ratio, but the study was small and not powered to show survival outcome differences.³⁶

After the mode of ventilation is decided, the tidal volume, respiratory rate, F_{IO₂}, and inspiratory flow rate must be set on the ventilator. The range of tidal volumes used in mechanical ventilation is between 5 and 15 mL/kg of ideal body weight. When low tidal volumes (6 to 8 mL/kg ideal body weight) are used, positive end-expiratory pressure (PEEP) or sighs (generally each sigh volume is 2 to 3 × tidal volume) should be given at set intervals to prevent microatelectasis. As a general rule, with severe airway obstruction or ARDS, 6 mL/kg up to 8 mL/kg tidal volume is reasonable [refer

to ARDSnet.org ventilator chart]. Postoperative patients with normal lungs are frequently started on 8 to 12 mL/kg, whereas patients with neuromuscular disease receive 10 to 15 mL/kg. It is generally safe to select a tidal volume that generates a peak alveolar pressure less than or equal to 35 cm H₂O (with plateau pressures less than 30 to 32 cm H₂O). The rate should be chosen in conjunction with the tidal volume to provide minute ventilation that maintains a normal pH. A rate of 12 to 18 breaths/min will usually be adequate. Once the patient is stable, the ventilator rate is often adjusted 2 to 4 breaths/min below the total respiratory rate. This prevents excessive work of breathing in the SIMV mode and provides an adequate backup rate in the AC mode.

In emergent situations, the FIO₂ should be set at 0.9 or 1.0 with later adjustments guided by arterial blood gases. The FIO₂ can be titrated down to achieve an SaO₂ of more than 90% (usually a PaO₂ of 60 mm Hg). More than 24 hours with an FIO₂ greater than or equal to 0.9, or prolonged use of an FIO₂ greater than or equal to 0.6, requires the addition of PEEP for prevention of oxygen toxicity. In general, this can be achieved with a PEEP of 5 to 15 cm H₂O. The inspiratory flow rate is usually set by the respiratory therapist at a level of 40 to 55 L/min. It is mandatory for the peak flow setting (inspiratory flow rate) of the ventilator to be greater than the patient's inspiratory flow demand. Otherwise the patient breathes against the resistance of the ventilator circuitry, and this results in the patient "fighting the ventilator." The flow setting should be three and one half to four times the minute ventilation to achieve an I/E ratio of 1:1.2 to 1:1.5. In patients with severe obstructive lung disease, I/F ratios of 1:4 to 1:6 may be necessary.

Complications may arise during the course of mechanical ventilatory support. A deliberate and stepwise approach should be followed in the management process. Patient distress may arise from general discomfort or, frequently, from inadequate ventilation or the feeling of dyspnea. If hypoventilation is part of the overall strategy, then the patient needs to be sedated. Accidental hypoventilation may result from kinking of the endotracheal tube, mucus plugging, accidental mainstem intubation, pneumothorax, ventilator circuit leak, or ventilator disconnection. If the ventilator alarms have been set properly, they are frequently the first indicator of the acute problem, especially in a comatose, sedated, or paralyzed patient. A high pressure alarm is usually caused by obstruction of the airway or acute change in lung compliance, whereas a low volume alarm suggests decreased respiratory drive, a leak within the system, or a disconnected ventilator. During a high pressure alarm distress, the patient should be disconnected from the ventilator and hand ventilated with an ambu bag at an FIO₂ of 1.0, while a systematic search for the cause is being done. Unequal breath sounds may suggest a pneumothorax or slippage of the endotracheal tube into a mainstem bronchus. Acute changes in hemodynamics are more suggestive of the former. Difficulty in hand ventilation should suggest kinking of the tube or mucous plugs; therefore a suction catheter should be passed for diagnostic and therapeutic purposes. Chest radiography may aid the diagnosis and demonstrate lobar or complete collapse of the lung. If aggressive chest physiotherapy and inhaled mucolytics (e.g., Pulmozyme) are not effective, bronchoscopy may be required. If tension pneumothorax is strongly suspected, placement of a 14-gauge needle [angiocatheter] into the second intercostal space along the mid-clavicular line can relieve the tension immediately. Once this is done, a chest tube should always be placed whether a tension

pneumothorax was present or not since the patient is receiving positive pressure ventilation and the catheter may have punctured the visceral pleura.

When a leak in the circuit is suspected, the ventilator tubing can be changed. If the leak is from the endotracheal tube, it can happen anywhere from the valve of the pillow to the cuff. A three-way stopcock inserted into the valve may correct the problem if the leak comes from the valve, obviating the need to change the endotracheal tube. If it does not stop the leak, then the site of the leak may be in the pillow, the pilot line, or the cuff itself and may necessitate replacement of the endotracheal tube over a flexible stylet.

Pneumonia occurs in approximately 30% of patients receiving ventilator support. The risk increases with the duration of ventilator support at a rate of about 1% per day.³⁷ Pneumonia may be difficult to diagnose in patients with a "white" chest radiograph and may require either empirical therapy with a presumptive diagnosis or the use of bronchoscopy with a sterile brush with greater than or equal to 10³ colony forming units/milliliter on quantitative culture considered a significant finding [or 10⁴ on bronchoalveolar lavage or 10⁵ on endotracheal aspirate].

Physiologic measurements such as maximum inspiratory pressure (P_Imax = -20 cm H₂O), vital capacity (VC = 10 mL/kg), and minute ventilation (MV = 15 L/min) are used to determine when a weaning trial should be done. Recently, the ratio of respiratory frequency (f) to tidal volume (V_T) during 1 minute of spontaneous breathing was found to be more accurate.³⁸ If f/V_T is less than 100 breaths/min/L, a weaning trial is likely to be successful. The usual method of weaning includes trials of increased spontaneous breathing through a T tube or on pressure support ventilation (PSV, up to 10 cm H₂O). When patients can breathe spontaneously for more than 30 minutes to 2 hours without a significant change in their hemodynamics, respiratory rate, or minute ventilation, they can usually be successfully extubated.³⁹

Conclusion

Acute respiratory failure implies an inability to maintain adequate oxygenation for tissues or adequate removal of carbon dioxide from tissues. The differential diagnosis should be suggested by the radiographic appearance of the chest radiograph and by the patient's history and physical examination. A specific diagnosis should be pursued and frequently requires ancillary studies such as blood or sputum cultures, bedside spirometry, pulmonary artery catheterization, perfusion lung scan, or a CT angiogram using multidetector scanners. This allows the physician to initiate specific therapy for the underlying cause of acute respiratory failure. These patients often require supportive therapy.

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Massive Acute Pulmonary Embolism

Guy Meyer

CHAPTER 32

Definition	Thrombolytic Agents
Diagnosis of Massive Pulmonary Embolism	Pulmonary Embolectomy
General Medical Support	Conclusion

IN-HOSPITAL MORTALITY of clinically stable patients without major comorbidity receiving anticoagulant treatment for pulmonary embolism (PE) has been reported to vary between 1% and 2% in recent controlled trials.^{1,2} By contrast, more than 25% of patients having a pulmonary embolism and low blood pressure die in the hospital.³⁻⁵ A subgroup of patients with normal blood pressure who have right ventricular failure on admission as detected by echocardiography may have a higher mortality rate than patients with normal echocardiographic findings.⁶ Recent data further suggest that cardiac biomarkers, such as troponin and brain natriuretic peptide (BNP), also help identify patients with adverse outcomes among those with normal blood pressure.^{7,8} Accordingly, it has been suggested that PE be classified into two main categories: (1) massive PE defined by a systolic blood pressure of 90 mm Hg, or a pressure drop of 40 mm Hg for at least 15 minutes, and (2) nonmassive PE.⁹ An additional category, submassive PE, is considered to be a subcategory of nonmassive PE with evidence of right ventricular dysfunction.⁹ Suspected cases of massive PE require prompt confirmation using bedside tests. In these patients, supportive measures are needed and thrombolytic therapy is indicated.¹⁰ Pulmonary embolectomy is useful in a small subset of patients with massive PE, whereas catheter embolectomy requires additional evaluation. The clinical benefit of thrombolytic therapy in patients with submassive PE is less clear and international experts currently advise against using thrombolytic therapy in these patients.¹⁰

Definition

Pulmonary vascular obstruction has long been considered the main criteria for defining massive pulmonary embolism; however, recent studies strongly suggest that clinical tolerance rather than vascular obstruction is the main determinant of hospital mortality in patients with PE. As a result, massive PE is now defined as PE with persistent systemic hypotension (i.e. systolic blood pressure of 90 mm Hg for at least 15 minutes or a drop of systolic blood pressure of at least 40 mm Hg).⁹ Alpert and associates reported on 144 patients with angiographically proven PE: they found that PE-related mortality was 5% in patients with a vascular obstruction below 50% and 16% in those patients with a pulmonary vascular obstruction exceeding 50%. However, the excess mortality in the latter group was limited to patients with cardiogenic shock as a result of PE. The mortality rate was

greater in this group of patients (32%) than in those with high vascular obstruction but normal blood pressure (6%).⁴ More recently, 1001 patients with pulmonary hypertension because of PE were grouped into four categories by Kasper and associates: (1) those with normal blood pressure; (2) those with isolated arterial hypotension; (3) those with cardiogenic shock; and (4) those who sustained cardiopulmonary resuscitation.⁵ Hospital mortality was 8% in group 1, 15% in group 2, 25% in group 3, and 65% in group 4. The mortality rate listed in the International Cooperative Pulmonary Embolism Registry (ICOPER) was 58% for patients who were hemodynamically unstable at the time of presentation, and 15% for those who were hemodynamically stable.³ In that study, systolic blood pressure below 90 mm Hg was used as an independent predictor for early death (hazard ratio: 2.9 [95% confidence interval: 1.7 to 5.0]). Those patients represented only 4.2% of the total population included in the study.

Patients with normal blood pressure have a much better clinical outcome and are considered as having nonmassive PE.⁹ However, several studies have identified a subgroup of patients considered as having submassive PE with normal blood pressure who may have an increased risk of mortality. Ribeiro and colleagues were the first to suggest that patients with right ventricular failure may have increased mortality. In that study, 126 consecutive patients with PE were examined with echocardiography on the day of diagnosis. Patients were divided into two groups: group A ($n = 56$) with normal or slightly reduced RV function and group B ($n = 70$) with moderately or severely reduced RV function. Four deaths occurred in group A and 15 in group B ($p = 0.04$).⁶ However, the patient population was composed of stable and unstable patients, and the outcome of patients with normal blood pressure with and without right ventricular dysfunction was not specified. Five studies have evaluated the value of echocardiography as a prognostic tool in hemodynamically stable patients with PE.¹¹⁻¹⁵ Right ventricular dysfunction was associated with a 2.4-fold (95% CI: 1.3 to 4.4) increased risk of hospital mortality. Criteria used to define right ventricular dysfunction differed from one study to another and the risk of death was not adjusted for major confounding factors. More recently, the role of cardiac biomarkers as early predictors of outcome has been investigated in several studies. Four studies assessed brain natriuretic peptide in clinically stable patients with PE.^{8,13,14,16} A high BNP level was associated with a ten-fold increase in the risk of hospital death (95% CI: 3.2 to 35.3).

Similarly, increased values of pro-brain natriuretic peptide and troponin are associated with a 5.7-fold (95% CI: 2.2 to 15.1) and 7.5-fold (95% CI: 3.1 to 18.1) increased fatality risk.^{8,12,17} However, most studies were carried out in individual medical centers and included a small number of patients. Also, the threshold values for each biomarker differed from one study to another and the risk was not adjusted for major confounders. As a result, the role of these biomarkers in selecting patients at risk requires further evaluation in larger multicenter cohorts.

Diagnosis of Massive Pulmonary Embolism

The risk of death in patients with massive PE is maximal during the first few hours following their admission to the hospital and prompt diagnostic confirmation and treatment are mandatory. In addition, in-hospital transportation of hemodynamically unstable patients is associated with an increased risk of morbidity and mortality; thus every effort should be made to confirm the diagnosis of suspected massive PE using bedside diagnostic tests. No specific literature is available on the diagnosis of massive PE; however, the basic principles for diagnosing clinically stable patients with suspected PE can probably be applied to unstable patients.¹⁸ Indeed, evaluating the clinical probability of PE should be the first step in the diagnosis process. Several rules have been published, but clinical probability can also be based on the clinical gestalt of risk factors, clinical signs and symptoms, chest radiography, blood gas analysis, and ECG.^{19,20} If the clinical probability is high, which is often the case when massive PE is suspected, a D-dimer test result is of little value.^{18,21,22} The positive likelihood ratio of bedside transthoracic echocardiography demonstrating right ventricular dilation (5.0; 95% CI: 2.3 to 10.6) is high enough to confirm PE when the clinical probability is high.¹⁸ Presence of clots in the right heart chambers is rare and is not required to confirm PE. In addition, echocardiography can rule out left ventricular dysfunction and pericardial tamponade,

which may clinically mimic massive PE. Conversely, the negative likelihood ratio of a normal echocardiography (0.6; 95% CI: 0.4 to 0.9) is not low enough to rule out PE when the clinical probability is high.¹⁸ If echocardiography is normal, spiral computed tomography of the pulmonary arteries is required to confirm or rule out PE after the patient's hemodynamic status has been stabilized (Fig. 32-1).

General Medical Support

Oxygen

Arterial hypoxemia is a common finding in patients with acute PE. The degree of hypoxemia is usually moderate; in 81 patients submitted to pulmonary embolectomy, the mean arterial partial pressure of oxygen breathing room air was 51 ± 12 mm Hg at the time of admission.²³ Oxygen administration by nasal cannula or facemask is usually sufficient for maintaining arterial oxyhemoglobin saturation within the normal range. Mechanical ventilation is only rarely required and positive pressure must be applied very cautiously because of its detrimental effects on cardiac output in right ventricular failure.

Fluid Loading

Acute pulmonary artery obstruction increases right ventricular afterload and end-diastolic and end-systolic right ventricular volumes and decreases right ventricular stroke volume. These changes may reduce left ventricular preload and impair left ventricular function as a result of ventricular interdependence, and a decrease in cardiac output with circulatory failure may ensue. Fluid loading increases the right ventricular end-diastolic volume and may increase cardiac output by the Frank-Starling mechanism, but it may also increase the leftward septal displacement, thereby worsening left ventricular diastolic function. Animal studies have addressed this issue with conflicting results. The effect of fluid loading in patients with PE and circulatory failure has been evaluated in two studies.^{24,25} In 13 mechanically ventilated patients with massive PE, the cardiac index increased

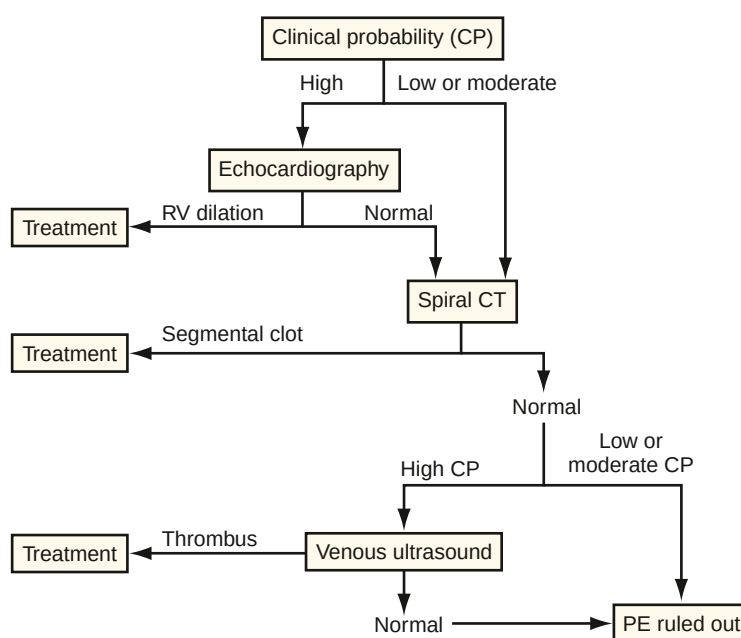


Figure 32-1. Suggested diagnostic algorithm for patients with suspected massive pulmonary embolism (PE). RV, right ventricular.

from 1.7 ± 0.6 L/min/m² to 2.0 ± 0.7 L/min/m² after a 600-mL fluid challenge.²⁵ More recently, we observed a significant 25% increase in the cardiac index from 1.7 ± 0.2 to 2.1 ± 0.2 L/min/m² in 10 patients after a 500-mL fluid challenge was administered over 15 minutes.²⁴

Inotropic Support

Inotropic support is required when shock persists despite fluid loading. Isoproterenol, dobutamine, dopamine, and norepinephrine all improve the hemodynamic status in animals with experimental massive PE and hypotension. However, severe hypotension is rarely observed in patients with massive PE and most of these drugs have not been evaluated in clinical studies. In 10 patients with massive PE, Jardin and colleagues found a 35% increase in the cardiac index during dobutamine infusion as a result of stroke volume increase, whereas the heart rate decreased significantly.²⁶

Thrombolytic Agents

Hemodynamic Effects

Thrombolytic treatment induces a rapid decline in pulmonary artery resistance in patients with acute PE and pulmonary hypertension. Alteplase, given as a 100 mg dose over 2 hours, reduces the mean pulmonary artery pressure from 30.2 ± 7.8 mm Hg to 21.0 ± 6.7 mm Hg and increases the cardiac index from 2.1 ± 0.5 L/min/m² to 2.4 ± 0.5 L/min/m² after 2 hours, whereas no significant change is observed with heparin.²⁷

Reduction of Pulmonary Vascular Obstruction

Thrombolytic treatment reduces vascular obstruction quicker than heparin alone. Pulmonary vascular obstruction as assessed by the Miller index decreased significantly from 28.3 ± 2.9 to 24.8 ± 5.2 two hours after the start of alteplase infusion, whereas no significant difference was observed in patients who received heparin alone.²⁷ Importantly, however, the differences between the thrombolysis and the heparin group disappeared after 7 days of follow-up.²⁷ Thus thrombolytic therapy restores

pulmonary vascular flow and right heart hemodynamics faster than heparin alone, but both treatments result in a similar degree of improvement after 1 week.

Effects of Thrombolysis on Recurrent PE, Major Bleeding, and Mortality

Eleven controlled studies compared thrombolytic therapy with heparin in patients with PE (Table 32-1).²⁷⁻³⁷ Only one small study included patients with massive PE alone,³² four studies included some patients with massive PE and a majority of patients with submassive PE,^{28,30,35,37} and six trials included clinically stable patients with or without right ventricular dysfunction.* To date, no study has compared thrombolytic therapy and heparin in patients with submassive PE. Eight studies had an open design and three were placebo controlled. PE diagnosis was confirmed using invasive procedures in seven trials.^{27-30,35-37} Recurrent PE was objectively confirmed in only two trials.^{28, 33} Criteria for major bleeding were not explicitly given in some studies and differed significantly among other studies. Overall, only 748 patients were included in these studies, and their outcome was analyzed in four meta-analyses.³⁸⁻⁴¹ The overall death rate was lower for patients who had thrombolytic therapy (4.3%) when compared with those that received heparin alone (5.9%; OR, 0.70; 95% CI, 0.37 to 1.30). The overall rate of major bleeding was 9.1% in patients who were allocated to thrombolytic treatment and 6.1% in those who received heparin. The relative risk for major bleeding associated with thrombolysis was 1.42 (95% CI, 0.81 to 2.46).³⁸ Most major bleeding cases occurred in studies that used central venous access for angiography and invasive hemodynamic monitoring (Table 32-2). Overall, the rate of major bleeding averages 20% in patients receiving fibrinolytic therapy and 12.5% in those receiving heparin. The rate of major bleeding reported in the most recent studies using noninvasive diagnostics and monitoring is far lower, averaging 2% in patients who were receiving thrombolytic treatment and 3% in patients who were receiving heparin.³¹⁻³⁴ Intracranial bleeding remains a major concern in patients receiving thrombolytic treatment for PE, with an estimated incidence of intracranial bleeding of 1.9%

*References 27, 29, 31, 33, 34, 36.

Table 32-1. Controlled Trials Comparing Heparin and Thrombolytic Therapy in Patients with PE

Study	n	Unstable patients (n)	Fibrinolytic drug	Diagnostic procedure
UPET ²⁸	160	Yes (11)	Urokinase	Invasive
Tibbitt ³⁷	30	Yes (14)	Streptokinase	Invasive
Ly ³⁵	25	Yes (2)	Streptokinase	Invasive
Dotter ³⁰	31	Yes (2)	Streptokinase	Invasive
Marini ³⁶	30	No	Urokinase	Invasive
PIOPED ²⁹	13	No	rtPA	Invasive
Levine ³⁴	58	No	rtPA	Noninvasive
Dalla-Volta ²⁷	36	No	rtPA	Invasive
Goldhaber ³¹	101	No	rtPA	Mainly noninvasive
Jerjes-Sanchez ³²	8	Yes (8)	Streptokinase	Noninvasive
Konstantinides ³³	256	No	rtPA	Mainly noninvasive

rtPA: recombinant tissue-type plasminogen activator

Table 32-2. Results of the Randomized Trials Comparing Thrombolytic Therapy and Heparin in Patients with PE

Study	<i>n</i>		<i>Major Bleedings* (n)</i>		<i>Recurrent PE* (n)</i>		<i>Deaths (n)</i>	
	Heparin	Fibrinolysis	Heparin	Fibrinolysis	Heparin	Fibrinolysis	Heparin	Fibrinolysis
UPET 1973 ²⁸	78	82	11	22	15	12	7	6
Tibbutt 1974 ³⁷	17	13	1	1	1	0	1	0
Ly 1978 ³⁵	11	14	2	4	0	0	2	1
Dotter 1979 ³⁰	16	15	0	0	1	0	2	1
Marini 1988 ³⁶	10	20	0	0	0	0	0	0
PIOPED 1990 ²⁹	4	9	0	1	0	0	0	1
Levine 1990 ³⁴	25	33	0	0	0	0	0	0
Dalla-Volta 1992 ²⁷	16	20	2	3	1	1	1	2
Goldhaber 1993 ³¹	55	46	1	3	5	0	2	0
Jerjes Sanchez 1995 ³²	4	4	0	0	0	0	4	0
Konstantinides 2002 ³³	138	118	5	1	4	4	3	4

*Some events (recurrent PE or bleedings) were fatal and counted both as events and in the deaths.

(95% CI, 0.7 to 4.1).⁴² Risk factors for major bleeding include old age and invasive diagnostic procedures.⁴³

Massive Pulmonary Embolism

One single small randomized trial has compared streptokinase with heparin in patients with massive PE. Although 40 patients were expected to be recruited, the trial was terminated early after only eight patients had been included. All patients had cardiogenic shock on inclusion; four were allocated to streptokinase and survived, and four were allocated to heparin and died during the 72 hours following randomization.³² These results prompted the ethics committee to stop the trial. In a recent meta-analysis of the controlled studies comparing thrombolytic therapy with heparin in patients with PE, a subgroup analysis was performed on the five studies that included patients with massive PE and shock.³⁸ The patients allocated to thrombolysis had a mortality rate of 6.2% and those who were receiving heparin alone had a rate of 12.7% (odds ratio, 0.47; 95% CI, 0.20 to 1.10). The difference was significant if recurrent PE and deaths were considered: odds ratio, 0.45; 95% CI, 0.22 to 0.92.³⁸ Notably, however, only a minority of the patients included in those trials had massive PE (see Table 32-1).

The high mortality rate seen in patients with massive PE who receive heparin alone, the early hemodynamic improvement observed with thrombolytic therapy, the results of the small randomized study by Jerjes-Sanchez and colleagues, and the recent meta-analysis all suggest that thrombolytic therapy is associated with significant clinical benefit in patients with massive PE. Thus most authorities recommend the use of thrombolytic therapy in this setting.^{9,10}

Submassive Pulmonary Embolism

To date, the largest randomized study assessing thrombolytic treatment for submassive PE included 256 patients with PE and normal blood pressure who were allocated to receive either heparin alone or both alteplase and heparin.³³ The primary end point consisted of the combination of in-hospital death or clinical deterioration requiring the escalation of treatment. This was

reached in 11% of the patients in the alteplase group and was reached in 24.6% in the heparin group ($p = 0.006$). The difference was mainly due to the use of secondary open-label thrombolytic therapy, which was more frequent in the patients assigned to receive heparin (23.2%) than in those receiving alteplase (7.6%; $p = 0.001$). The death rate did not differ significantly between the groups. The unexpected low mortality rate in patients receiving heparin (2%) may be related to the low (30%) proportion of patients with right ventricular dysfunction, or to the early use of rescue thrombolytic treatment for those patients who did not improve with heparin. Overall, thrombolytic therapy was compared with heparin in six studies, in which 494 clinically stable patients with submassive or nonmassive PE were included.* The death rate was 3.3% for those receiving thrombolytic therapy and was 2.4% for those allocated to heparin (OR, 1.16; 95% CI, 0.44 to 3.05). Thus the current evidence from controlled studies does not indicate that patients with submassive PE receiving thrombolytic treatment have a lower in-hospital mortality risk. As mentioned above, however, most of these studies included patients with nonmassive PE resulting in a low death rate in both groups. In addition, the number of patients remains low. As a consequence, the available clinical trials and meta-analyses are underpowered and are unable to detect clinically important differences between thrombolytic therapy and heparin in patients with submassive PE.

Some indirect evidence may suggest that thrombolytic therapy may improve the short-term outcome of patients with submassive PE, despite negative results from controlled studies. Goldhaber and coworkers did a post hoc analysis on a subgroup of 36 patients with right ventricular hypokinesia, who were included in their controlled study comparing alteplase and heparin. They observed five PE recurrences (two of them fatal) among 18 patients who were treated with heparin, whereas no deaths or recurrent PE occurred among the 18 patients who received alteplase.³¹ In the MAPETT study, the death rate was lower for patients receiving thrombolytic treatment, which

*References 27, 29, 31, 33, 34, 36.

was the only independent predictor of a favorable outcome.⁴⁴ However, this was an observational study and treatments were not randomly allocated. Experts have expressed contradicting opinions on indications for thrombolytic therapy in patients with submassive PE.^{4,41,45,46} A large international investigator-initiated randomized study comparing thrombolysis to heparin in 1000 patients with submassive PE, defined by elevated troponin and right ventricular failure (assessed by echocardiography or spiral CT), is under way to clarify this issue.

Results of Various Thrombolytic Regimens

Various thrombolytic regimens have been evaluated in controlled trials. Urokinase, given as a bolus dose of 4400 IU/kg followed by a 12-hour or 24-hour maintenance infusion of 4400 IU/kg/hr, was compared with streptokinase, given as a 250,000 IU bolus dose followed by a 100,000 IU/hr infusion given over 24 hours, in a large randomized trial.⁴⁷ The three regimens produced the same degree of hemodynamic and angiographic improvement with no significant differences in terms of major hemorrhage. Recombinant tissue-type plasminogen activator (rtPA) given as a 2-hour 100 mg infusion was compared with a 4400 IU/kg/hr infusion of urokinase, given over 12 or 24 hours.^{48,49} rtPA led to a faster hemodynamic and angiographic improvement, but the two drugs yielded similar hemodynamic results by the end of the urokinase infusion. Patients receiving rtPA had a nonsignificant reduction in major bleeding.^{48,49} A similar rtPA regimen was subsequently compared with a shorter urokinase regimen, given as a 3 million IU infusion over 2 hours.⁵⁰ No differences in hemodynamic improvement and bleeding between the groups were observed, suggesting that when the two drugs are given over the same time period they share similar efficacy and safety. The 2-hour rtPA regimen resulted in faster hemodynamic improvement than a 12-hour streptokinase infusion, whereas no difference was observed when the two drugs were given over the same 2-hour period.^{51,52} The rate of major bleeding was lower for patients receiving the 2-hour streptokinase infusion than the 2-hour rtPA regimen, but the difference was not significant.⁵¹ Two studies compared a rtPA dose of 0.6 mg/kg body weight given over a period of 15 minutes with the 100 mg regimen given over 2 hours.^{53,54} Hemodynamic improvement was slightly but significantly faster for the 2-hour regimen, but the 0.6 mg/kg dosage was associated with a nonsignificant reduction in major bleeding.^{53,54}

Contraindications to Thrombolytic Therapy

For patients with hemodynamic compromise who do not improve with anticoagulation and pressure support, the benefit of thrombolytic treatment outweighs its risk of bleeding, even in the presence of minor contraindications. The main contraindications to thrombolytic therapy are given in Table 32-3.

Additional Measures

As most bleeding episodes occur at the puncture site, it is mandatory to avoid invasive diagnostic procedures, such as pulmonary angiography, if thrombolytic treatment is being considered. Thrombolytic therapy can be given through a peripheral line. Central venous lines should be avoided. Heparin should be interrupted during thrombolysis and resumed as soon as the activated partial thromboplastin time is within the target range. There are still no data for the combination of thrombolytic and low-molecular weight heparin therapy in PE.

Table 32-3. Contraindications to Thrombolytic Therapy in Pulmonary Embolism

Major contraindications to thrombolytic therapy in patients with massive PE

- Active bleeding
- Stroke within the last 2 months
- Spontaneous intracranial bleeding at any date

Minor contraindications to thrombolytic therapy in patients with massive PE

- Major surgery within the past 10 days
- Major trauma within the past 15 days
- Ophthalmologic surgery or neurosurgery within 30 days
- Platelet count less than 100,000/mm³

Pulmonary Embolectomy

Surgical Pulmonary Embolectomy

Pulmonary embolectomy using cardiopulmonary bypass was first reported in 1961 and is now considered to be the best operative technique. In 17 large studies, the operative mortality averages 36%.⁵⁵ Ideally, pulmonary embolectomy should be attempted only in those patients who will not survive without surgery because of the high mortality rate in patients that have undergone this procedure. However, an unequivocal set of criteria that accurately identifies these patients remains elusive. As a result, the role of surgical embolectomy in the treatment of PE has been the subject of much discussion but few definitive conclusions. According to the last ACCP consensus, the candidate should meet the following criteria: (1) massive PE; (2) shock despite heparin and resuscitation efforts; and (3) failure of thrombolytic therapy or a contraindication for its use.¹⁰ In our experience, these patients represent only 3% of those referred for massive PE.²³

Percutaneous Procedures

Several transvenous procedures have been proposed for pulmonary embolectomy, including suction, clot fragmentation with angiography catheters, ultrasound-assisted aspiration, laser-assisted embolectomy, and clot fragmentation using several other devices.⁵⁶ Most of these procedures have been evaluated in vitro or in animal experiments, but clinical evaluation is still limited to small retrospective case series for most devices.⁵⁷ In addition, most devices were used with concomitant fibrinolytic treatment and the respective roles of catheter embolectomy and thrombolytic therapy in the patient's outcome is difficult to ascertain.^{56,57}

Conclusion

Patients who have massive PE with systemic hypotension and cardiogenic shock have a high mortality rate when receiving heparin alone. Available evidence strongly suggests the use of thrombolytic treatment in these patients. Recent data indicate that patients with so-called submassive PE may have a higher mortality risk than patients with normal right ventricular

function. Controlled studies available to date are insufficiently powered to confirm or exclude the clinical benefit of thrombolytic therapy in those patients. A large randomized controlled trial is currently under way to address this issue. Pulmonary embolectomy should be considered in the few patients with PE and cardiogenic shock receiving full hemodynamic support and who do not improve while receiving thrombolytic treatment or for whom thrombolytic treatment is contraindicated.

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Pulmonary Hypertension

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CHAPTER 33

Pulmonary Vascular Anatomy and Physiology Classification of Pulmonary Hypertension Postoperative Pulmonary Hypertension

Chronic Thromboembolic Pulmonary Hypertension Conclusion

SUBSTANTIAL ADVANCES have occurred over the past decade in understanding the pathophysiologic and pathobiologic basis of pulmonary hypertensive disorders. In concert with these advances, dramatic improvements have occurred in the diagnostic approach and therapeutic options available to patients afflicted with this disorder. The resulting development of both pharmacologic and surgical interventions has fundamentally transformed the natural history of a number of disease processes once considered uniformly fatal.

The purpose of this chapter is to review the normal physiologic control of the pulmonary vascular bed and to provide guidelines for a systematic approach to both diagnosis and therapy in patients with pulmonary hypertensive disorders.

Pulmonary Vascular Anatomy and Physiology

Starting from the main pulmonary arteries and proceeding distally towards the pulmonary capillaries, five structural regions can be identified.¹ These include: (1) the large elastic arteries with a diameter greater than 3200 μm ; (2) transitional arteries with diameters ranging from 2000 μm to 3200 μm ; (3) muscular arteries with diameters ranging from 150 μm to 2000 μm ; (4) partially muscularized arteries; and (5) nonmuscular arterioles with diameters ranging from 30 μm to 75 μm . The smallest muscular arteries and the partially muscularized arteries are felt to represent the resistance vessels of the pulmonary circulation.

The adult pulmonary circulation is a low resistance circulatory system that accommodates the whole cardiac output. Under normal circumstances, the resting pulmonary arterial pressure in man is fairly constant throughout life. The normal pulmonary artery pressure at sea level has a peak systolic value of 25 mm Hg, an end diastolic value of 10 mm Hg, and a mean value ranging from 12 to 16 mm Hg. By consensus, pulmonary hypertension is present when mean pulmonary arterial pressure exceeds 25 mm Hg at rest or 30 mm Hg with exercise.² By definition, pulmonary hypertension is considered mild when the mean pulmonary artery pressure is 26 to 35 mm Hg, moderate when it is 36 to 45 mm Hg, and severe when it exceeds 45 mm Hg.

Exercise-related increases in pulmonary blood flow are associated with only minimal increases in pulmonary arterial pressure. As flow increases, therefore, pulmonary vascular resistance decreases. This response is primarily the result of recruitment of

previously unperfused pulmonary vessels and, to a lesser extent, distention of already perfused vessels. Occasionally, especially in older subjects, pulmonary arterial pressure can increase to 50 mm Hg during exercise. This increase in pulmonary artery pressure is the result of an increase in pulmonary arterial wedge pressure, the probable result of decreased left ventricular diastolic compliance, rather than an increase in the pulmonary artery to pulmonary artery wedge pressure gradient.³

The hemodynamic evolution of pulmonary hypertensive disorders has been well described.⁴ Initially, the ability of the pulmonary vascular bed to dilate and to recruit unused vasculature is lost, resulting in increases in pulmonary artery pressure at rest and further elevations with exercise. In response to this increased afterload, the right ventricle undergoes hypertrophy. Early in the disease, the right ventricle is capable of sustaining a normal cardiac output at rest, although the ability to augment cardiac output with exercise is impaired. With disease progression, the right ventricle becomes incapable of maintaining a normal cardiac output at rest. As progressive right heart dysfunction develops, right heart diastolic and right atrial pressure increase, and right ventricular failure becomes clinically apparent. Although the left heart is not directly affected by pulmonary vascular disease, progressive right ventricular dilation can impair left ventricular compliance, leading to increased left ventricular end-diastolic and pulmonary capillary wedge pressures.

The main vascular changes in pulmonary arterial hypertension are vasoconstriction, smooth-muscle cell and endothelial-cell proliferation, and thrombosis. The endothelial cell plays a major role in the maintenance of normal pulmonary hemodynamics through the release of a variety of vasoactive substances, including nitric oxide (NO), prostanooids, and endothelin (ET), that contribute to vascular tone.⁵⁻⁷ Nitric oxide, previously known as endothelium-derived relaxing factor (EDRF), appears to play a central role in the modulation of pulmonary vascular tone. In addition to being a powerful vasodilator, nitric oxide acts as a bronchodilator, neurotransmitter, anticoagulant, anti-proliferative, and antimicrobial substance and inhibits platelet aggregation. Continuous release of nitric oxide from pulmonary endothelium appears to determine the characteristically low pulmonary vascular resistance in man. Prostacyclin (PGI_2), a product of cyclooxygenase metabolism of arachidonic acid, is a powerful vasodilator and inhibitor of platelet aggregation. Although it has been suggested that release of PGI_2 by the endothelium modulates vasoconstriction, the continuous

release of PGI₂ does not appear necessary to maintain pulmonary arterial vasodilation. Endothelin, consisting of three discrete isoforms, represents one of the most powerful pulmonary arterial vasoconstrictors.

A wide array of other mediators has been found to be involved in pulmonary vascular remodeling, including transforming growth factor receptors (TGF- β), bone morphogenic protein receptor 2 (BMPR2), vascular endothelial growth factor (VEGF), vasoactive intestinal peptide, 5-hydroxytryptamine (5-HT), adrenomedullin, and natriuretic peptides among others. Although an imbalance among these mediators has been implicated in the initiation and progression of certain variants of idiopathic and secondary forms of pulmonary hypertension, their respective effects on smooth muscle cells and the circumstances under which one class of mediators predominates remain undefined and the subjects of intense investigation.

Classification of Pulmonary Hypertension

Pulmonary hypertension results when there is an absolute loss of pulmonary vascular cross-sectional area or an increased resistance to flow at any point within the pulmonary circulation. The pulmonary circulation is defined as extending from the pulmonic valve to the left atrium and consists of the pulmonary outflow tract, the right and left main pulmonary arteries and their lobar branches, the intrapulmonary arteries, the pulmonary arterioles, capillaries, venules, and large pulmonary veins. As a result, a diverse group of disease processes affecting any aspect of this circulation can result in pulmonary hypertension (Table 33-1). The term *primary pulmonary hypertension* (PPH) has been abandoned in favor of *idiopathic pulmonary arterial hypertension* (IPAH). The term *pulmonary arterial hypertension* (PAH) is reserved for those with a genetic basis for pulmonary hypertension, those with collagen vascular disease or other conditions associated with pulmonary arterial hypertension (APAH), and for the idiopathic variant (IPAH).

Pulmonary hypertension can result from a variety of obstructive and restrictive pulmonary parenchymal disorders.⁸⁻¹⁰ The basis for pulmonary hypertension in these disorders involves both an absolute loss of pulmonary cross-sectional area (bronchiectasis, emphysema) and, of greater importance, the chronic alveolar hypoxia, acidosis, and polycythemia that accompanies these disease states.

Independent of pulmonary parenchymal disorders, pulmonary hypertension is a frequent hemodynamic complication associated with a range of respiratory system disorders whose common physiologic abnormality are alveolar hypoxia and arterial hypoxemia of longstanding duration.¹¹ Such disease processes include the obesity-hypoventilation syndrome, chest wall disorders, and neuromuscular disease.

Small-vessel pulmonary arterial changes may ultimately develop from an augmented pulmonary flow state (Eisenmenger syndrome), from vasculitides or toxic injuries affecting the small pulmonary arteries, or as a consequence of idiopathic pulmonary hypertension.

There is also a group of disorders for which occlusion or narrowing of the large to medium-size pulmonary arteries is the site of increased resistance to flow. Included in this category is chronic thromboembolic disease, Takayasu arteritis, primary

Table 33-1. Classification of Pulmonary Hypertension⁷⁵

Group I: Pulmonary arterial hypertension (PAH)
Idiopathic PAH (IPAH)
Familial PAH
Associated with PAH (APAH)
Collagen vascular disease
Congenital systemic to pulmonary shunts (large, small, repaired, or nonrepaired)
Portal hypertension
HIV infection
Drugs and toxins
Other (glycogen storage disease, Gaucher disease, hereditary hemorrhagic telangiectasis, hemoglobinopathies, myeloproliferative disorders, splenectomy)
Associated with significant venous or capillary involvement
Pulmonary veno-occlusive disease (PVOD)
Pulmonary capillary hemangiomatosis (PCH)
Persistent PH of the newborn (PPHN)
Group II: Pulmonary venous hypertension
Left-sided atrial or ventricular heart disease
Left-sided valvular disease
Group III: Pulmonary hypertension associated with intrinsic lung disease or hypoxemia
Chronic obstructive pulmonary disease (COPD)
Interstitial lung disease
Sleep-disordered breathing
Alveolar hypoventilation disorders
Chronic exposure to high altitude
Group IV: Pulmonary hypertension caused by chronic thrombotic or embolic disease
Thromboembolic obstruction of proximal pulmonary arteries
Thromboembolic obstruction of distal pulmonary arteries
Pulmonary embolism (tumor, parasites, foreign material)
Group V: Miscellaneous
Sarcoidosis
Histiocytosis X
Lymphangiomatosis
Compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

pulmonary artery tumors, and compression from mediastinal or hilar processes (carcinoma, fibrosis).¹²⁻¹⁵ Although it might be assumed that the progressive nature of the pulmonary hypertension in this group is primarily the result of the initiating disease process, there is increasing evidence that small vessel changes in the unobstructed vascular bed resulting from high pressure or flow, or mediator imbalance, may contribute significantly to the progression of the disease.¹⁶

Increased resistance to pulmonary venous drainage is a mechanism common to a number of diverse processes in which pulmonary hypertension occurs. Altered resistance to pulmonary venous drainage may be the result of diseases affecting the left atrium, the left ventricle (both systolic and diastolic), mitral or aortic valvular disease, or the large (mediastinal fibrosis) or small (pulmonary veno-occlusive disease) pulmonary veins. Additional

Table 33–2. Functional Assessment of Patients with Pulmonary Hypertension⁷⁶

Class I: Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.
Class II: Patients with pulmonary hypertension resulting in slight limitation of physical activity. These patients are comfortable at rest, but ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.
Class III: Patients with pulmonary hypertension resulting in marked limitation of physical activity. These patients are comfortable at rest, but less than ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.
Class IV: Patients with pulmonary hypertension resulting in inability to perform any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may be present at rest, and discomfort is increased by any physical activity.

vascular remodeling or vasoconstriction may contribute to the elevated pulmonary artery pressures and increased transpulmonary gradient, especially when left heart filling pressures have been markedly and protractedly increased.¹⁷

Finally, there is a group of disorders in which the association between pulmonary hypertension and the primary disease state remains obscure. Included among these is the pulmonary hypertension associated with HIV infection, and with cirrhosis and/or portal vein thrombosis.^{18–20}

Clinical Presentation

The first challenge in the diagnostic evaluation of a patient with pulmonary hypertension is recognizing that pulmonary hypertension is, in fact, present. Diagnostic delay, especially in the absence of a history of an associated disease process, occurs commonly. Symptoms specifically attributed to the presence of pulmonary hypertension are nonspecific and dependent on the stage of the disease at which the patient presents (Table 33–2). A gradual decline in exercise tolerance and exertional dyspnea represent the initial manifestation and are present in essentially all patients with significant pulmonary hypertension. Other symptoms may include cough, chest pain, hemoptysis, and easy fatigability. These symptoms are also nonspecific and may lead the clinician, in the case of isolated pulmonary hypertension, to ascribe them to other causes (coronary artery disease, chronic obstructive pulmonary disease, psychogenic dyspnea); and, in the case of secondary pulmonary hypertension, to mistakenly ascribe them to a progression of the underlying disease.

Findings on physical examination in pulmonary hypertension are similarly reflective of the stage of the disease at which the patient presents. Unless the pulmonary hypertension or accompanying right ventricular dysfunction is severe, findings on physical examination can be deceptively subtle. Before the development of significant pulmonary hypertension or overt right ventricular failure, physical examination abnormalities may be limited to narrowed physiologic splitting of the second heart sound or a subtle accentuation of its pulmonic component. In time, obvious findings such as a right ventricular heave, jugular venous distention with prominent A- and V-wave

pulsations, widened or fixed splitting of the second heart sound, a fourth or third heart sound of right ventricular origin, murmurs of tricuspid regurgitation or pulmonic insufficiency, hepatomegaly, and ascites may develop. The presence of digital clubbing can suggest the possibility of bronchiectasis, idiopathic interstitial fibrosis, or right-to-left intracardiac or intrapulmonary shunting. Cyanosis is a relatively late finding in pulmonary hypertension not resulting from pulmonary parenchymal disorders, chronic alveolar hypoxia, or right-to-left shunts. In pulmonary hypertension resulting from diseases of the large and small pulmonary arteries, cyanosis may develop late in the disease as a consequence of shunting through a patent foramen ovale secondary to elevated right atrial pressure.

One unique physical finding described in chronic thromboembolic pulmonary hypertension and congenital pulmonary artery stenosis is the presence of flow murmurs over the lung fields.²¹ The detection of these often subtle bruits, which appear to originate from turbulent flow through partially obstructed pulmonary arteries, can be instrumental in differentiating a large vessel from a small vessel etiology of pulmonary hypertension. These flow murmurs are detected over the lung fields rather than the precordium, are accentuated during inspiration, and are frequently heard only during periods of breath-holding.

Diagnostic Evaluation

In the evaluation of the patient with suspected pulmonary vascular disease, historical information should be gathered with the intent of identifying a disorder with a known association with pulmonary hypertension. In most instances, the presence or history of obstructive lung disease, restrictive lung disease, digital clubbing, obesity-hypoventilation syndrome, rheumatic fever, collagen vascular disease, HIV infection, or thromboembolism will antedate the occurrence of pulmonary hypertension and suggest a likely etiology. Intravenous drug use and the ingestion of certain anorexigenic medications (e.g., fenfluramine) have also been associated with the development of pulmonary hypertension.^{22–25} If the patient's place of residence is a region endemic for histoplasmosis, this information is useful in suggesting the possibility of fibrosing mediastinitis. Although familial pulmonary hypertension is extremely rare, a family history of pulmonary hypertension should be explored with any individual having suspected pulmonary hypertension.²⁶

Once an abnormality of the pulmonary vasculature has been considered as a basis for the patient's complaints, the diagnostic sequence, despite the diverse diagnostic possibilities, is relatively straightforward if an orderly approach is followed (Fig. 33–1).

Findings on standard laboratory tests are dependent on the point in the natural history of the disease at which they are obtained. Abnormalities usually reflect the hemodynamic and gas exchange consequences of the pulmonary vascular obstruction and accompanying cardiac dysfunction. Electrocardiographic findings can suggest the possibility of pulmonary hypertension but are unlikely to differentiate among the diverse cardiac and pulmonary etiologies. Routine hematologic and blood chemistry studies are often unremarkable. Secondary polycythemia, resulting from long-standing hypoxemia, may be encountered. Abnormalities of liver function studies may be a consequence of hepatic congestion or may suggest the possibility of portopulmonary hypertension. Elevations in blood urea nitrogen (BUN) or uric acid levels may reflect the depressed cardiac output present in the latter stages of the disease.

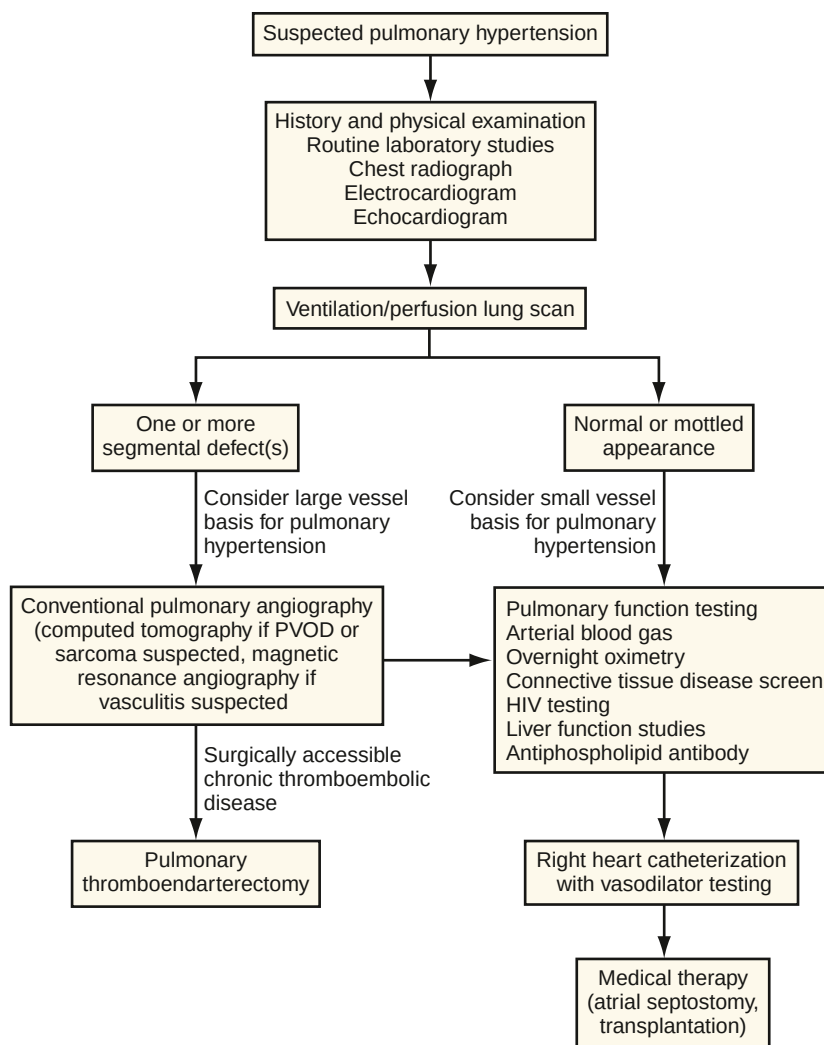


Figure 33-1. Guideline for evaluating pulmonary hypertension. A wide range of differential diagnostic possibilities must be considered, including conditions amenable to surgical and medical therapies. PVOD, pulmonary veno-occlusive disease.

Alterations in gas exchange may represent either an accompaniment of pulmonary hypertensive disorders or a causal factor. In disease processes not affecting the lung, chest wall, or respiratory control mechanism, hypoxemia is the consequence of a decreased mixed venous oxygen saturation (SvO_2) resulting from a depressed cardiac output or from right-to-left shunting at either a cardiac or pulmonary level. In those processes which do affect the respiratory apparatus and which result in chronic hypoxia, vasoconstriction and vascular remodeling occur as a result of the hypoxemia, resulting in reduction of the pulmonary vascular bed to the degree necessary for the development of pulmonary hypertension.²⁷ A central differential point is the presence of hypercarbia, which suggests advanced obstructive or restrictive parenchymal lung disease, disorders of the chest wall, or the presence of alveolar hypoventilation on either a central or neuromuscular basis.

Patients with chronic obstructive lung disease tend to have less severe pulmonary hypertension than other forms of pulmonary vascular disease although severe pulmonary hypertension may occur. The development of pulmonary hypertension in patients with chronic obstructive pulmonary disease represents a poor prognostic sign in terms of both mortality and quality of life. Mean pulmonary artery pressures rarely exceed 40 mm Hg,

even in the presence of severe hypoxemia. This differs greatly from idiopathic pulmonary arterial hypertension, thromboembolic pulmonary hypertension, and from pulmonary hypertension associated with left heart and congenital heart diseases. In the latter stage of these disease processes, mean pulmonary artery pressure often exceeds 50 mm Hg, and can reach levels comparable to those of the systemic circulation. For this reason, pulmonary hypertension out of proportion to the degree of gas exchange impairment, or a rapid worsening of previously mild pulmonary hypertension in a patient with obstructive lung disease, should raise suspicion for a superimposed process such as thromboembolism, left ventricular dysfunction, or sleep apnea.^{28,29}

The chest radiograph may provide useful clues in the evaluation of a patient with suspected pulmonary hypertension (Fig. 33-2). If pulmonary hypertension is severe, enlargement of the right ventricle and pulmonary arteries (>16 mm enlargement of right interlobar pulmonary artery) may be recognized. Chest radiography can also be useful in suggesting the presence of pulmonary parenchymal, mediastinal, or cardiac problems responsible for the pulmonary hypertension.

Two noninvasive studies, echocardiography and ventilation-perfusion scanning, can provide valuable information regarding

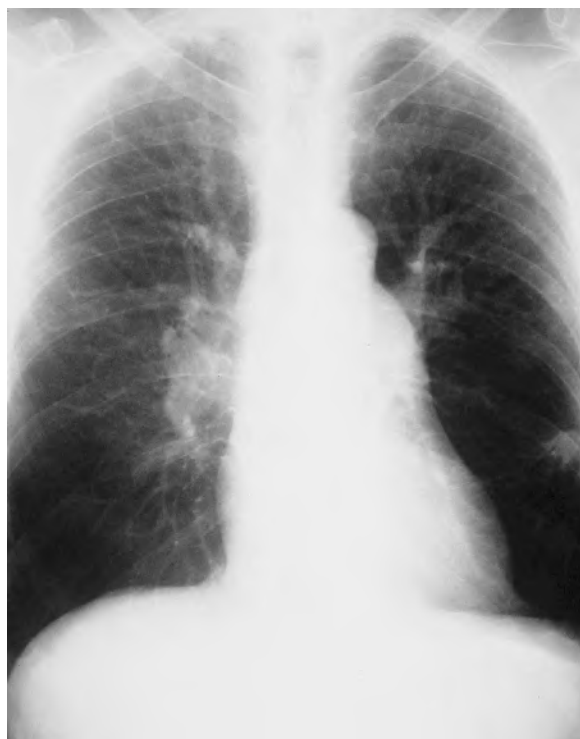


Figure 33-2. Chest radiograph in a patient with pulmonary hypertension. Right hilar structures are markedly enlarged. Asymmetry of the two hilar silhouettes and oligemia of the left lower lobe suggest chronic thromboembolic pulmonary hypertension.

the severity and etiology of pulmonary hypertension. Transthoracic echocardiography (TTE), although often technically difficult in patients with advanced lung disease, has evolved as an important noninvasive means of assessing the degree of pulmonary hypertension and right heart enlargement.³⁰ Echocardiography has proved to be sensitive although somewhat less specific in detecting the presence of pulmonary hypertension in appropriate populations. Correlation between the echo-derived estimate of pulmonary artery pressure and that obtained at right heart catheterization is quite good within the range of pulmonary artery systolic pressures of 50 and 100 mm Hg.^{30,31} Echocardiography is useful in detecting disorders of the left atrium, left ventricle, and aortic and mitral valves. Systolic and/or diastolic left ventricular dysfunction can result in pulmonary venous hypertension that may be responsible for elevated pulmonary artery pressure. The addition of a contrast study is useful in the detection of intracardiac shunts.

Right heart catheterization remains the gold standard for the diagnosis of pulmonary hypertension and in the evaluation of response to therapeutic measures. Analysis of mixed venous oxygen saturation can allow diagnosis of intracardiac shunts, provide information regarding prognosis and response to therapy, and provide an improved measure of cardiac output in patients with severe tricuspid regurgitation in whom thermodilution measurements might be inaccurate. An elevated pulmonary capillary wedge pressure in the setting of a normal transpulmonary gradient suggests pulmonary venous or left ventricular disease as the etiologic basis of the pulmonary hypertension.

Ventilation/perfusion ($\dot{V}/\dot{Q}$) scanning, although having been supplanted by computed tomography in acute pulmonary embolism diagnosis, continues to play a central role in helping define the etiology of pulmonary hypertension. High-probability $\dot{V}/\dot{Q}$ (segmental and larger defects) scan results are very sensitive for detecting chronic thromboembolic pulmonary hypertension.³² Segmental defects also occur in patients with large vessel vasculitides, pulmonary artery sarcoma, extrinsic compression of large pulmonary arteries or veins, and on occasion in pulmonary veno-occlusive disease.³³ Patients with pulmonary hypertension resulting from abnormalities of the distal pulmonary bed have scan results that are normal or exhibit a mottled appearance (Fig. 33-3).

The $\dot{V}/\dot{Q}$ scan findings can often dramatically understate the actual degree of central pulmonary vascular obstruction in patients with chronic thromboembolic pulmonary hypertension.³⁴ The presence of even a single segmental or larger mismatched defect in a patient with pulmonary hypertension should raise the possibility of chronic thromboembolic disease and should lead to consideration of right heart catheterization and pulmonary angiography.

Imaging of the pulmonary vascular bed is best achieved using pulmonary angiography. The appearance of the normal pulmonary vasculature is one of smoothly tapering branches that extend to the periphery of the lung fields (Fig. 33-4). Two types of branching have been described: bifurcational branching in which the parent artery divides into two branches at an angle of 10 to 60 degrees; and collateral branching in which the trunk divides into two branches, one of which is virtually the size of and continues in the same direction as the parent trunk, the other which comes off at an angle of 30 to 80 degrees. In both types of branching, the sum of the diameters of both branches is greater than the diameter of the trunks. Angiographic evaluation should involve attention to the capillary and venous phases of the study in addition to the arterial phase. Evidence of pulmonary venous obstruction or of anomalous venous return can provide critical information regarding the etiology of the pulmonary hypertensive disorder.

Because major-vessel chronic thromboembolic pulmonary hypertension has been shown to be surgically remediable, establishing this diagnosis has become increasingly relevant. It is important to recognize that the angiographic patterns created by organized thrombi (pouch defects, webs or bands, intimal irregularity, abrupt vascular narrowing) are distinct from the intraluminal filling defects of acute thromboembolic disease or from the distal hypovascularity of small-vessel pulmonary hypertension (Fig. 33-5).³⁵ Although there are risks in performing pulmonary angiography in pulmonary hypertensive patients, the National Institutes of Health registry, the PIOPED (Prospective Investigation of Pulmonary Embolism Diagnosis) study, and the University of California, San Diego, Medical Center's experience suggest that this procedure can be performed safely by experienced angiographers taking certain precautions.^{36,37}

Other imaging modalities can also prove valuable in the evaluation of pulmonary hypertension. Computed tomography imaging is particularly useful in defining abnormalities of the pulmonary hilum, the mediastinum, the lung parenchyma, and the pulmonary vascular bed that could account or be contributing to a patient's pulmonary hypertension (Fig. 33-6). Arch aortography or magnetic resonance angiography may detect evidence of systemic involvement in cases of suspected Takayasu arteritis or other vasculitides.³⁸⁻⁴⁰

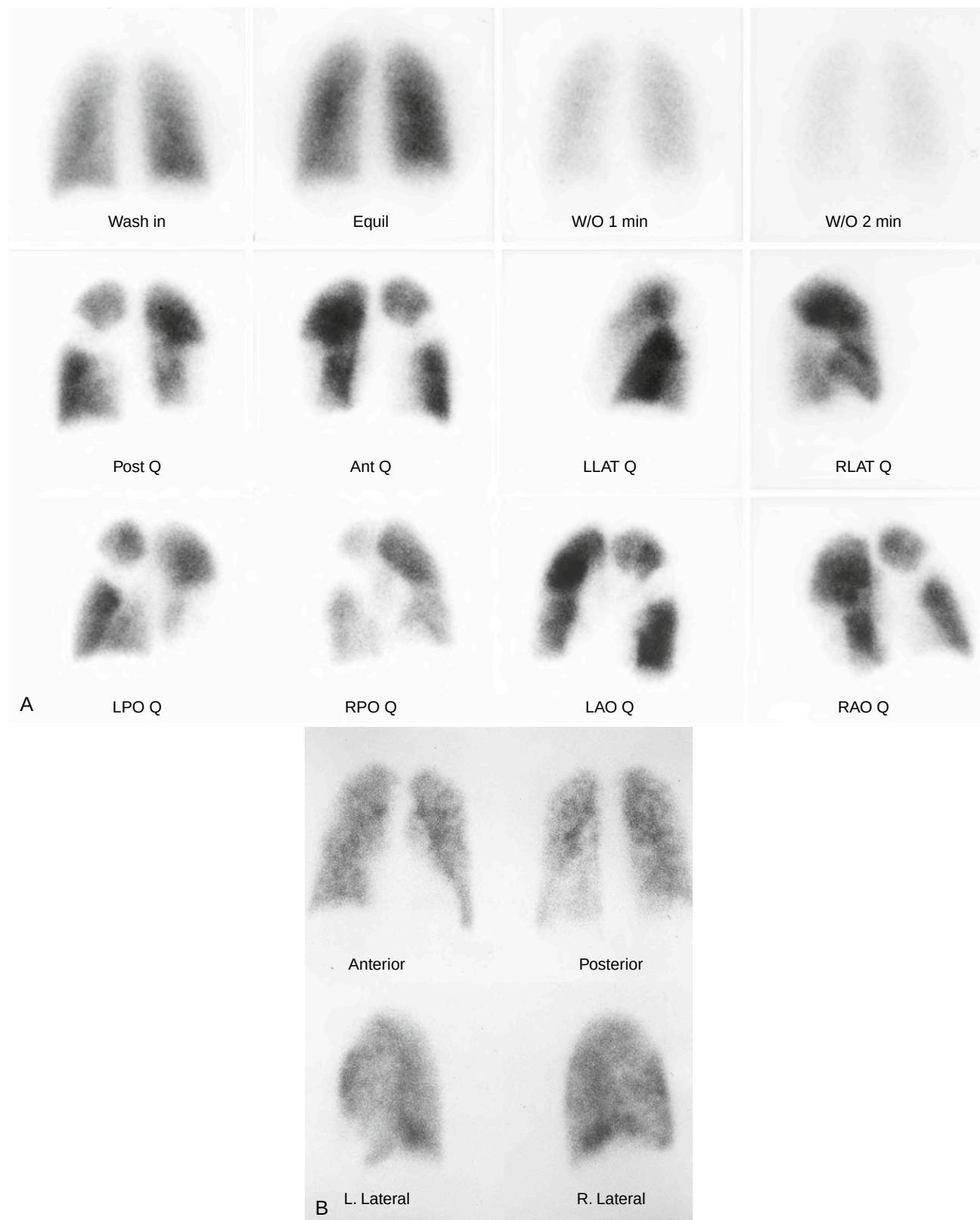


Figure 33-3. **A,** Ventilation-perfusion scan in chronic thromboembolic pulmonary hypertension showing multiple mismatched segmental defects. **B,** Perfusion scan in small vessel variant of pulmonary hypertension showing diffuse mottled appearance without segmental defects.

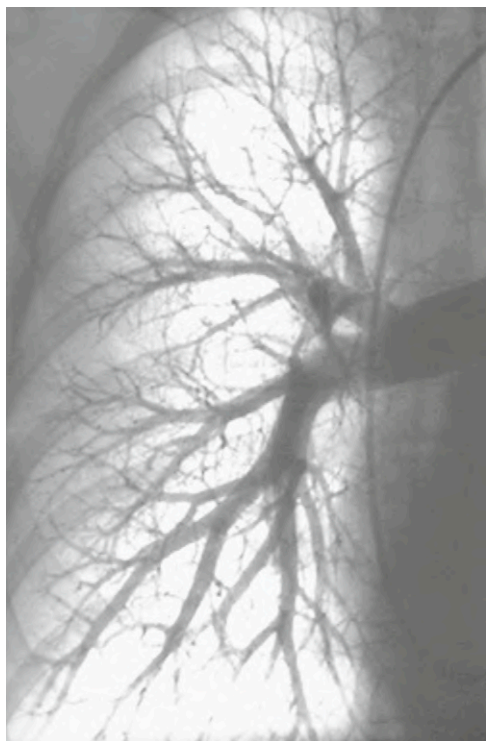


Figure 33-4. Normal right-sided pulmonary angiogram showing normal tapering vessels extending to the periphery of the lung.

The clinical utility of lung biopsy in the overwhelming majority of patients with small-vessel pulmonary hypertension is quite limited.⁴¹ When considering such an intervention, the information to be gained must be carefully weighed against the morbidity and mortality of the procedure, which are not insignificant, and the effect of open biopsy on future transplantation decisions. Biopsy should be considered only when there is a suspicion of unusual disease processes (pulmonary hemosiderosis, alveolar proteinosis, interstitial fibrosis), when the diagnosis cannot be established by less invasive serologic or radiographic techniques, and when the possibility of effective therapeutic intervention is present.

Therapeutic Approach

Idiopathic Pulmonary Arterial Hypertension

Extraordinary advances have been made in the diagnostic and therapeutic approach to idiopathic pulmonary arterial hypertension (IPAH), once considered a rare, almost uniformly fatal disease, which pursued a progressive course with a median survival time of less than 3 years. These advances have been based on a better understanding of the pathobiologic mechanisms of the disease and the mediators involved in its progression, the development and introduction of several classes of vasodilating or antiproliferative agents, and on the use of lung transplantation in those patients in whom pharmacologic management is ineffective.

Although not systematically studied in patients with pulmonary hypertension, oxygen supplementation, diuretics, anticoagulation, and cardiac glycosides are routinely used but should be applied in a targeted fashion. The basis for each can be justified clinically given the physiologic consequences of the disease: oxygen therapy to reduce pulmonary vasoconstriction in

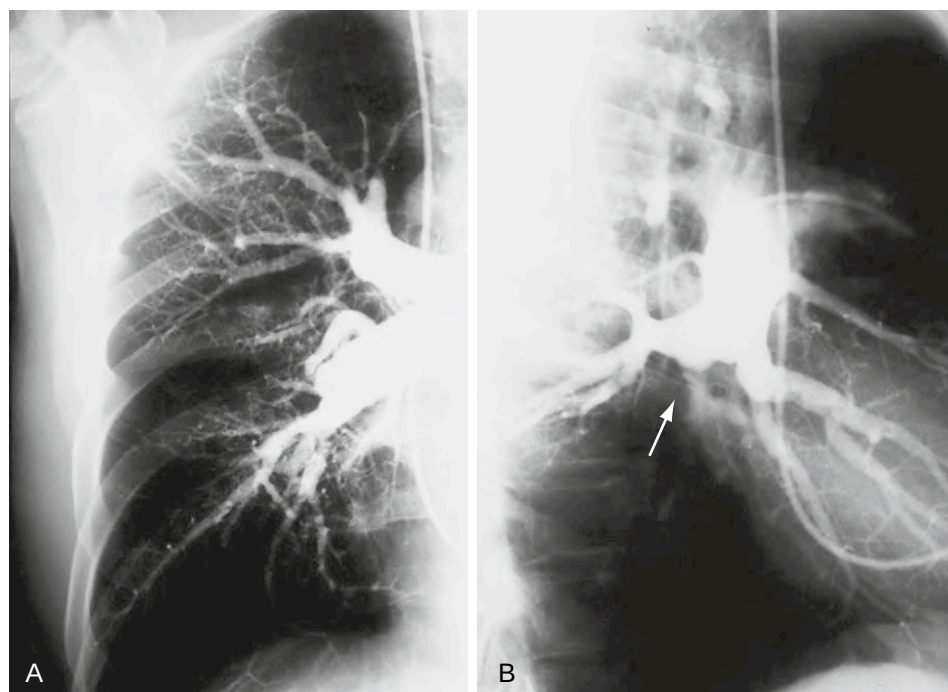


Figure 33-5. **A** and **B**, Biplane pulmonary angiograms showing several of the characteristic findings in chronic thromboembolic disease. Note segmental level cutoffs in upper lobe vessels and marked irregularity of lower lobe pulmonary artery. On the lateral view (**B**), complete obstruction of the lower lobe artery below a dilated right middle lobe branch and the superior segment branch is apparent (arrow).

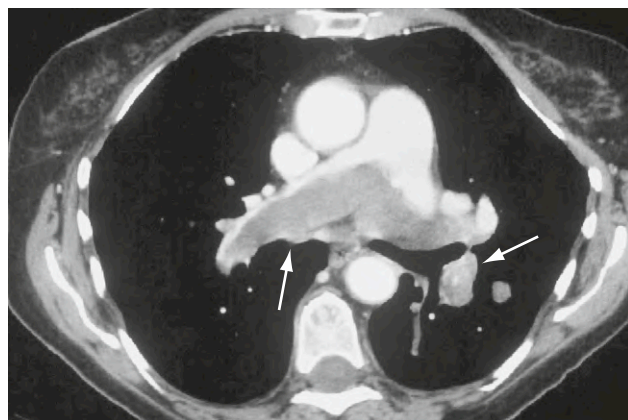


Figure 33-6. CT scan showing filling defect in the pulmonary outflow tract, both main pulmonary arteries, and the left lower lobe artery consistent with pulmonary artery sarcoma.

patients with hypoxemia, diuretics for volume overload and its adverse effect on right and left ventricular function, anticoagulants for the prothrombotic state that accompanies the disease, and digoxin to enhance ventricular function in patients with evidence of right ventricular failure.⁴²

Four classes of drugs are currently available for pulmonary hypertension therapy: prostanoids (epoprostenol, treprostinil, iloprost); endothelin blockers (bosentan, ambrisentan); phosphodiesterase inhibitors (sildenafil); and calcium channel blockers. Each differs in terms of its indication for use, mechanism of action, and side-effect profile.⁴³⁻⁴⁵

Epoprostenol, the first drug approved by the FDA for the treatment of pulmonary artery hypertension, is a potent, short-acting vasodilator and antiproliferative agent. Administered by constant intravenous infusion, it is the only medication for PAH that has demonstrated a survival benefit in a randomized clinical trial.⁴⁶ Epoprostenol is stored as a dry powder, reconstituted with a sterile diluent, and then continuously infused via an ambulatory infusion pump worn by the patient. Common side effects include flushing, diarrhea, headache, arthralgias, tachycardia, and jaw pain. High doses may produce hypotension and heart failure, and, because of epoprostenol's potent vasodilatory properties, patients with coronary artery disease may develop a coronary steal phenomenon and experience cardiac ischemia with its administration. Sudden reductions in dose or abrupt cessation of the drug may result in severe rebound pulmonary hypertension or even sudden death. The necessity for a tunneled catheter places patients at risk for line infections and thrombotic complications.

Treprostinil is a stable prostacyclin analogue approved by the FDA for continuous subcutaneous administration, although it can also be delivered as a continuous intravenous infusion or by inhalation. Advantages of treprostinil include a longer half-life than epoprostenol (55 to 117 minutes vs. <5 minutes), its stability at room temperature, and its ability to be infused subcutaneously. Infusion site complications, most notably pain often associated with erythema and induration, limit its usefulness.

Iloprost, another prostacyclin analogue, has a half-life of approximately 30 minutes and is approved for inhalation therapy. The inhalational route theoretically provides the advantage of minimizing systemic side effects and of delivering the drug to

well-ventilated regions of the lung, thereby minimizing ventilation-perfusion mismatch in patients with parenchymal lung disease. Each iloprost treatment requires 5 to 10 minutes through a special nebulizer device and must be administered six to nine times a day, thereby limiting its utility.

Bosentan, the second drug approved by the FDA for the treatment of pulmonary artery hypertension, is a dual, nonselective endothelin receptor antagonist that has demonstrated improved exercise capacity and cardiopulmonary hemodynamics compared to a placebo in patients with IPAH and pulmonary hypertension associated with connective tissue disease.⁴⁷ Small trials have also demonstrated that bosentan has positive hemodynamic and symptomatic effects in patients with HIV-related pulmonary hypertension and in those with Eisenmenger syndrome.^{48,49} The most important adverse effect associated with bosentan is hepatocellular injury, which occurs in 5% to 10% of patients. The injury appears to be reversible on withdrawal of the drug and the FDA requires that liver function studies be performed monthly in patients receiving the drug. Bosentan is a pregnancy category X drug. Therefore pregnancy must be excluded before the start of therapy and a second form of birth control used in addition to hormonal therapy because bosentan can affect hormone levels.

Ambrisentan has recently been approved for pulmonary hypertension treatment. Unlike bosentan, ambrisentan is an ET (A)-selective endothelin receptor antagonist. In phase 3 clinical trials in patients with PAH, ambrisentan (2.5 to 10 mg daily) improved exercise capacity, Borg dyspnea index, time to clinical worsening, World Health Organization (WHO) functional class, and quality of life compared with the placebo.⁵⁰ Advantages of ambrisentan include a lower incidence and severity of hepatocellular injury and decreased interference with P450 enzymes, thereby lowering the risk of certain drug-drug interactions.

Sildenafil, a phosphodiesterase-5 inhibitor, functions through the nitric oxide/cyclic GMP (NO/cGMP) pathway by slowing the metabolism of cGMP and increasing delivery of nitric oxide to the lung. The SUPER trial demonstrated significant improvement in symptomatic, functional, and hemodynamic status in patients in WHO class II and III status when compared with the placebo.⁵¹ The optimal dose of sildenafil has not been determined but seems to be in the range of 60 to 240 mg daily. In the SUPER trial, 20 mg every 8 hours was as effective as 40 or 80 mg during the initial 12 weeks of the study. Patients in the extension study were treated with 80 mg three times daily and demonstrated stability in functional status as defined by the 6-minute walk distance after 1 year. Whether a lower dose would have been effective is not known. In another trial, sildenafil administered at a dose of 50 mg three times daily was equivalent to bosentan at improving a 6-minute walk distance and pulmonary hemodynamics in WHO class III patients with IPAH or pulmonary arterial hypertension associated with a connective tissue disease.⁵² The role of the longer-acting phosphodiesterase-5 inhibitors, tadalafil and vardenafil, in the therapy of pulmonary arterial hypertension remain to be determined.

The use of combination therapy is an appealing concept in that it would allow different pathogenic pathways to be targeted and minimize the toxicity associated with higher doses of individual agents. To date there have been few prospective trials conducted to appraise the benefit of combination therapy although a number of trials using a variety of drug combinations are planned or underway.⁵³ Until the development and approval

of bosentan and sildenafil, calcium channel antagonists were the only class of oral agents demonstrated to provide long-term benefit in this patient population. In 1992, Rich and coworkers reported their experience with 64 IPAH patients receiving high-dose calcium channel blockers.⁵⁴ Seventeen patients (26%) experienced a decline in pulmonary vascular resistance of 20% or more, a response that was maintained up to 5 years in all but one patient. In the patients who had a response, not only were quality-of-life measures improved, but 5-year survival was considerably higher (94% vs 38%) relative to patients who did not manifest an acute response to vasodilator challenge.

The risks of empirically initiating calcium channel antagonist therapy in patients with IPAH cannot be overemphasized. Patients being considered for treatment of IPAH should be referred to specialized centers where an acute vasodilator challenge study can be performed under hemodynamic monitoring. This recommendation is based on several considerations. Less than 10% of patients with IPAH will demonstrate a degree of vasodilator responsiveness, defined as a decrease in the mean pulmonary artery pressure of at least 10 mm Hg to less than 40 mm Hg with a normal cardiac output, predictive of a satisfactory long-term outcome when treated with calcium channel blockers alone.⁵⁵ For those who do not meet these stringent response criteria, the failure rate of calcium channel blocker therapy is substantial and the negative inotropic and systemic vasodilating effects of calcium channel antagonists can result in a number of adverse consequences, which include worsening right ventricular failure, hypotension, and sudden death.⁵⁶ The dose of calcium channel antagonists used in idiopathic pulmonary arterial hypertension is considerably higher than that used in other disease states.

An acute vasodilator challenge can be performed using a number of agents. Intravenous epoprostenol in a dose of 2 to 12 ng/kg/min has been used as a vasodilator-challenging agent. It is particularly useful because of its potency and short biologic half-life (around 3 minutes), making it easy to titrate and minimizing the duration of any adverse hemodynamic consequence. Side effects include headache, flushing, abdominal pain, diarrhea, and systemic hypotension, all of which resolve quickly after the infusion is discontinued. Because of its short serum half-life, adenosine is a desirable agent to use as a vasodilator in the assessment of PH. Schrader and colleagues studied 15 patients (11 patients with IPAH) with IV adenosine administered at a dose of 50 g/kg/min and increased by 50 µg/kg/min every 2 minutes to a maximum dose of 500 µg/kg/min to acutely assess vasodilator response. Inhaled nitric oxide also has been used as a vasodilator challenging agent. Significant advantages of this agent compared with intravenous prostacyclin and adenosine include its short duration of activity and its lack of systemic hemodynamic effects. Channick and coworkers examined the effects of inhaled nitric oxide (40 ppm) in 16 patients with IPAH and demonstrated a response in 5 (31%). With one exception, patients who responded to nitric oxide also responded to epoprostenol. A significant decline in mean arterial pressure and systemic vascular resistance occurred with epoprostenol, an effect not seen with inhaled nitric oxide.⁵⁸

Patients having right ventricular decompensation represent a medical emergency. The role of vasopressors and inotropes in this population must be guided by an understanding of their effect on cardiac output and pulmonary and systemic vascular resistances. The goals of enhancing cardiac output and reducing

pulmonary vascular resistance while avoiding disproportionate decreases in systemic vascular resistance can be problematic and may require combination therapy. Dobutamine, norepinephrine, and dopamine have been used successfully in conjunction with more specific pulmonary vasodilating/antiproliferative agents, such as epoprostenol, nitric oxide, and sildenafil. The role of diuresis in patients with intravascular volume overload cannot be emphasized too strongly. Volume overload can result in overdistention of the right ventricle, thereby increasing right ventricular wall tension and oxygen demands, decreasing contractility, impairing left ventricular filling and compliance, and reducing systemic cardiac output and oxygen delivery.

The role of atrial septostomy in patients with idiopathic pulmonary arterial hypertension remains undefined.^{59,60} Preliminary observations suggest that it may represent a potential, albeit high-risk option as a bridge to transplantation in patients with severe pulmonary hypertension whose clinic status is deteriorating despite maximal pharmacologic management. The purpose of the procedure is to “unload” the right ventricle and to improve left ventricular function, cardiac output, and systemic oxygen delivery. These benefits, however, come at the price of significantly worse gas exchange as the result of the newly created or enlarged right-to-left shunt, which may result in refractory and life-threatening hypoxemia. The procedure can be performed by blade septostomy or, preferably, by graded balloon dilation, which allows the hemodynamic benefit to be balanced against the gas exchange consequence.

For IPAH refractory to medical therapies, lung transplantation has become a therapeutic option.⁶¹ With an awareness that the right ventricle is capable of resuming normal function once reduction in right ventricular afterload has been achieved, single lung transplantation has become an alternative to double lung or heart-lung transplantation.⁶² Recently published data from the Registry of the International Society for Heart and Lung Transplantation demonstrated, however, that 90% of the lung transplant procedures for pulmonary hypertension between 1995 and 2006 were double lung rather than single. During that time frame, transplantation for “primary pulmonary hypertension” represented only 3.6% of the total number of lung transplant procedures. This decrease in both the absolute and relative number of lung transplant procedures performed for pulmonary hypertension is a tribute to the substantial gains that have been made over the past decade in the pharmacologic management of the disease. Primary pulmonary hypertension remains the second most frequent indication for heart-lung transplant. Early survival (3 months and 1 year) in patients undergoing lung transplantation for pulmonary hypertension is below that for other indications, such as cystic fibrosis and chronic obstructive pulmonary disease. However, at 10 years, pulmonary transplant recipients recover to an intermediate survival position among the diseases. Four-year survival for both lung and heart-lung transplantation remains less than 60%. For this reason, organ transplantation must still be considered a treatment of last resort in patients with IPAH.

Chronic Lung Disease

Recent reviews have discussed the therapeutic approach to pulmonary hypertension complicating chronic lung disease.⁶³ Although the degree of baseline pulmonary hypertension is generally mild to moderate in patients with chronic respiratory disease, significant worsening can occur during acute

exacerbations, exercise, and sleep. Furthermore, it has been demonstrated that the development of pulmonary hypertension adversely affects prognosis. In selected cases, the pulmonary hypertension and right ventricular dysfunction can dominate the clinical picture.²⁹

The primary approach to therapy involves optimization of lung function and gas exchange. The only form of therapy demonstrated to improve survival in chronic lung disease has been the administration of supplemental oxygen. Although no clear relationship between improved survival with supplemental oxygen and an improvement in pulmonary hemodynamics has been demonstrated, results from the British MRC and the NOTT suggest that oxygen therapy may prevent any further increases studies in pulmonary arterial pressure.^{64,65} In addition to improving survival, oxygen therapy has been demonstrated to improve neurologic function and exercise performance.

Guidelines for oxygen therapy, based on the NOTT entry criteria, include the administration of oxygen to patients with PaO_2 less than 55 mm Hg while breathing room air or those with a PaO_2 less than 60 mm Hg with peripheral edema, a hematocrit greater than 55%, and/or electrocardiographic evidence of right ventricular hypertrophy. In terms of survival and neuropsychologic function, continuous oxygen therapy appears more efficacious than that administered for shorter daily durations.

Except for measures designed to specifically improve arterial oxygenation, it is difficult to demonstrate the benefit of adjunctive measures used in patients with chronic obstructive lung disease. Although commonly used, cardiac glycosides have not been demonstrated to improve right ventricular function in patients with chronic obstructive lung disease. Digitalis, therefore, should be used with great care in hypoxic individuals, especially those being treated with sympathomimetic amines because of the threat of induced arrhythmias. Digitalis may be indicated, however, in patients with supraventricular arrhythmias and in those with coexisting left ventricular dysfunction. Likewise, care should be taken in the use of diuretics in patients with chronic lung disease and normal left ventricular function. Excessive diuresis can induce a metabolic alkalosis and worsen carbon dioxide retention, increase pulmonary vascular resistance through an increase in hematocrit and blood viscosity, adversely affect right ventricular preload and cardiac output, and predispose the patient to electrolyte abnormalities and the risk of superimposed arrhythmias.

The use of prostanoids, endothelin blockers, or phosphodiesterase inhibitors has not been demonstrated to be of proven benefit in patients with obstructive or restrictive lung disease. Although a reduction in pulmonary vascular resistance may accompany their use, the use of vasodilators in chronic obstructive lung disease may worsen gas exchange by relieving hypoxic vasoconstriction and thereby shunting blood to poorly ventilated areas of the lung. The use of agents such as calcium channel blockers may worsen cardiac output as a result of their negative inotropic effect and reduction in right ventricular preload.

In pulmonary hypertension associated with certain types of parenchymal lung disease, specific therapies can be directed to improve vascular resistance and right ventricular function. For example, if vessel inflammation is felt to be a substantive contributor to an increase in pulmonary vascular resistance (i.e., idiopathic interstitial fibrosis, sarcoidosis, Takayasu arteritis), a trial of corticosteroids, or other immunosuppressants, is indicated. The use of assisted ventilator devices in patients with

chronic alveolar hypoventilation, or of nasal continuous positive airway pressure devices in patients with obstructive sleep apnea, can effectively prevent the hypoxemia and hypercarbia responsible for the pulmonary vasoconstriction and right ventricular dysfunction present in these disease processes.

In patients with end-stage chronic lung disease, particularly when complicated by pulmonary hypertension, single or double lung transplantation represents a viable intervention. In addition to improvement in lung function and gas exchange following transplantation, pulmonary hemodynamics may return to normal levels and even severe right ventricular dysfunction appears to be reversible with alleviation of the increased right ventricular afterload.

Postoperative Pulmonary Hypertension

Cardiothoracic surgical procedures may be complicated by postoperative pulmonary hypertension. The etiology of this phenomenon is uncertain but may be related to endothelial injury associated with cardiopulmonary bypass or ischemic-reperfusion injury. In small series, both inhaled iloprost and nitric oxide have been demonstrated to have positive hemodynamic effects although a mortality benefit has not been confirmed in a prospective study.⁶⁶⁻⁶⁸

Portopulmonary hypertension represents a major risk factor for perioperative mortality in patients undergoing liver transplantation, which approaches 100% when the mean pulmonary artery pressure exceeds 45 mm Hg. Case reports and series have described successful transplantation in selected patients using intravenous epoprostenol or oral sildenafil as a bridge to transplantation.^{68,69}

Chronic Thromboembolic Pulmonary Hypertension

Chronic thromboembolic pulmonary hypertension (CTEPH) represents a potentially curable form of pulmonary hypertension. Based on recent data, it appears to be more common than idiopathic pulmonary arterial hypertension, occurring in approximately 1% of patients after an episode of acute pulmonary embolism.⁷⁰ In the majority of surgically treated patients, marked improvement in pulmonary hemodynamics and functional status can be achieved following pulmonary thromboendarterectomy.^{12,13}

Patient selection for thromboendarterectomy is essential to assure an optimal surgical outcome. The decision to proceed to thromboendarterectomy is based on several objective factors. First, the presence of pulmonary vascular obstruction should result in hemodynamic or ventilatory impairment at rest or with exercise. The majority of operated patients have a pulmonary vascular resistance in excess of $300 \text{ dynes} \cdot \text{sec} \cdot \text{cm}^{-5}$, at rest or with exercise. Occasional patients, especially those with involvement of one main pulmonary artery, have a significant exercise impairment due to high minute ventilation demands, without substantially altered pulmonary hemodynamics. Surgery is also indicated in those patients with only mild or modest degrees of pulmonary hypertension at rest but who develop striking levels of pulmonary hypertension with exercise-related increases

in cardiac output. Because this hemodynamic response reproduces events during the patient's activities of daily living, it may reflect the true work load of the right ventricle. Furthermore, there is increasing evidence to suggest that the small vessels of the "open" pulmonary vascular bed, if exposed to these high pressures and flows over a sufficient period of time, will develop secondary hypertensive changes, thereby perpetuating the cycle of pulmonary hypertension. Surgical intervention, before fixed, small-vessel changes or right ventricular failure occurs, results in improved operative mortality risk and long-term hemodynamic and functional status.

Although a thoracotomy approach has been used in the past, sternotomy with cardiopulmonary bypass and hypothermic circulatory arrest appears to be the procedure of choice. Sternotomy allows access to both pulmonary arteries and assures more complete removal of the obstructing material. The use of cardiopulmonary bypass allows periods of complete circulatory arrest, necessary to provide the bloodless operating field essential for meticulous lobar and segmental dissections. It should be emphasized that thromboendarterectomy bears no resemblance to acute pulmonary embolectomy. The neointima in chronic thromboembolic disease is deceptive and is often not easily recognizable as chronic thrombi. The procedure is a true endarterectomy of chronic, endothelialized material from the native intima to restore pulmonary arterial patency (Fig. 33-7).

The operative and perioperative mortality rate in the 1959 patients who have undergone thromboendarterectomy at UCSD Medical Center, San Diego, has been 6.0%. Over the last 5 years, during which 720 patients have undergone surgery, 32 patients have died, for an in-hospital mortality of 4.4%. In addition to the complications common to other forms of cardiac surgery, patients undergoing pulmonary thromboendarterectomy face two additional and potentially fatal risks: postoperative lung injury (reperfusion pulmonary edema) and persistent postoperative pulmonary hypertension and right ventricular failure.

Reperfusion pulmonary edema, biochemically and clinically, appears to represent a localized form of high-permeability lung

injury. It may appear up to 72 hours after surgery and is highly variable in severity, ranging from a mild form of edema to an acute, hemorrhagic, and fatal complication. Management of reperfusion injury, as with other forms of acute lung injury, is supportive until resolution occurs. Investigations are ongoing to determine the basis for reperfusion lung injury and to find effective means of prevention or therapy.

In terms of residual postoperative pulmonary hypertension, this most commonly occurs in patients with longstanding disease in whom a secondary pulmonary arteriopathy has developed or in patients with a distal location of the occluding thromboembolic material. Residual postoperative pulmonary hypertension represents a significant cause of postoperative mortality with the mortality rate thirtyfold greater in patients with a postoperative pulmonary vascular resistance (PVR) greater than 500 dynes·sec·cm⁻⁵ than those in whom the postoperative PVR is less than 500 dynes·sec·cm⁻⁵.¹³

Lung transplantation remains a therapeutic alternative for patients not deemed candidates for thromboendarterectomy and for those who have undergone thromboendarterectomy with an inadequate hemodynamic outcome. Case series suggest that patients not deemed candidates for thromboendarterectomy by nature of the distal location of their disease and those who have residual postoperative pulmonary hypertension may benefit from the endothelin receptor antagonists sildenafil or prostanooids.⁷¹⁻⁷³ Epoprostenol has also been used as a bridge to thromboendarterectomy in patients with thromboembolic pulmonary hypertension and severely altered hemodynamics. Although such an intervention is capable of improving pulmonary hemodynamics, it remains to be established whether it reduces postoperative mortality or complications.⁷⁴

The need for a coordinated, experienced, multidisciplinary team dedicated to managing the complex problems often associated with the care of these patients cannot be emphasized too strongly. The often intricate details of the evaluative, surgical, and postoperative phases of care require an extensive experiential base to master. However, compared with lung transplantation, the only therapeutic alternative, thromboendarterectomy has much to recommend it in terms of long and short-term mortality, quality of life, and lack of need for immunosuppressant therapy.

Conclusion

Advances during the past decade in the pharmacologic and surgical management of several forms of pulmonary hypertension, namely chronic thromboembolic pulmonary hypertension and idiopathic pulmonary arterial hypertension, have been evolutionary, transforming disease processes once considered uniformly fatal into those consistent with a normal quality and duration of life. With an increasing understanding of pathophysiologic and pathobiologic mechanisms, and the role of various mediators in the initiation and progression of pulmonary arterial hypertension, new and innovative therapies can be envisioned. The progress that has been achieved in the diagnostic and therapeutic approach to patients with idiopathic and thromboembolic pulmonary hypertension, therefore, should not be considered the culmination of research and clinical efforts, but rather a model to apply to other forms of pulmonary hypertensive disease.



Figure 33-7. Surgical specimens obtained at the time of thromboendarterectomy. Note organized thrombotic material involving multiple branches beyond the area of central obstruction.

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Hemodynamically Unstable Presentations of Congenital Heart Disease in Adults

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CHAPTER 34

Anatomic and Pathophysiologic Classification
of Congenital Heart Disease
Heart Failure in the Adult with Congenital
Heart Disease

Other Catastrophic Emergencies
Conclusion

AMONG THE large number of patients with cardiac emergencies, the patient with congenital heart disease is a rarity. However, with growing numbers of patients with complicated congenital cardiac lesions surviving childhood and with larger numbers with serious, but more common lesions palliated by surgery, the cardiologist increasingly is seeing more patients with congenital heart disease, some of whom will have cardiac emergencies. Between 1985 and 2000, the number of adults with congenital heart disease has doubled, resulting in approximately 1 million adult survivors in the United States who are increasingly having late complications.¹ Although the anatomy and nomenclature of congenital heart disease is often intimidating to an adult cardiologist, the care in most cases is analogous to that of other adult patients. For example, the care of a young adult with heart failure from a failing systemic right ventricle is modeled after the deep clinical experience caring for patients with left heart failure. Being aware of congenital anatomy and the complications that are frequently seen in common congenital lesions, however, is important to help focus on the likely diagnosis and optimal treatment plan.

In general, patients with congenital heart disease are seen as adults because they have one or more of the following conditions²:

1. Simple lesions that may escape early diagnosis (native disease) or have had early repair:

Native lesions in this category include:

- Congenital aortic stenosis
- Isolated mitral valve disease
- Isolated patent foramen ovale or small atrial septal defect
- Isolated small ventricular septal defect
- Mild pulmonary stenosis

Repaired conditions in this category include:

- Previous ligated or occluded PDA
- Repaired isolated ASD
- Repaired isolated VSD

2. Moderately complex lesions that were asymptomatic in childhood and not repaired (e.g., atrial septal defects [ASD], patent ductus arteriosus [PDA], Ebstein disease, coarctation of the aorta) or underwent palliative repair (e.g., tetralogy of Fallot, coarctation of the aorta).

3. Lesions of great complexity including lesions that were palliated in childhood (e.g., single ventricle D-transposition of the great vessels with atrial or arterial switch, tricuspid atresia with Fontan operation) or were not amenable to a surgical procedure. (Severe pulmonary vascular disease [Eisenmenger syndrome] or patients with very small pulmonary arteries located where focalization or shunts are not possible). Even these patients are now often candidates for lung or heart-lung transplant.

The majority of these lesions never present as cardiac emergencies. However, with incisions in the atrium affecting the pacemaker or conduction system; with incisions in the ventricle forming fibrous scars as the basis for re-entrant ventricular arrhythmias, with anatomic right ventricles functioning as a systemic ventricle; and with residual lesions forming the substrate for developing infective endocarditis, cardiac emergencies do occur and form the content of this chapter (Table 34-1).

There are emergencies that are unique to the patient with congenital heart disease: For example, the occurrence of pregnancy in the patient with Eisenmenger syndrome. The drop in systemic vascular resistance in these patients increases the right-to-left shunt and results in arterial desaturation. However, most emergent complications seen in congenital heart disease are similar to the emergency situations seen in cardiovascular problems of other more common etiologies. The diagnosis of ventricular tachycardia in a patient with repaired tetralogy of Fallot is treated in a manner similar to the patient with coronary disease and ventricular tachycardia and, unfortunately, with the same uncertain efficacy. It is important to remember that a patient with repaired tetralogy of Fallot is at risk of developing ventricular tachycardia and to recognize the importance of investigating palpitation and presyncope and syncope. Substantial analogies to the care of general cardiac patients exist, but this needs to be combined with knowledge of what complications to expect with what lesion and management needs to be tailored to a congenital patient's unique anatomy (Table 34-2).

In the patient with a cardiac emergency, congenital heart disease can predispose the patient to certain complications that may be responsible for the cardiac emergency. For example, in a patient with L-transposition of the great vessels and shortness

Table 34–1. Cardiac Emergencies

	Life-Threatening*	Not Life-Threatening
Arrhythmia	AF with bypass tract Atrial flutter Mustard Frontan CHB with hypotension or CHF and/or ventricular escape Ventricular tachyarrhythmias with symptoms	AF without bypass tract CHB: normal hemodynamics and nodal escape Isolated PVCs Asymptomatic, nonsustained VT
Ischemia	Ongoing chest pain with ischemic ECG changes	Chronic nonischemic chest pain
Ventricular failure	New murmur + fever Compromising pleural effusion or ascites	
Cyanosis	Loss of continuous murmur in patient with BT or central shunt Acute pulmonary infection	Chronic cyanosis
Noncardiac	Hemoptysis Transient ischemic attacks or seizures (new onset)	Gout Biliary colic

*Warrants admission to CICU.

Abbreviations: AF, atrial fibrillation; BT, Blalock-Taussig shunt; CHB, complete heart block; VT, ventricular tachyarrhythmias.

of breath, the right ventricle is acting as the systemic ventricle and is prone to failure. The diagnosis of heart failure is not difficult, and treatment of congestive heart failure in these patients is similar to the treatment of congestive heart failure in those with other conditions.

Anatomic and Pathophysiologic Classification of Congenital Heart Disease

During the formation of the heart and cardiovascular system, there are many opportunities for the development of the lesions of congenital heart disease. The large variety of lesions forming the body of congenital heart disease can be confusing. It is helpful for the cardiologist seeing adult patients to think of these lesions in an organized manner. The following classification is helpful in that all congenital heart patients fit into one or more of these categories.

1. Predominant left-to-right shunt. Blood that has gone through the lungs, recirculates to the right side of the heart, and as a result the pulmonary blood flow is greater than the systemic blood flow. The shunt can occur at any level (e.g., at the venous level, anomalous pulmonary vein to the superior vena cava; at the atrial level, ASD; at the ventricular level, VSD; at the arterial level, PDA).
2. Predominant right-to-left shunt, or “cyanotic disease.” The blood is shunted from the right heart to the systemic circulation, bypassing the lungs. The arterial blood is therefore desaturated. If the amount of desaturated hemoglobin is 5 g/dL or greater, cyanosis can be observed. The systemic blood flow is greater than the pulmonary blood flow. This shunt also can occur at any level of the cardiovascular system (e.g., at the venous level, superior vena cava draining into the left atrium; at the atrial level, tricuspid atresia with an ASD; at the ventricular level, tetralogy of Fallot; at the arterial level, truncus arteriosus).
3. Stenotic or atretic valves and hypoplastic or atretic ventricles. The valves can also be incompetent. Either ventricle may be hypoplastic or atretic.

4. Great vessel abnormalities. Transposition of the great vessels, coarctation of the aorta, PDA, vascular rings, and truncus arteriosus.
5. Abnormalities of position. Transposition of the great vessels, L-transposition, dextroposition, and dextrocardia.

Arrhythmias

Arrhythmias are some of the more common emergencies seen in patients with congenital heart disease. There are two types of arrhythmias: bradyarrhythmias (e.g., sick sinus syndrome, sinus arrest, varying degrees of heart block including complete heart block) and tachyarrhythmias (e.g., atrial fibrillation, atrial flutter, ventricular tachycardia, and fibrillation).

The arrhythmic patient may have palpitations, presyncope, or syncope. With atrial tachyarrhythmias, the patient usually complains of palpitations, which sometimes are severe enough to frighten the patient. Presyncope or syncope occurs with extremely rapid ventricular response, raising pulse rates to 200 beats/min or more. If the left ventricle is noncompliant with an atrial tachyarrhythmia, especially atrial fibrillation—in which there is no atrial contraction—stroke volume can fall dramatically, and the patient may develop syncope. The diagnosis of this type of arrhythmia can be made by electrocardiogram (ECG) if the arrhythmia is persistent. However, even if the patient having syncope or presyncope is in sinus rhythm at the time of the examination, it is most important to consider the patient with congenital heart disease, with or without repair, as having a potentially fatal arrhythmia.

The atrial bradyarrhythmias and tachyarrhythmias encountered in patients with congenital heart disease may result from hemodynamic alterations of the atrium or involve areas of slowed conduction in the areas of scar associated with prior surgery. These may include surgery for ASD repair,³ both ostium secundum and ostium primum defects, Fontan procedures for tricuspid atresia or single ventricle,^{4,5} and the Mustard or Senning procedure for transposition of the great arteries.^{6,7}

Lesions affecting the conduction system and causing AV block have become less common since surgeons have learned to avoid the conduction system during surgery. However, with any

Table 34–2. Complications of Congenital Heart Disease

Lesion	Special Considerations
Tetralogy of Fallot	Ventricular tachycardia Atrial fibrillation Right ventricular dysfunction Pulmonary regurgitation (late complication usually associated with moderate to severe regurgitation)
Fontan	Ventricular dysfunction Sinus node dysfunction Atrial flutter/intra-atrial re-entrant tachycardia (IART) Fontan obstruction or leak Pulmonary embolus
D-transposition of great arteries	Atrial flutter/IART Systemic right ventricular dysfunction AV block (uncommon late) Baffle systemic AV valve regurgitation Sinus node dysfunction with junctional rhythm (usually asymptomatic)
L-transposition of great arteries	Systemic ventricular failure AV block Systemic AV valve regurgitation WPW (2%–4%)
Coarctation	Dissection Bicuspid valve with endocarditis, regurgitation, or stenosis Early coronary artery disease or heart failure Cerebral aneurysm
Left-to-right shunt	Pulmonary hypertension (Eisenmenger syndrome) Atrial fibrillation Endocarditis (VSD or PDA, rare with ASD)
Right-to-left shunt (cyanotic)	Paradoxical embolus Worsening cyanosis Brain abscess Bleeding diathesis Hyperviscosity syndrome with erythrocytosis Protein-losing enteropathy
Marfan	Dissection Aortic valve regurgitation Mitral valve prolapse

VSD repair, immediate injury or later injury as a result of fibrosis is a possible cause of progressive heart block. With advances in surgical technique and knowledge of the path of the conduction system, heart block after repair of VSD is increasingly rare with persistent heart block seen in less than 1% of patients.⁸

L-transposition, or corrected transposition of the great vessels, is a lesion in which ventricular inversion has occurred without inversion of the atria or great arteries. In this condition, the anatomic right ventricle is the systemic ventricle and the anatomic left ventricle is the pulmonic ventricle, but the physiologic passage of blood is normal (i.e., the systemic venous return is pumped to the lungs, and the pulmonary venous return is ejected into the aorta). The conduction system is also inverted

and the AV node is abnormally located and often dual with elongation of the bundle of His.⁹ As a result, these patients have a high rate of AV block, which can occur at all levels of severity—from first to third degree—and which increases in incidence with age at a rate of about 1% to 2% per year.

Atrial Tachyarrhythmias

The diagnosis and treatment of bradyarrhythmias and tachyarrhythmias are the same in patients with congenital heart disease as for those with other lesions. When symptomatic bradycardia and hemodynamic instability, such as hypotension or syncope, are present, a pacemaker is indicated.

Atrial fibrillation, tachycardia, and flutter, when they occur in patients with congenital heart disease, are usually relatively not life-threatening.^{10,11} These arrhythmias occur in about 20% of patients with ASDs and can recur even after the ASD is repaired, especially when the repair is performed late in life (after the age of 40).³ In some defects, atrial fibrillation or atrial flutter can be very serious and even life-threatening. The treatment is similar to that of atrial fibrillation or atrial flutter due to other causes; with rapid atrial tachycardia in patients with hemodynamic instability, immediate cardioversion is indicated. In patients who are hemodynamically stable with noncontracting atria, which may be seen in conditions such as atrial fibrillation and atrial standstill, anticoagulation therapy for 3 weeks before cardioverting is indicated. In such cases, the patient should receive anticoagulation for 3 weeks after cardioversion until mechanical atrial contraction is well established. If the patient is hemodynamically stable, the ventricular response can be slowed with amiodarone, β -blockers, verapamil, or diltiazem. If it is necessary to cardiovert before achieving stability, a period of anticoagulation can be provided. Transesophageal echocardiography (TEE) to rule out evidence of atrial thrombus is desired and allows safe cardioversion. With atrial tachycardia, 6 mg adenosine given intravenously usually converts the patient to sinus rhythm. If this treatment is unsuccessful, another 6 to 12 mg of adenosine can be given.

Atrial flutter or intra-atrial re-entrant tachycardia occurs frequently in patients who have undergone a Fontan procedure, with the prevalence estimated as high as 50% in adult patients. The presentation is usually subacute but occasionally hemodynamic instability and even sudden death especially in the setting of 1:1 conduction.¹² The patient should be converted to normal sinus rhythm either pharmacologically or by cardioversion with the caution that antiarrhythmics may exacerbate sinus node dysfunction, AV conduction, or promote 1:1 conduction of an atrial arrhythmia. If atrial flutter recurs, the patient should be referred to an electrophysiologist to map the pathways of flutter, if possible. If this can be done, catheter ablation of the pathway is possible. If atrial flutter or atrial tachycardia recurs incessantly and ablation attempts fail, then ablation of the AV node with placement of a dual-chamber (DDD) pacemaker should be considered. If the patient does not remain in sinus rhythm, then a physiologically responsive (VVIR) pacemaker is the treatment of choice.

Another atrial arrhythmia that can be fatal is atrial tachycardia and subsequent atrial fibrillation in a patient with an antegrade conducting bypass tract. In this condition, the impulse conducts from the atrium to the ventricle over the bypass tract. Especially with sympathetic stimulation or increased conductivity induced by digitalis, the ventricular response can approach

250 to 300 beats/min, and the patient may develop ventricular fibrillation. In patients with a possible AV bypass tract, digoxin should always be avoided. Patients with Ebstein anomaly have 25% incidence of bypass tracts in the posteroseptal location and a bypass tract may be present in 2% to 4% of patients with L-TGA.

In patients with atrial fibrillation and an AV bypass tract (i.e., Wolff-Parkinson-White syndrome), digoxin should always be avoided. In these patients, the ventricular response is controlled with a β -blocker or calcium channel blocker. When present, the AV bypass tract should be ablated.

Ventricular Tachyarrhythmias

Ventricular tachyarrhythmias can occur as a result of incisions in the right or left ventricle with fibrous scar forming the basis for re-entrant arrhythmias or more commonly with progressive ventricular enlargement with decreased left or right ventricular function, or a hypertrophied left or right ventricle.

The development of ventricular tachyarrhythmias late after surgery is not uncommon. This is especially true in patients with tetralogy of Fallot; sudden death later after surgery is seen in about 6% of patients in long-term follow-up.¹³ Late sudden death and ventricular arrhythmias in tetralogy correlate well with the degree and duration of pulmonary regurgitation, with arrhythmias increasing as continued pulmonary regurgitation results in progressive right ventricular enlargement.¹⁴ As the right ventricle enlarges, there is increased fibrosis, QRS prolongation, and Q-T dispersion that appears to provide the substrate for ventricular tachycardia.^{15,16} Fortunately, it appears that timely pulmonary valve replacement may decrease the incidence of arrhythmias.¹⁷

The patient may have palpitations, presyncope, or syncope. The diagnosis of ventricular tachycardia can be made on ECG, either on presentation or on the 24-hour ambulatory ECG. If the arrhythmia is frequent but short-lived, an event recorder, which allows continuous ECG monitoring and activating capture of the rhythms when symptoms occur, can be worn for several days.

Any patient with congenital heart disease, either before or after surgery, with presyncope or syncope must be considered as having had a potentially life-threatening arrhythmia. In such patients, if the diagnosis cannot be made on an ECG, electrophysiologic testing should be considered for prognostication and to potentially assist with therapy. As with degenerative cardiac disease, anti-arrhythmic therapy has not been shown to be of life-sustaining benefit in congenital heart disease, although it may be important for symptom control. The use of an implantable cardioverter-defibrillator (ICD) should, therefore, be considered in patients considered at high risk for sudden death. Randomized trials of congenital heart patients, however, do not exist to guide selection.

Ischemic Complications

In adult patients with congenital heart disease, ischemic complications causing cardiac emergencies are rare. More commonly, the anomalous origin of the left coronary artery from the pulmonary artery causes acute severe ischemia and myocardial infarction in infants who usually have heart failure due to an extensive antero-lateral myocardial infarction. Occasionally, the murmur of mitral regurgitation or "angina" manifested by poor feeding or suckling or crying at times of exertion (such as feeding) and consequently brings the infant to the attention of the physician. By the age of 1 year, most of these children have been diagnosed or died.

The potential reasons for the occurrence of myocardial ischemia in adults with congenital heart disease include the following:

1. Anomalous left coronary artery arising from a pulmonary artery (ALCAPA) with late presentation or with complications resulting after repair in infancy.
2. A left coronary artery arising from the right sinus of Valsalva or the right coronary artery arising from the left sinus of Valsalva when these malformations are associated with an inter-arterial course between the aorta and the pulmonary artery.
3. Coronary arteries transposed in the arterial switch operation for transposition of the great vessels, with subsequent compromise.
4. Coronary aneurysm, with congenital or postinflammatory, such as Kawasaki disease or panarteritis nodosa with associated thrombosis.¹⁸
5. Coronary artery compressed by myocardial muscle bridge.
6. Coronary arteriovenous or coronary-cameral fistula.
7. Aortic stenosis with myocardial ischemia or pulmonary stenosis with right ventricular ischemia.

Rarely, the cardiologist sees an adult patient with a coronary artery anomalously arising from the pulmonary artery that was transplanted or repaired with a tunnel repair, or occasionally, with simple ligation of the left coronary artery. Prior to surgical repair, when the entire coronary circulation is dependent on the right coronary artery and collaterals, patients can develop progressive ischemia with growth, resulting in angina or heart failure. If there are symptoms or signs consistent with myocardial ischemia, the patient should have an estimation of ventricular function by echocardiography or radionuclide scanning and some measure of myocardial viability by positron emission tomography, dobutamine echocardiography, or resting thallium-201 scanning. If ischemic myocardium is found, then revascularization of the left coronary artery should be performed.

Rarely, adult patients have unrepaired ALCAPA. Presentations include ischemia, sudden death, dilated cardiomyopathy with heart failure, and progressive mitral regurgitation. Extensive collateral flow from a dilated coronary right artery permits survival into adulthood but the resulting left-to-right shunt and a coronary steal place a significant hemodynamic burden on the left ventricle. Prompt repair is indicated.

An uncommon condition causing myocardial ischemia is the left coronary artery arising from the right sinus of Valsalva. This lesion may not, and probably usually does not, cause myocardial ischemia in most patients. However, in some patients, usually young adults, most often during or just after exercise, sudden and usually transient occlusion of the left coronary artery can occur. This causes profound ischemia to the left ventricle and is usually manifested by sudden death or syncope and occasionally by profound angina, with or without myocardial infarction.

The reason for the sudden ischemic episode is not known. The usual course of such a vessel is obliquely posterior, between the right ventricular outflow tract and the aortic root. This could result in a kinking or compression of the artery during exercise, or possibly in collapse of the orifice of the coronary ostium. However, coronary spasm cannot be ruled out. This type of event occurs only rarely because patients on many previous occasions have exercised as or more vigorously without difficulty. Furthermore, in a few patients who have exercised after an event has occurred, frequently no ischemia can be precipitated.

Less commonly, the right coronary artery arises from the left sinus of Valsalva and causes sudden death, syncope, or inferior

myocardial infarction. This is less often a cause of sudden death because sudden occlusion of the right coronary artery generally leads to inferior myocardial infarction.

Any patient under age 30 years who has presyncope or syncope during exercise or a life-threatening ventricular arrhythmia with an apparently normal heart on echocardiogram should be suspected of having an anomalous origin of the left or right coronary artery from the opposite sinus of Valsalva. At present, cardiac CT and MRI may provide the best spatial resolution to define coronary anomalies¹⁹; however, transesophageal echocardiography (TEE)²⁰ or definitive identification with invasive catheterization can be useful. If such an anomaly is identified, bypass grafting should be considered.

Heart Failure in the Adult with Congenital Heart Disease

The underlying mechanisms for the development of congestive heart failure in the setting of congenital heart disease are similar to those in acquired disease. Broadly defined, congestive heart failure can result from:

1. Primary pump failure involving either the right or left ventricle.
2. Ventricular hypertrophy and fibrosis leading to diastolic dysfunction.
3. Mechanical dysfunction, usually on the basis of valvular disease or failure of palliative procedure.

The onset of heart failure in adults with congenital heart disease is usually gradual; thus patients usually have chronic or subacute symptoms. Acute presentations are most common in those with sudden valvular incompetence, ischemia (discussed previously), new onset of arrhythmia, or sudden exacerbations of chronic congestive heart failure. Identifying the cause of congestive heart failure in these patients requires an accurate and detailed clinical history and physical examination, a systematic noninvasive evaluation, and frequently a referral for an invasive hemodynamic evaluation when information remains incomplete.

The clinical history is an essential key in diagnosing the cause of heart failure in adults with congenital heart disease. Critically important are knowledge of the primary lesion and the presence of associated lesions. One example is coexistence of a bicuspid aortic valve that becomes clinically manifest with stenosis or insufficiency many years following a repair for aortic coarctation. Second, the timing and nature of both palliative procedures and surgical repairs strongly influence late manifestations. Occasionally, a palliative procedure may produce residual long after primary repair has been performed; for example, congenital aortic stenosis treated with surgical valvotomy may have recurrent stenosis or progressive aortic regurgitation. Third, the specific procedure performed to achieve the primary repair influences late outcome; for example, a patch placed across the pulmonary annulus (i.e., transannular) to alleviate pulmonary stenosis in teratology of Fallot is associated with progressive pulmonary insufficiency, whereas other procedures are more likely associated with residual stenosis. Finally, the development of acquired disease may influence the natural history of congenital heart disease, such as accelerated atherosclerotic coronary disease in patients with coarctation of the aorta.

The physical examination should be directed toward identifying signs of systemic venous congestion (e.g., elevated jugular venous pressure, leg edema, ascites, pleural effusion) and pulmonary venous congestion (e.g., pulmonary rales). Evidence of ventricular enlargement will be evident on precordial palpation, but the right and left ventricles may be transposed. Murmurs of valvular stenosis and insufficiency should be carefully noted. When present, prosthetic valve sounds should be crisp and constant in their intensity; dampened or irregular clicks may reflect valve dysfunction or arrhythmia. The absence of a continuous murmur in a patient with a Blalock-Taussig shunt may herald obstruction or pulmonary vascular disease and explain worsening cyanosis.

The approach to the noninvasive diagnosis of heart failure in the adult with congenital heart disease is similar to that for patients with acquired disease, except that knowledge of the anatomy unique to the primary congenital lesion and to the surgical repairs is required. Inspection of the ECG for conduction defects and arrhythmias occasionally reveals the cause of heart failure. Echocardiography should be considered early in the presentation of these individuals, with the following specific goals:

1. Establishing or confirming the primary and secondary diagnoses.
2. Establishing the adequacy of prior surgical repairs, including patch competency and shunt patency.
3. Evaluating ventricular systolic and diastolic function.
4. Identifying hemodynamically significant valvular dysfunction, either native or prosthetic, and intracardiac shunts.

TEE may be superior to surface imaging, especially in evaluation of the atria, interatrial septum, conduits, and prosthetic valves. Although it is a semi-invasive procedure, TEE has proven safe in critically ill patients once respiratory status is stabilized. Cardiac MRI and CT may be helpful as well, providing both a cardiac assessment and helping delineate extracardiac pulmonary anatomy; however, both procedures may be difficult in unstable patients.

When the clinical and noninvasive data are inconclusive, and specifically, to exclude superimposed disease, cardiac catheterization may be necessary. It is important that the goals of the study be predetermined and that the catheterization be performed by personnel familiar with congenital heart disease. Incomplete information can lead to inappropriate treatment.

Etiologies of Pump Failure

There are several causes of pump failure unique to the population of adults with congenital heart disease. The right ventricle functioning in the systemic circulation is encountered in two groups of patients: those with congenitally corrected transposition of the great arteries (L-transposition), and those with transposition of the great vessels palliated with an interatrial baffle operation (i.e., Mustard or Senning procedure). Although the right ventricle hypertrophies and is thus able to pump against the increased afterload for many years, late failure is a feature of the natural history of the patient population usually presenting in the fourth or fifth decade of life.²¹ The signs and symptoms are those of pulmonary congestion and occasionally low output. It is necessary to exclude obstruction of the pulmonary venous limb of the interatrial baffle, which may also lead to pulmonary venous congestion and be confused with failure of the systemic ventricle. Likewise, systemic venous congestion may occur in the presence of obstruction to the systemic venous limb of the baffle.

These structural lesions may require percutaneous intervention or surgery. Precipitants should be identified such as incessant atrial tachyarrhythmias, which can lead to ventricular dysfunction. Occasionally excessive alcohol use or superimposed viral myocarditis can impact ventricular function. Treatment with inotropic agents may be indicated acutely until adequate afterload reduction can be instituted. The use of β -blocker therapy in the failure of the systemic right ventricle may be of long-term benefit by analogy to left ventricular failure, but only limited studies have been performed in this patient group. Biventricular pacing has also been used to a limited extent in congenital heart disease and systemic right ventricles and may also be of benefit in advanced cases.²² Patients with intractable cases should be considered for heart transplantation.

Another group of patients who are likely to develop heart failure are those whose anatomy falls within the broad category of single ventricles. These include the rare patients with double outlet right ventricles, double-inlet left ventricles, tricuspid atresia, and pulmonary atresia with intact ventricular septum. By adulthood, these patients have been treated with a variety of palliative procedures, in most cases to increase pulmonary blood flow most frequently through a cavopulmonary connection (i.e., Fontan or Glenn procedure), although adults are still occasionally seen with a systemic-pulmonary arterial connection (i.e., Potts or Waterston procedure). Heart failure may be an inevitable feature of the natural history of the single ventricle, but patients may present at earlier stages with failure of palliative procedure. The latter is of particular concern in patients with one of the variants of the Fontan procedure. In the previous iteration of this procedure, direct connection, usually via a conduit, between the right atrium and the pulmonary artery was established. Sluggish flow within the right atrium can lead to thrombus formation, rising pressures within the Fontan circuit and increasing coronary sinus pressures with decreased coronary perfusion pressures. The left ventricle develops diastolic dysfunction. Additionally, the enlarging right atrium may cause atrial septal shift that obstructs the flow of the right pulmonary veins leading to increases in pulmonary pressure. Fontan conversion to an extracardiac conduit may be considered for these patients. When combined with a Maze procedure, this operation may help control atrial arrhythmias. The role of this procedure, which carries considerable morbidity and mortality, is still under debate. Whether younger patients with Fontan surgery who received extracardiac conduits fare better in terms of late heart failure remains to be seen.

Other potential causes of late systolic failure include lesions which lead to chronic volume overload of the systemic ventricle. Included in this group are congenital causes of aortic and atrioventricular valve regurgitation (mitral in the systemic left ventricle and tricuspid in the systemic right ventricle), ventricular septal defect, or patent ductus arteriosus with large left to right shunts.

Abnormalities of Diastolic Function

Diastolic dysfunction as the cause of right or left ventricular failure is less common in patients with congenital heart disease than in those with acquired heart disease, but its incidence will increase as congenital patients continue to age. Symptoms of pulmonary congestion may occur in the setting of left ventricular hypertrophy and fibrosis due to long-standing left ventricular outflow tract obstruction, congenital valvular aortic stenosis, or

aortic coarctation. Once obstruction is relieved, the hypertrophy regresses, but fibrosis may persist, producing late arrhythmias and even sudden death. A well-recognized consequence of impairment in left ventricular diastolic function that occurs with age is increased left-to-right shunting across an ASD. The increased shunting may contribute to the almost ubiquitous atrial arrhythmias in patients older than 60 years with ASD and ultimately right ventricular failure.

Right ventricular hypertrophy is most common in the setting of pulmonary valve stenosis. The overwhelming success of surgical and balloon valvuloplasty for this condition in childhood has generally insured normal survival in those treated. Patients with tetralogy of Fallot demonstrate left and right ventricular fibrosis by late gadolinium enhancement on MRI that correlates with ventricular dysfunction, exercise intolerance, and arrhythmia,¹⁶ and similarly increased fibrosis after atrial switch procedures correlates with aging, declining function, and clinical events.²³

Abnormalities of Valve Function

The sudden development of left-sided valvular regurgitation is most likely to present as acute heart failure. Acute aortic regurgitation associated with congenital heart disease is most likely from destruction of a bicuspid valve due to endocarditis or from dissection of the aorta in Marfan syndrome. Aortic valve endocarditis may also occur in the setting of discrete fibromuscular subaortic stenosis and may complicate a so-called supracristal (subarterial) VSD. An acute manifestation of the latter is rare.

Acute mitral regurgitation may also occur in the setting of endocarditis or as a result of chordal rupture in the presence of mitral valve prolapse. Prosthetic valve dysfunction is discussed later in this chapter.

Management

Initial management of the patient should be aimed at acute stabilization by reducing preload using diuretics and nitrates, reducing afterload using vasodilators, and providing inotropic support when necessary. However, therapies for heart failure must be tailored to the individual. For example, in patients with Eisenmenger syndrome or unrepaired tetralogy of Fallot, excessive diuresis can result in a severe fall in cardiac output, and afterload reduction with systemic vasodilators may result in worsening right-to-left shunt. Correction of inciting or aggravating conditions such as arrhythmias and fever may benefit the patient. Once the patient is acutely stabilized, further diagnostic procedures can be performed to determine definitive therapy.

Patients with outflow tract obstruction and secondary hypertrophy are highly dependent on adequate preload and, therefore, are subject to hypotension with diuresis. Thus, treatment of congestive heart failure due to diastolic dysfunction includes relief of obstruction when present, careful diuresis with avoidance of hypovolemia, and slowing of the heart rate when appropriate. For patients in atrial fibrillation, restoration of sinus rhythm may improve cardiac output.

Failed Palliative Procedures

Systemic-Pulmonary Arterial Shunts

Systemic-pulmonary shunts (Table 34-3) are employed in cyanotic patients with severely reduced pulmonary arterial blood flow, usually due to outflow obstruction. The three most commonly used shunts were the Waterston procedure, which connects the ascending aorta to the right pulmonary artery; the

Table 34–3. Palliative Shunts

	Anatomy	Comment
Systemic Arterial–Pulmonary Arterial		
Classic BT	Subclavian artery to PA	Absent ipsilateral radial pulse; continuous murmur
Modified BT	Subclavian to PA conduit	Preserved pulse; continuous murmur
Central shunt	Aorta to PA conduit	Continuous murmur
Waterston	Ascending aorta to RPA	Continuous murmur*
Potts	Descending aorta to LPA	Continuous murmur*
Systemic Venous–Pulmonary Arterial		
Glenn	Superior vena cava to PA	No murmur; arrhythmias uncommon
Fontan	Total cavopulmonary shunt	No murmur; atrial arrhythmias common
Other		
Rastelli	Right ventricle to PA	Valve degeneration may lead to pulmonary insufficiency murmur

*Continuous murmur may disappear in presence of pulmonary hypertension.

BT, Blalock-Taussig; LPA, left pulmonary artery; PA, pulmonary artery; RPA, right pulmonary artery.

Potts procedure, which connects the descending aorta to the left pulmonary artery; and the Blalock-Taussig shunt, which connects the subclavian artery directly (classic) or indirectly via a Gore-Tex graft (modified) to the pulmonary artery. The Waterston and Potts procedures are no longer performed because they are associated with a high incidence of congestive heart failure and pulmonary vascular disease; however, adults with tetralogy of Fallot and pulmonary atresia who have had palliative procedures are still occasionally encountered. Congestive heart failure, endocarditis, brain abscess, and severe cyanosis due to outgrowing of the shunt or development of pulmonary vascular disease are potential sequelae in these patients.

Patients with the classic Blalock-Taussig shunt have an absent pulse in the ipsilateral arm; in those with a modified Blalock-Taussig shunt, the pulse is preserved. A continuous murmur is a normal finding; its absence heralds obstruction of the shunt. Thus worsening cyanosis and a diminished murmur should prompt urgent catheterization and intervention. Endarteritis may also complicate this type of shunt.

Cavopulmonary Connections

Cavopulmonary connections (see Table 34-3) consist of a group of palliative procedures commonly performed in patients with tricuspid atresia and other single ventricle lesions, broadly categorized into the Glenn procedures and the Fontan procedure. In the Glenn procedure, the superior vena cava is anastomosed to the right pulmonary artery. However, in older children and adults, the blood supply from the head and neck is rarely adequate for relief of cyanosis; thus many patients proceed to a total cavopulmonary connection (i.e., Fontan procedure), which is accomplished through a variety of surgical techniques. Supplemental systemic-pulmonary arterial shunts are also used. Pulmonary blood flow is predominantly passive; thus systemic venous pressures are elevated.

The family of Fontan procedures is associated with frequent complications that include chylous pleural effusions, liver failure, protein-losing enteropathy, and pulmonary thromboembolic disease. Although they are more likely to present chronically,

these complications may occasionally result in an acute decompensation, especially in patients with limited cardiopulmonary reserve and may be triggered by arrhythmia or a pulmonary thromboembolic event. In addition, increasing pleural effusions compromise respiratory status through atelectasis, exacerbating cyanosis. Ascites are a result of liver failure, and hypoalbuminemia may also reduce lung volumes by elevating the diaphragm. Thrombi arising in the deep venous system and right atrium can result in pulmonary emboli, with a rise in pulmonary artery pressures and consequent reduction in pulmonary blood flow. Acutely, TEE and catheterization with angiography may be necessary to exclude conduit obstruction and thromboembolic disease. Acute management may include thoracentesis, paracentesis, and anticoagulation or thrombolytic therapy.

Prosthetic Valve and Prosthetic Material Failure

The presentation of prosthetic valve dysfunction in adults with congenital heart disease is generally similar to that in patients who have had valve replacement for acquired heart disease; however, there are several important differences in patients who had valve replacement during childhood. First, the size of the valve may be an important factor because growth of the patient produces increased requirements for higher stroke volumes. Thus the patient with prosthetic valve mismatch may have diminished exercise tolerance and heart failure. Second, the rate of degeneration of bioprostheses or homografts is faster in young patients; the leaflet thickening and tearing may occur as early as 5 years following implantation instead of the expected 10 to 15 years in adult patients.²⁴ Third, prosthetic valves are more frequently combined with a conduit that can also become obstructed through a process known as pseudointimal thickening.

Other complications of prosthetic valves common in those with acquired and congenital valve disease include endocarditis and thrombosis; the latter is confined primarily to mechanical prostheses. Primary failure is rare in the types of mechanical valves (most frequently, St. Jude bileaflet valves) usually encountered in this population.²⁵

The clinical presentation may be that of sudden heart failure, syncope, or a cerebral, cardiac, or peripheral embolic event. Acute valve thrombosis can result in cardiopulmonary arrest. Transthoracic echocardiography may detect stenosis by identifying an increased gradient across an obstructed valve or conduit and regurgitation of a prosthetic aortic valve, but it is rarely adequate for identifying the cause of obstruction or detecting prosthetic mitral regurgitation. In these cases TEE is usually required.²⁶ Moreover, when prosthetic valve endocarditis or thrombosis is suspected, TEE is virtually mandated because of the low sensitivity of surface imaging in these entities. Degeneration of bioprosthetic leaflets and perivalvular leaks are also accurately diagnosed with TEE. Conduit obstruction is more likely to present subacutely and may require catheterization and angiography for diagnosis. The preferred treatment of an acute thrombosis of a mechanical prosthesis is surgery; if surgery is not possible, thrombolytic therapy has met with some success, albeit with a high rate of hemorrhagic complications.²⁷ The management of anticoagulation during surgery and pregnancy in patients with prosthetic valves is similar to that for those with acquired disease.

Other prosthetic materials are used for patch closures of ASDs and VSDs. Operations performed before 1970 were more prone to patch leaks. Although these persistent defects are rarely hemodynamically significant, they represent an important nidus for endocarditis at the site of the jet lesion and are a potential cause of hemolysis.

The long-term sequelae of palliative procedures most often have slow chronic deterioration of functional capacity. The less common acute presentations are potentially life-threatening and require prompt diagnosis and, frequently, emergency intervention.

Other Catastrophic Emergencies

Cerebrovascular Disease

Among the neurologic complications of congenital heart disease is subarachnoid hemorrhage as a result of rupture of an aneurysm of the circle of Willis in association with aortic coarctation. Although rupture is more common in those with unrepaired coarctation, patients with repairs remain at risk, especially in the presence of persistent hypertension. Patients with coarctation of the aorta are also at increased risk of thrombotic strokes as a result of long-standing hypertension.

Additional neurologic complications of congenital heart disease include brain abscesses and embolic stroke in the presence of right-to-left shunt. Brain abscesses may have new onset of seizures, headache, or unexplained fever. The diagnosis can be made by computed tomography scanning or magnetic resonance imaging. In young patients with acute cerebral ischemia, an intracardiac communication responsible for right-to-left shunting should be suspected. Many patients have been shown to have a patent foramen ovale by transthoracic echocardiography or TEE. An ASD may also have a cerebral ischemic stroke.

Thrombotic strokes are rare in patients with cyanotic heart disease and secondary erythrocytosis.²⁸ Prophylactic phlebotomy is not indicated in the asymptomatic patient with an elevated hematocrit; however, the patient with decompensated erythrocytosis, defined as an increasing hematocrit or iron deficiency,²⁹ may have headaches, lethargy and, less frequently, seizures. These patients can benefit from iron replacement in the

event of iron-deficiency states and phlebotomy in the event of extreme polycythemia. A reasonable target for phlebotomy is a hematocrit of less than 60%, which should be achieved gradually by serial phlebotomy with volume replacement.

Pulmonary Hemorrhage

Pulmonary hemorrhage can occur in patients with Eisenmenger syndrome as a result of pulmonary infarction and pulmonary arteriolar rupture. These life-threatening events may complicate pregnancy and are potentially fatal; however, the differential diagnosis of hemoptysis includes pulmonary edema, which may respond to diuretic therapy, and pulmonary infections.³⁰ When chest radiography is nondiagnostic, bronchoscopy may be required.

Pulmonary artery hemorrhage more commonly complicates right heart catheterization with a flow-directed balloon-tipped catheter, in particular in the presence of severe pulmonary vascular disease. When it is necessary to perform invasive monitoring, care should be taken not to inflate the balloon in a small pulmonary branch artery but rather to inflate it in a larger branch, then float it out to a smaller branch to obtain the pulmonary capillary wedge pressure.

Control of hemoptysis may be thwarted by the bleeding diathesis that accompanies the polycythemia of cyanotic heart disease. These management issues are beyond the scope of this chapter.

Eisenmenger Syndrome

In Eisenmenger syndrome, irreversible pulmonary vascular disease develops in response to left-to-right shunt (e.g., VSD, ASD, PDA).³¹ There is consequent reversal of shunt flow to right-to-left and cyanosis. The oxygen saturation is markedly decreased, and polycythemia is present. There is ECG and radiographic evidence of right ventricular hypertrophy. These patients have tenuous hemodynamics and are susceptible to severe hypotension in the setting of dehydration or hypovolemia from many causes, including diuretic treatment. Because of the fixed pulmonary vascular resistance, there is limited ability to increase cardiac output. Systemic vasodilators are contraindicated because they may result in hypotension and worsening cyanosis with increased right-to-left shunting. Pregnancy is poorly tolerated; a high fetal and maternal mortality is associated with Eisenmenger syndrome.³² Pulmonary thrombosis, hemorrhage, or both may complicate pregnancy. Endocarditis and arrhythmias are common (discussed previously). Also as mentioned previously, brain abscess may occur in this setting.

Conclusion

The numbers of adult patients with congenital heart disease are increasing at a steady rate. These patients require ongoing surveillance for potential residual complications related both to the natural history of their primary lesion and to the palliative and reparative procedures performed. They are not likely to present frequently to emergency rooms and CICUs; however, appropriate treatment requires an understanding of how the physiology of the particular congenital heart lesion influences the clinical presentation and the response to conventional therapies. Awareness of the likely complications to expect with common lesions coupled with a consciousness of the unique anatomy of each individual will raise diagnostic accuracy and help institute the best treatment plan, often based on analogies to general cardiac care.

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Overdose of Cardiotoxic Drugs

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CHAPTER 35

Calcium Channel Antagonists	Propoxyphene
β-Adrenergic Antagonists	Carbamazepine
Digoxin	Chloroquine
Sodium Channel Blocking Agents	Management of Sodium Channel Blocking
Cyclic Antidepressants	Drug Toxicity
Antipsychotics (Phenothiazines, Butyrophenones, and Atypical Agents)	Illicit Drugs
Antihistamines	Conclusion

CARDIAC DYSRHYTHMIAS, myocardial depression, and vasodilation are the major cardiovascular effects observed in poisonings. A large number of therapeutic and nontherapeutic agents possess toxicity directed toward the cardiovascular system, whether in the setting of actual overdose or merely therapeutic misadventure. In this chapter we address some of the most significant and most common cardiovascular toxins. We describe these toxicants briefly, review their relevant pharmacology, delineate their known pathophysiology, describe clinical manifestations of their poisonings, and discuss their current management recommendations. In all such cases, consultation with a medical toxicologist or a certified regional poison control center should be considered.

We begin with a review of poisoning due to calcium channel antagonists and β-adrenergic receptor antagonists (β-blockers). These two primary cardiovascular drug classes account for well more than half of the life-threatening events and deaths due to cardiovascular agents reported to the American Association of Poison Control Centers each year.¹ Digitalis poisoning is also discussed. Finally, agents that produce cardiotoxicity primarily through sodium channel blockade and those with prominent sympathomimetic toxicity are also reviewed.

Not included in this chapter are a number of other cardiotoxic agents that are less commonly encountered or that demonstrate unique mechanisms of toxicity that are beyond the scope of this general discussion. The reader is referred elsewhere for review of these agents, which include clonidine and other antihypertensive agents, antidysrhythmics not noted earlier, cyclosporine, colchicine, chemotherapeutic agents (doxorubicin; anthracyclines such as daunorubicin, and idarubicin), and certain metals (notably selenium, cobalt, copper, and arsenic).

Calcium Channel Antagonists

Pharmacology

The calcium channel blocking drugs are a heterogeneous class of drugs that block the inward movement of calcium into cells from extracellular sites through “slow channels.”² There are

three major classes of these agents: phenylalkylamines (e.g., verapamil), benzothiazepines (e.g., diltiazem), and dihydropyridines (e.g., nifedipine, amlodipine, nicardipine, nimodipine, felodipine). They are used in the treatment of coronary vasospasm, supraventricular dysrhythmias, hypertension, migraine headache, Raynaud phenomenon, subarachnoid hemorrhage, and many other disease states.³ In general, calcium channel antagonists are rapidly and completely absorbed from the gastrointestinal tract and, with the exception of nifedipine, undergo extensive first-pass hepatic metabolism yielding low systemic bioavailability. The volume of distribution is large for all but nifedipine, and protein binding is high (>90% for all but diltiazem). Elimination is almost entirely by the liver; impaired renal function does not affect clearance with the exception of a somewhat pharmacologically active metabolite of verapamil that is renally excreted.⁴ Terminal half-lives are generally from 3 to 10 hours, but all three classes of calcium channel antagonists are available in sustained-release preparations, which can result in greatly prolonged half-lives.

Pathophysiology

In susceptible individuals or in overdose, these agents can exert profound effects on the cardiovascular system. They work by antagonizing L-type voltage gated ion channels in the cardiac pacemaker cells, and through depression of calcium ion flux in smooth muscle cells of blood vessels. Sinus node depression, impaired atrioventricular (AV) conduction, depressed myocardial contractility, and peripheral vasodilation may result.

Electrophysiologic effects are most prominent for verapamil and diltiazem and are seen much less often with nifedipine and other dihydropyridines, which work primarily on the peripheral vasculature. Sinus node function may be significantly altered by verapamil and diltiazem in patients with underlying sinus node disease; in excess, these agents may prolong AV nodal conduction sufficient to produce advanced heart block. Depression of myocardial contractility by impeding phase 2 calcium influx is most pronounced in overdose or in patients who already have depressed myocardial function from underlying disease or

concomitant drugs. Contraction of vascular smooth muscle, particularly arterial smooth muscle, is also mediated by calcium influx that is inhibited by calcium antagonists. In overdose, the effect of vasodilation on systemic blood pressure may be profound. However, in some cases, especially those involving the dihydropyridines, vasodilation may be ameliorated by a reflex increase in sympathetic activity, with increased heart rate and cardiac output.

Clinical Manifestations

The most serious consequences of calcium antagonist toxicity result from their effects on the cardiovascular system. Generally, these effects are an extension of the pharmacodynamic effects of the specific agent, although unique features of the different agents' specificity profiles may be lost in overdose.⁵ Clinical features are summarized in Table 35-1. Bradycardia and conduction defects are among the most frequent findings in overdose of verapamil or diltiazem. Additionally, hypotension is present in most significant exposures to any calcium antagonist. These features generally develop within 1 to 2 hours of exposure, but the onset of moderate to severe cardiovascular manifestations may be delayed for more than 12 hours when a sustained release preparation has been ingested.⁶

Patients at particular risk for toxicity from calcium antagonists include those with sinus node dysfunction, AV nodal conduction disease, severe myocardial dysfunction, obstructive valvular disease, hypertrophic cardiomyopathy, hepatic failure (leading to impaired elimination), and combined treatment of a calcium antagonist with β -blockers or digoxin.⁷ In addition, verapamil may dangerously accelerate conduction through accessory pathways when administered intravenously

to patients with accessory or anomalous AV connections such as in Wolff-Parkinson-White syndrome.⁸ It should not be given to patients with atrial fibrillation and evidence of pre-excitation on electrocardiography.

Profound hypotension is the major manifestation of overdose with nifedipine and may produce reflex tachycardia, flushing, and palpitations. Conduction defects are rare unless there is an underlying conduction disease, a very large ingestion, or the presence of coingestants such as β -blockers.^{5,7}

Lethargy, confusion, dizziness, and slurred speech are common in calcium channel antagonist poisoning. Coma usually occurs in the setting of cardiovascular collapse with profound hypotension; seizures are rare. Nausea and vomiting may occur. Metabolic acidosis is common in severely poisoned patients and likely represents hypoperfusion. Hyperglycemia is also common in overdose with calcium antagonists, and can serve as an important diagnostic clue to differentiate poisoning with these medications from others with similar clinical effects.

Management

Initial management of poisoning due to calcium antagonists is similar to that for other toxic drug exposures with initial support of the airway, adequate ventilation, and attention to circulatory status, followed by gastrointestinal decontamination when appropriate. If accidental or intentional oral overdose has occurred, the administration of activated charcoal orally or through a nasogastric tube is indicated when the patient's airway is not at risk of compromise by potential aspiration. In general, gastric lavage is no longer routinely advocated in the management of overdose patients, except perhaps in recent massive ingestions that present within the first hour. Repeated doses of activated charcoal and the use of whole bowel irrigation with an iso-osmotic, isotonic lavage solution, such as polyethylene glycol (Go-Lytely) should be considered early in cases involving a slow-release preparation. Recommended rates of whole bowel irrigation are 2 L/hr in adults and 500 mL/hr in children, via nasogastric tube. Continuous cardiac monitoring should be instituted in anticipation of cardiovascular collapse.

Specific therapy for sinus node depression or AV nodal conduction abnormalities is only necessary when hemodynamic status is compromised. Calcium salts may be administered, but routine doses are often ineffective at improving conduction. Atropine may be given, but is often ineffective at reversal of conduction defects, and pacing may need to be employed. Because of the effects of calcium antagonists on the myocardium and on the peripheral vasculature, hypotension may persist despite correction of electrical activity and conduction.

Hypotension should be addressed based on the pathophysiology discussed earlier. Intravenous fluids and vasoconstriction with agents such as norepinephrine, epinephrine, phenylephrine, or dopamine may be successful in hypotension primarily due to peripheral vasodilation. Hypotension due to depressed myocardial contractility may be responsive to intravenous administration of calcium salts (calcium chloride 10% solution, 10 to 20 mL, or calcium gluconate 10% solution, 30 mL, followed by continuous infusion). The optimal dose of calcium is unclear from the available literature, and the danger of hypercalcemia-induced impairment of myocardial contractility and vascular tone must be kept in mind.¹⁰ However, calcium levels have been elevated to as high as 15 to 20 mg/dL in previous case reports without any adverse effects, and with an improvement in blood pressure.¹¹

Table 35-1. Clinical Features of Calcium Antagonist and β -Blocker Overdose

Cardiovascular
Hypotension, shock
Dysrhythmias
Sinus bradycardia
Second- and third-degree atrioventricular block with nodal or ventricular escape
Sinus arrest with atrioventricular nodal escape
Asystole
Prolonged QRS, ventricular ectopy/tachycardia (propranolol)
Hypertension, tachycardia (pindolol)
Central Nervous System
Lethargy, confusion, coma
Respiratory arrest
Seizures (especially from propranolol)
Gastrointestinal
Nausea, vomiting
Metabolic
Hyperglycemia (verapamil, diltiazem)
Hypoglycemia (β -blockers)
Lactic acidosis

Glucagon has had some anecdotal success in cases of calcium antagonist overdose, and several animal models have shown its efficacy in this setting.¹² Its use is discussed further in the section on treatment of β -blocker toxicity. Calcium antagonists are generally both highly protein bound and extensively distributed in tissue. Therefore, enhanced elimination techniques such as hemodialysis and hemoperfusion are unlikely to be of benefit, and clinical reports have failed to support a role in either therapeutic or overdose settings.^{13,14}

Finally, a newer treatment using a hyperinsulinemia/euglycemia protocol has shown impressive results in case reports of calcium antagonist poisoning.¹⁵ Laboratory research in this area has also been promising.¹⁶ Numerous reports of the success of this treatment, along with published reviews of the management of calcium channel blocker toxicity, support its use early in the management of these poisonings. Insulin is thought to improve ionotropy and increase peripheral vascular resistance. Although the mechanisms are not completely known, it is thought to have a direct ionotropic effect on cells and to improve calcium pumps in myocardial cells.^{16,17,19} The most common insulin dosing regimen is 0.5 to 1 unit/kg/hr, along with 0.5 g/kg/hr of glucose using D₅, D₁₀, D₂₅, or D₅₀ (the latter two typically require central venous access due to their vascular irritant effects). In general, however, these patients are often already hyperglycemic and may not require the glucose component of the regimen while they remain toxic from the poisoning. Serum glucose concentrations should be checked hourly while the patient is on this therapy.

In severe refractory cases, cardiovascular bypass remains a viable option. Implementation has revealed successful results in previous reports, as patients are supported through the toxic effects of their poisoning.^{20,21} If patients can survive through the metabolism of the medication, they can often demonstrate a full recovery, both cardiovascularly and neurologically.

β -Adrenergic Antagonists

Pharmacology

Many β -adrenergic antagonists (β -blockers) are available, with profiles varying to greater or lesser degrees in the pharmacodynamic properties of receptor selectivity, intrinsic sympathomimetic activity, membrane stabilization, bioavailability, lipid solubility, protein binding, elimination route, and half-life. β -blockers are generally rapidly absorbed from the gastrointestinal tract, with peak plasma concentrations achieved after 1 to 2 hours and with elimination half-lives of 2 to 12 hours for nonsustained release preparations. Reduced first-pass hepatic extraction and impaired hepatic metabolism in liver disease or in massive overdose may contribute to toxicity by prolonging the half-life of the primary agent or an active metabolite.

Pathophysiology

Poisoning from β -blockers primarily affects the cardiovascular system, disrupting normal coupling of excitation-contraction and impairing ion transport in myocardial and vascular tissue. The mechanism of toxicity from β -blocker poisoning is difficult to fully explain, but appears to be related to impaired response to catecholamine stimulation of β -receptors, to disturbances of sodium and calcium ion homeostasis, and to membrane stabilization. Receptor subtype (β_1 versus β_2) selectivity may suggest the predominant effect of toxicity due to a given agent, but

in large overdoses this selectivity is often lost. Quinidine-like (membrane-stabilizing) effects, especially seen in propranolol poisoning, and to a lesser extent with acebutolol, oxprenolol, and betaxolol, may result in impaired conduction, prolonged QRS duration, and ventricular ectopy or tachycardia. The lipophilicity of propranolol also facilitates CNS penetration, frequently leading to seizures.

Clinical Manifestations

β -blocker toxicity is most commonly due either to administration to patients with underlying cardiac disease or to acute massive overdose. In the setting of acute overdose with a nonsustained release product, the onset of symptoms can be expected to occur within 6 hours of ingestion.²²

Generally, poisoning due to β -blockers shares many features of clinical presentation with poisoning due to calcium channel antagonists (see Table 35-1), but the hallmark of β -blocker poisoning is hypotension, due predominantly to impaired contractility. Sinus node depression and conduction abnormalities are also common. As noted earlier, membrane-stabilizing properties seen most prominently with propranolol may lead to impaired conduction, QRS prolongation, and ventricular dysrhythmias.^{23,24} Highly β -selective agents (atenolol, nadolol) may produce hypotension with a normal heart rate, but selectivity is frequently lost in large overdose. Overdose of agents with intrinsic sympathomimetic activity, most notably pindolol, may actually manifest with hypertension and tachycardia due to a stimulation. Sotalol is a unique agent that possesses some class III antiarrhythmic properties and therefore may produce Q-T interval prolongation, ventricular tachycardia, and torsades de pointes.²⁵

Lethargy and coma may be present in patients with β -blocker poisoning. Seizures are rare manifestations of β -blocker poisoning, except for propranolol. This appears to correspond with CNS effects of the drug rather than to hypoperfusion of the CNS.^{23,24} Bronchospasm and respiratory depression may occur from overdose with β -blockers, but are infrequent. Hypoglycemia may also occur in contradistinction to calcium channel antagonists that result in hyperglycemia.²⁶

Management

The initial approach to managing a patient with β -blocker overdose is similar to that for calcium channel antagonist overdose. However, β -blockers are receptor antagonists as opposed to calcium channel antagonists, which block ion channels and movement of calcium into the cell. This may explain why β -blocker poisoning is more responsive than calcium channel antagonist poisoning to therapeutic approaches that either competitively overcome the agent at the blocked receptor (high-dose norepinephrine, epinephrine) or bypass the receptor to achieve a common physiologic end point (glucagon).

Glucagon is the mainstay of antidotal therapy for symptomatic β -blocker toxicity. Glucagon is a polypeptide hormone that appears to bypass the β -adrenergic receptor on a cardiac myocyte and increases intracellular levels of cyclic AMP by stimulating a distinct glucagon receptor on the membrane. The resultant promotion of transmembrane calcium flux and intracellular calcium release leads to restoration of chronotropy and inotropy.²⁷ Although not universally effective, glucagon is of benefit in the majority of β -blocker overdoses. The initial dose of glucagon for a symptomatic β -blocker poisoning in the average adult is 3 to

5 mg bolused intravenously. The bolus may be repeated, and a continuous infusion of 2 to 5 mg/hr or higher may be necessary to maintain conduction and contractility. Mild nausea and vomiting, along with mild hyperglycemia, may occur with these doses, but otherwise the use of glucagon is without significant side effects.

As with calcium channel antagonist toxicity, calcium salts have been reported to be useful in β -blocker toxicity. In studies, calcium infusion can increase blood pressure in hypotensive β -blocker poisonings without any concomitant effect on heart rate.²⁸ Thus calcium therapy may augment glucagon treatment in these cases. Recommended starting doses are 1 to 3 grams of calcium chloride 10% solution (10 to 30 mL) given intravenously. If central line access is not available, calcium gluconate should be used, as calcium chloride can be irritating to peripheral veins.

Some β -blocking agents, such as propranolol and acebutolol, can also act as membrane-stabilizing drugs, and can cause QRS prolongation in overdose. When the QRS duration is widened to greater than 120 milliseconds, treatment with sodium bicarbonate boluses may be required (see later). Some animal models and case reports have shown proven benefit with sodium bicarbonate in such circumstances.²⁹

Phosphodiesterase inhibitors such as amrinone have not been shown to be of any additional benefit when compared with glucagon for management of β -blocker overdose, but their use might be considered if other therapy is failing.^{30,31} These agents may vasodilate and should be discontinued if blood pressure does not immediately respond.

There is no clear advantage to a specific β -adrenergic agonist in the treatment of β -blocker poisoning, although many toxicologists prefer epinephrine, norepinephrine, or their combination. Isoproterenol was commonly used in the treatment of these poisonings in the past, but may not be available at some hospitals. Dose should be titrated to effect with restored perfusion or return of an appropriate heart rate.

Successful use of an intra-aortic balloon pump support in patients in whom other measures were unsuccessful has been reported.³² This may allow sufficient time for elimination of the toxicant and should be considered when the patient remains profoundly hypotensive despite glucagon and high-dose vasopressors.

Enhanced elimination measures such as hemodialysis are unlikely to be of benefit for most of these medications. Exceptions include those patients with impaired renal function or in the setting of toxicity by a renally excreted agent, such as atenolol, acebutolol, nadolol, or sotalol.

Digoxin

Pharmacology

Cardiac glycosides such as digoxin have been used for centuries in the treatment of a variety of heart diseases. Poisonings, both accidental and intentional, from these agents were once among the most difficult to manage, and fatalities were common. With recent advances in the management of congestive heart failure using newer classes of drugs, and the development of digoxin-specific Fab antibody fragments, the incidence of severe digoxin toxicity has declined.

Digoxin is well absorbed after ingestion, and although intravascular concentrations may rise rapidly and dramatically after oral overdose, tissue distribution may be delayed. The

estimated volume of distribution in adults is 7 to 8 L/kg. The kidney excretes over 60% of digoxin unchanged, while digitoxin is metabolized by hepatic enzymes.

Pathophysiology

Cardiac glycosides inhibit the sodium-potassium ATPase pump on cell membranes. As a result, in acute toxic exposures, extracellular and serum potassium concentrations rise, along with intracellular sodium and calcium concentrations. Both conduction and contractility are impaired by the drug's effect on cardiac myocytes, but enzyme inhibition occurs throughout the body. There is an increase in automaticity and a decrease in depolarization and conduction velocity, which is mediated by an increase in vagal tone.

Clinical Manifestations

There are no dysrhythmias diagnostic of digoxin toxicity. Several rare dysrhythmias, such as ventricular bigeminy and bidirectional ventricular tachycardia, are highly suggestive of poisoning by this agent. The classic early cardiac presentation of chronic toxicity is the appearance of premature ventricular contractions in a patient with atrial fibrillation whose ventricular response rate had been previously well controlled. Most patients with chronic, unintentional toxicity will complain first of anorexia and fatigue and will often have nausea and vomiting. Neurologic symptoms can begin subtly as visual changes, described as blurred vision, decreased visual acuity, or yellow halos, and progress on to confusion, hallucinations, seizures, or coma.^{33,34}

Fatalities from digoxin poisoning result most often from cardiovascular collapse. Ventricular dysrhythmias, severe AV block, and depression of myocardial contractility are seen in massive overdose and may be refractory to most conventional therapies. Hyperkalemia can also be significant, especially in acute poisonings, and may contribute to dysrhythmias.

Management

Before digoxin-specific Fab fragments, the treatment of severe digoxin poisoning consisted of the administration of large doses of atropine and vasopressors, along with the early use of external or transvenous cardiac pacemakers. These therapies are often of little benefit in significantly toxic victims. The development of digoxin-specific Fab antibody fragments has revolutionized the management of these poisonings.

Digoxin-specific Fab fragments (Fab) are ovine IgG antibodies to digoxin that have had the Fc portion removed by papain digestion to reduce immunogenicity. When administered intravenously into a victim with digoxin toxicity, Fab fragments reverse conduction disturbances, restore contractility, and re-establish sodium-potassium ATPase activity by removing digoxin off receptor sites.³⁵ Hyperkalemia is also reversed after Fab administration. Signs and symptoms of toxicity should resolve in less than an hour but are often gone within 10 minutes. Patients with severe hypotension or cardiac arrest may not be able to circulate the antibody fragments and may therefore be refractory to treatment.³⁶

The dose of Fab fragment recommended to reverse digoxin toxicity is an equimolar dose to that of the ingested cardiac glycoside. A dose of 50 to 100 mg will neutralize 1 mg of digoxin. One vial contains 40 mg, and the manufacturer recommends a starting dose of 10 vials when the amount ingested or the level is unknown. Tables are available in the Fab package insert or

through regional poison control centers to relate the dose of Fab to the measured serum digoxin concentration. Allergic reactions to Fab are extremely rare, and skin testing is unnecessary.³⁵ Fab has also been shown to be effective in the treatment of severe cardiac glycoside cardiotoxicity from plants such as oleander containing similar compounds, but larger doses of the Fab may be required.³⁷

Sodium Channel Blocking Agents

Of all categories of cardiotoxic drugs, perhaps the most heterogeneous contains those that impair sodium conduction through membrane channels (Table 35-2). These substances are commonly described as having “quinidine-like” or “membrane stabilizing” effects on the myocardial cell. Substances exhibiting these properties include analgesics, antihistamines, psychotropics, antidepressants, antidysrhythmics, anticonvulsants, and local anesthetics. Many of these medications have unique clinical effects at therapeutic doses, but in overdose, each can produce similar cardiotoxicity. The most common group of sodium channel blocking drugs, and the one to which all others are compared, is the class I antiarrhythmic agents.

Pathophysiology

All sodium channel blocking substances affect conduction of impulses throughout the myocardium by influencing the movement of ions through the cell membrane. Sodium, potassium, and calcium ion exchange through channels in the myocardial cell membrane is responsible for the various phases of the action potential. All class I antiarrhythmics block fast sodium channels, decreasing the slope of phase 0 of the action potential. In overdose, this effect leads to a gradual widening of the QRS complex, eventually culminating in heart block or ventricular dysrhythmias. Depression of myocardial contractility contributes to the hypotension produced by these agents.

The subclassification of class I agents is partly based on the effect of these agents on potassium channels during cell repolarization. Blockade of potassium channels, most commonly displayed by class Ia drugs, leads to prolongation of repolarization and a subsequent increase in Q–T interval duration.³⁹ As the duration of repolarization and therefore the Q–T interval

lengthens, the opportunity for early afterdepolarizations during this relative refractory period increases. Episodes of polymorphic ventricular tachycardia (torsades de pointes) can occur in this situation, especially in the presence of low potassium or magnesium concentrations.⁴⁰ Class Ib agents shorten repolarization and reduce the duration of the action potential, while leaving potassium channels open and the Q–T intervals unaffected.³⁹ Class Ic drugs are the most potent sodium channel blockers³⁸ but have little effect on the repolarization phase of the action potential.

Pharmacology and Clinical Manifestations

Class Ia Antiarrhythmics

As noted earlier, all drugs in this class inhibit fast sodium channels in a dose-dependent manner. Generally, class Ia drugs are high potency sodium channel blockers.³⁸ Depression of slow inward calcium and outward potassium movement may account for reduced action potential plateau and prolonged repolarization. The result is prolongation of the relative refractory period, decreased pacemaker automaticity, and a generalized slowing of conduction through the heart.

Quinidine

Quinidine, the prototype of class Ia antiarrhythmics, was released in the United States in the early 1900s. Orally ingested quinidine has good bioavailability. The sulfate reaches peak plasma concentrations within 90 minutes, while the absorption of gluconate and polygalacturonate salts may be delayed 3 to 6 hours.⁴¹ Quinidine is highly protein-bound, with a large volume of distribution throughout the body (3.0 L/kg).⁴¹ Up to 40% of an ingested dose of quinidine may be eliminated by the kidneys, but the remainder is metabolized to inactive products in the liver. High “therapeutic” plasma concentrations of quinidine were found in some individuals that developed both QRS and Q–T interval prolongation, and a sudden loss of consciousness associated with its use was soon described.⁴¹ These symptoms, referred to as “quinidine syncope,” were found to be caused by ventricular tachydysrhythmias.³⁸ The incidence of these attacks is estimated to be 2% to 4%, and they are usually associated with polymorphic ventricular tachycardia.³⁸ This dysrhythmia is often related to a prolonged Q–T interval, but some studies have determined that quinidine-associated ventricular tachycardia often does not present as torsades de pointes and may not be associated with a prolonged Q–T interval.⁴² Studies have also demonstrated little relationship between quinidine concentrations and the incidence of this dysrhythmia.^{44,48} Hypokalemia, however, is frequently found in patients with quinidine-associated syncope.^{40,45}

As quinidine serum concentrations increase, Q–T interval prolongation is the earliest and most predictable electrocardiographic effect,⁴⁶ followed closely by QRS widening. In overdose, QRS widening is almost always present, with bundle branch blocks, sinoatrial and AV blocks, sinus arrest, and junctional or ventricular escape rhythms noted at high concentrations.^{39,40}

Hypotension from quinidine, like many other of the drugs discussed in this section, is multifactorial. Unlike quinidine syncope, quinidine-induced generalized myocardial depression is dose-dependent.^{40,47} At low doses, especially when administered intravenously, quinidine exerts little negative inotropic effect but is an antagonist of peripheral α -receptors, leading to vasodilation.⁴⁰ This effect can result in orthostatic syncope in some

Table 35-2. Common Sodium Channel Blocking Drugs

Class Ia antiarrhythmics
Class Ib antiarrhythmics
Class Ic antiarrhythmics
Chloroquine
Quinine
Propoxyphene
Cyclic antidepressants
Phenothiazines
Antihistamines (sedating and nonsedating H ₁ antagonists)
Cocaine
Propranolol
Carbamazepine

patients. At toxic concentrations, quinidine causes circulatory collapse due to a profound negative inotropic effect.⁴⁷ In addition to shock, severely poisoned patients can have recurrent dysrhythmias, central nervous system depression, and renal failure.

The optical isomer of quinidine is quinine, and this compound has the capability to produce the same signs and symptoms in overdose.^{48,49} Toxic doses of either of these agents can also lead to cinchonism, a condition named after the tree from which these compounds are derived.⁴⁹ This syndrome results in tinnitus, blurred vision, photophobia, confusion, delirium, and abdominal pain.⁴⁹ Quinine amblyopia may result from large ingestions of these compounds, and the visual loss may be complete and sudden. Although vision returns in some patients as toxicity resolves, the loss may be permanent.⁵⁰ Coma and seizures can occur with toxic concentrations of these drugs, even in hemodynamically stable individuals.⁴⁰ Cinchonism is not reported with poisonings of the other class Ia agents.

Quinidine also has antimuscarinic effects and it may exacerbate the ventricular response to atrial flutter via enhanced conduction of the atrioventricular (AV) node. Furthermore, its potassium channel blockade may cause increased insulin release in the pancreatic islet cells, leading to hypoglycemia.⁵¹

Procainamide

A therapeutic oral dose of procainamide reaches peak plasma concentration within an hour, but massive ingestions can greatly delay absorption and prolong toxicity.⁴⁹ Like quinidine, up to 40% of a given dose of procainamide may be eliminated unchanged in the urine. Unlike quinidine, procainamide is metabolized to a compound with cardiac activity similar to that of the parent drug, *N*-acetylprocainamide (NAPA), which may complicate the correlation of plasma levels of the parent compound with clinical effects.⁴⁹ The therapeutic volume of distribution of procainamide is 2.0 L/kg, with a plasma half-life of 3 to 4 hours. The plasma half-life in overdose may increase significantly.⁴⁹

Cardiotoxicity from procainamide is mechanistically similar to that described from quinidine. Myocardial depression, polymorphic ventricular tachycardia, and other cardiac dysrhythmias are all expected at high serum concentrations of procainamide.⁴⁹ However, procainamide exerts a less negative inotropic effect, and a lower incidence of ventricular dysrhythmia than quinidine.^{52,53} Hypotension is mostly seen with intravenous use and usually only during infusions faster than 20 mg/min.⁴⁰ Procainamide overdose can result in severe hypotension and dysrhythmias identical to those described with quinidine. Inability to electrically pace the heart of a procainamide-intoxicated patient due to high pacing thresholds has been described.⁵⁴ Serious toxicity from procainamide includes lethargy, confusion, and depressed mentation along with the cardiotoxicity.³⁹⁻⁴¹ Other adverse events in acute overdoses include seizures and antimuscarinic effects.⁵⁵ Hematologic abnormalities such as agranulocytosis, thrombocytopenia, and hemolytic anemia have been reported in long-term use of procainamide.⁵⁶ Procainamide may also produce a lupus-like syndrome.

Disopyramide

Peak serum concentrations of disopyramide may be delayed up to several hours in toxic ingestions owing to its antimuscarinic effects on intestinal motility.⁴⁰ The protein binding (50% to 60%) and volume of distribution (<1 L/kg) of disopyramide

are less than those of quinidine or procainamide and suggest the possibility that hemodialysis could be effective in removing toxic concentrations.^{40,57} A therapeutic dose of disopyramide has a mean plasma half-life of 6 to 8 hours and is 40% to 60% eliminated by the kidneys.⁴⁹ The main hepatic metabolite, mono-*N*-dealkylated disopyramide, has little cardiac activity, but produces more antimuscarinic effects than the parent compound.

Disopyramide is the newest of the Class Ia antiarrhythmic agents and demonstrates electrophysiologic effects similar to quinidine and procainamide. Although Q-T interval prolongation does not usually occur with therapeutic concentrations of disopyramide, syncopal episodes have been reported.⁵⁸ Of all class Ia agents, the negative inotropic effects of disopyramide are most pronounced, and hypotension can be seen in disopyramide poisoning without concomitant electrocardiographic changes.^{40,59,60} This may in part be related to its ability to block myocardial calcium channels.⁶¹ Although mild antimuscarinic effects can be noted in poisonings of all class Ia agents, those following disopyramide toxicity are the most clinically significant⁴⁰ and can result in sinus tachycardia, blurred vision, altered mental status, seizures, urinary retention, and ileus, at times without accompanying serious cardiotoxicity.⁴⁰ Overdose experience with disopyramide is limited in the United States.

Class Ib Antiarrhythmics

Drugs in this class suppress automaticity similarly to the class Ia agents but shorten the action potential refractory phase and increase conduction through hypoxic myocardial tissue.⁶² Class Ib drugs have rapid "on-off" binding kinetics for myocardial sodium channels and possess the highest affinity for sodium channels that are in the inactivated state.⁴⁹ At therapeutic concentrations, these compounds moderately depress phase 0 of the myocyte action potential. The resultant effects on the electrocardiogram include a normal or shortened Q-T interval and an unchanged QRS duration.⁶³

Lidocaine

A large first-pass effect is seen with oral dosing of lidocaine, and only 30% to 35% of an ingested dose is bioavailable.⁶⁴ However, large ingestions have resulted in significant absorption, resulting in toxicity.⁶⁵ Lidocaine is well absorbed topically through abraded epithelium and from the trachea and bronchi after endotracheal administration.⁶⁶ The apparent volume of distribution of lidocaine is 1.3 L/kg, but it is significantly reduced in the presence of congestive heart failure.⁶⁷ The liver metabolizes virtually all of a lidocaine dose, with an elimination half-life in therapeutic concentrations of about 2 hours.⁴⁹ The most significantly active metabolite is monoethylglycinexylidide (MEGX), with a half-life also of 2 hours.⁶⁸

Lidocaine is the prototype of class Ib antiarrhythmics, and in poisoning it causes cardiovascular and CNS toxicity. Lidocaine is primarily metabolized in the liver to MEGX. Both compounds are neurotoxic at high concentrations and can cause seizures and apnea.⁶³ Some individuals experience mild neurologic symptoms at therapeutic plasma concentrations.⁶³ Since lidocaine rapidly passes through the blood-brain barrier, patients with toxicity usually manifest CNS dysfunction as initial symptoms.⁶⁹ Early signs of CNS toxicity from lidocaine include lightheadedness, agitation, confusion, hallucinations, and dysarthria. Some individuals initially complain of tongue or

perior numbness. Progression to convulsions or coma can be rapid. Cardiovascular toxicity occurs primarily in massive overdose. Following central nervous system dysfunctions, intrinsic cardiac pacemakers are depressed, conduction is delayed, and myocardial contractility is impaired.^{70,71} Large intravenous lidocaine doses greater than 1 g have resulted in asystole, complete heart block, and refractory hypotension.^{63,70,72}

Phenytoin

Phenytoin absorption from the gastrointestinal tract can be erratic, and peak levels after an oral overdose can be delayed up to 24 hours or more.⁷³ Phenytoin is 90% protein bound, and the volume of distribution of the free drug is 0.5 L/kg.^{49,73} Signs of toxicity correlate better with free phenytoin levels, but most laboratories still assay for both bound and unbound fractions. Phenytoin is metabolized to nontoxic metabolites by the liver. At high concentrations, these enzymes become saturated, and the half-life may increase to several days as elimination kinetics change from first order to zero order.⁷⁴ Patients with low serum albumin concentrations may be particularly prone to chronic phenytoin toxicity, owing to the higher relative fraction of free drug.⁴⁹

Like lidocaine, phenytoin is classified as a class Ib agent. Poisoning with phenytoin occurs most often during long-term therapy for epilepsy when a medication inhibiting phenytoin metabolism is added, or when the patient develops a disease state impairing hepatic mixed function oxidase activity. Acute overdoses occur less frequently, but the resulting clinical presentation is similar.

Phenytoin poisoning primarily causes neurotoxicity, manifested as drowsiness, ataxia, dysarthria, and nystagmus. In massive poisonings, coma and seizures can be seen, but respiratory depression is infrequent. Cardiac dysrhythmias and hypotension are rarely reported with toxic phenytoin ingestions but are often encountered during rapid intravenous infusions.⁷⁵ Although phenytoin does have sodium channel blocking effects on myocardial tissue, the diluent of the intravenous solution, propylene glycol, has been implicated as the source of myocardial depression and dysrhythmias associated with intravenous infusion.⁷⁶ Slowing the rate of infusion prevents the majority of these complications.

Tocainide, Mexilitine

Overdose experience with other class Ib drugs has been limited. Tocainide toxicity has resulted in gastrointestinal symptoms, seizures, and cardiac dysrhythmias similar to other class I agents.⁷⁷ Therapeutic use of tocainide resulting in blood dyscrasias⁷⁸ and pulmonary fibrosis⁷⁹ has also been reported. Mexilitine poisoning has caused seizures, ventricular dysrhythmias, and impaired myocardial conduction.⁸⁰ Other adverse effects of mexilitine are primarily neurologic and comparable to symptoms that occurred with lidocaine.

Class Ic Antiarrhythmics

Class Ic drugs (encainide, flecainide, propafenone) bind to sodium channels in the activated state and have the most potent sodium channel blocking effects of all class I antiarrhythmics.⁴⁹ Therapeutic concentrations of class Ic agents produce little effect on myocyte repolarization compared to other class I antiarrhythmics.⁸¹ At higher concentrations, these agents exert a significant negative inotropic effect.⁸² Overdose experience with these

drugs is limited, but they would be expected to produce similar cardiovascular effects as other class I compounds, with no antimuscarinic features. Seizures, hypotension, and dysrhythmias have been reported after a 3- to 4-g overdose of encainide.⁸²

Class III Antiarrhythmics

Class III agents (amiodarone, ibutilide, dofetilide) block the rapidly activating component of the delayed rectifier potassium channels.⁴⁹ These potassium channels are responsible for phase 3 repolarization in cardiac action potentials. Therefore Class III drugs delay repolarization and cause an increase in duration of the action potential and an increase in the effective refractory period. On the electrocardiogram, this results in prolonged Q-T intervals. By increasing the refractory period, these drugs are very useful in terminating re-entrant dysrhythmias.

Amiodarone

Amiodarone is an antidysrhythmic with a multitude of pharmacologic effects. It undergoes hepatic metabolism through cytochrome oxidase systems to produce another pharmacologically active but less potent metabolite, desethylamiodarone.⁸³ The main mechanism of action of amiodarone is prolongation of cardiac myocyte repolarization through blockade of the rapidly activating delayed rectifier potassium channel. Collectively this represents a class III antidysrhythmic effect. However, amiodarone is also a weak α - and β -adrenergic receptor antagonist and may block inactivated sodium channels and L-type calcium channels.⁸⁴ Expected electrocardiographic outcomes are prolonged Q-T intervals, ventricular dysrhythmias, and conduction blocks. Amiodarone is used to terminate re-entrant atrial or ventricular dysrhythmias and it has recently been added to the Advanced Cardiac Life Support (ACLS) tachydysrhythmia guidelines.⁸⁵ Despite its more frequent use today, there are few reported cases of oral amiodarone overdose resulting in significant cardiac toxicity. The low toxicity is likely due to its low and unpredictable oral bioavailability (22% to 86%) and large volume of distribution (>6.0 L/kg).⁸⁶ Intravenous overdose of amiodarone has not been reported although hypotension, bronchospasms, and hepatitis from therapeutic doses have been described. Most of the toxic effects reported from amiodarone in the literature are from long-term treatment and appear to be dose-related. Chronic use of amiodarone has been associated with pneumonitis, hypothyroidism, thyrotoxicosis, hepatitis, skin discoloration, and corneal damage.⁸⁷ Although not well studied, cholestyramine has been suggested as treatment for both acute and chronic amiodarone toxicity by its gastrointestinal binding of unabsorbed amiodarone and blockade of enterohepatic circulation of the drug.⁸⁸

Ibutilide, Dofetilide

Both ibutilide and dofetilide are newer class III antiarrhythmics used for chemical cardioversion of atrial fibrillation or flutter. Because of their effect on the rapidly activating delayed rectifier potassium channels, both drugs can delay action potentials and prolong Q-T intervals.⁴⁹ Experiences with overdoses of either drug are limited but expected toxicity would be induction of ventricular dysrhythmias. Toxic effect of either drug occurs within 60 minutes of administration and therapeutic use has resulted in torsades de pointes.^{84,89} Therefore a reasonable observational period of 4 to 6 hours is recommended in all patients who received ibutilide or dofetilide.

Cyclic Antidepressants

Toxicity from cyclic antidepressants is perhaps the most well-described of all fast sodium channel blocking compounds. These substances are responsible for more fatalities each year than any of the other drugs in this group.⁹⁰ After being originally studied for their antihistaminic properties in the 1940s, cyclic antidepressants were introduced into the pharmaceutical market in the United States in the 1960s, rapidly replacing electroshock therapy as a more “humane” treatment for severe depression.

Pharmacology

The “first generation” of cyclic antidepressant compounds, known as the tertiary amines, includes amitriptyline, imipramine, doxepine, and trimipramine. All are potent inhibitors of myocyte sodium channels. Each undergoes metabolism in the liver. Amitriptyline and imipramine are hepatically converted to the active secondary amines nortriptyline and desipramine, respectively, and these latter compounds were soon marketed as second-generation therapies for depression.⁴⁹ The membrane-stabilizing effects of these second-generation agents were soon appreciated as being similar to that of their parent compounds.⁴⁹

Newer marketed antidepressants, categorized as serotonin or norepinephrine reuptake inhibitors (i.e., trazodone, fluoxetine, sertraline, bupropion, paroxetine, and others) have so far demonstrated far less sodium and potassium channel impedance. Although each of these drugs may cause adverse reactions in overdose, their cardiotoxicity appears to be minimal in comparison to the first- and second-generation cyclic drugs.

In therapeutic doses, cyclic antidepressant drugs are rapidly absorbed. Although one might expect delayed gastric emptying as a result of an antimuscarinic effect in large ingestions, clinical signs of cyclic antidepressant toxicity usually appear within 6 hours.⁹¹ Asymptomatic patients without concomitant ingestions should not develop toxicity after 6 hours. Antimuscarinic effects on the central and peripheral nervous systems usually precede cardiotoxicity, but large ingestions of agents with less muscarinic receptor activity, such as imipramine, may present initially with hypotension and dysrhythmias. Cardiotoxicity, mental status depression, and seizures resulting from these agents can proceed rapidly, necessitating continuous monitoring.

Cyclic antidepressants are significantly protein bound in circulation and widely distributed in the body (40 L/kg).⁴⁹ Hepatic metabolism is the major route of elimination for these compounds, with some, such as amitriptyline and imipramine, producing active metabolites. Elimination half-life can be prolonged in overdose due to enzyme saturation.

Pathophysiology

The pathophysiology of cyclic antidepressant cardiotoxicity results from four main properties: (1) fast sodium channel or membrane-stabilizing effects, (2) muscarinic receptor blockade, (3) α -receptor blockade, and (4) norepinephrine reuptake blockade. Animal data also suggest blockade of delayed rectifier potassium channel and the γ -aminobutyric acid (GABA) receptor complex in the brain.^{92,93}

Cyclic antidepressants block fast sodium channels in a manner similar to quinidine and other class Ia antiarrhythmics, markedly decreasing the slope of phase 0 of the action potential.⁴⁹ Prolongation of both the QRS and Q–T interval durations have been demonstrated clinically in overdose, but in vitro

experiments show that cyclic antidepressants block primarily fast depolarizing sodium currents and actually shorten repolarization.^{94,95} The Q–T prolongation resulting from cyclic antidepressant toxicity is mainly attributed to the result of progressive QRS widening with globally impaired myocardial conduction.⁹⁵ However, the potential blockade of the delayed rectifier potassium channels may also contribute to the Q–T prolongation.⁹³ The cardiotoxic effects include ventricular dysrhythmias and depressed myocardial contractility.⁹⁵

Cyclic antidepressants block several receptor sites in both the central and peripheral nervous system, including H₁ and H₂ receptors, dopamine receptors, and muscarinic receptors.⁹⁶ This effect on the autonomic nervous system produces a clinical syndrome of dry mouth, blurred vision, sinus tachycardia, altered mental status (ranging from confusion and hallucination to seizures and coma), ileus, urinary retention, and anhidrosis. These signs and symptoms frequently precede the sodium channel blocking effects and are more common with doxepin and amitriptyline than imipramine.^{49,96}

Cyclic antidepressants are potent α -receptor antagonists. This effect is responsible for the orthostatic hypotension often experienced by patients at the initiation of therapy with these compounds.⁴⁹ The resulting vasodilation can be severe in overdose and combined with the impaired cardiac output from myocardial depression can lead to refractory hypotension and cardiovascular collapse.⁹⁷ α -Receptor blockade of the pupil in patients with cyclic antidepressant toxicity can prevent the anticipated antimuscarinic mydriasis, resulting in an unanticipated miotic pupillary effect.

The hypothesized mechanism of antidepressant action of cyclic antidepressants lies in their ability to block the catecholamine reuptake pump on the presynaptic terminal of neurons.⁹⁶ In overdose, this effect can deplete presynaptic catecholamine concentrations, thought to contribute to dysrhythmias and hypotension.⁴⁹

Hypotension can be present in cyclic antidepressant poisoning without significant dysrhythmias. Sinus tachycardia is usually present before the development of ventricular dysrhythmias or heart block.⁹⁸ Several studies have evaluated the electrocardiographic abnormalities predictive of toxicity from these agents. One review found that 33% of patients with QRS intervals greater than 100 ms developed seizures and 14% developed ventricular dysrhythmias.⁹⁹ There was also a 50% incidence of ventricular dysrhythmias in patients with QRS duration exceeding 160 ms.⁹⁹ Unfortunately, up to 25% of normal individuals may have a QRS duration greater than 0.10 second.⁴⁹ Another study suggested that a rightward terminal vector, best seen in the R wave of lead aVR, may correlate with the degree of cyclic antidepressant toxicity.^{100,101} In this study, an R wave of lead aVR greater than 3 mm notably predicted toxicity. Although having electrocardiographic abnormalities can be useful in assessing potential toxicity, none of the findings is 100% sensitive. Absence of these concerning findings is more indicative that cardiac toxicity is not developing.

Antipsychotics (Phenothiazines, Butyrophenones, and Atypical Agents)

Phenothiazine derivative compounds such as Thorazine, thioridazine, and prochlorperazine may have clinical effects similar to the cyclic antidepressants. Antimuscarinic toxicity is frequently

more pronounced in poisonings from these drugs, rather than their membrane-stabilizing cardiac effects. However, heart block and wide complex tachycardias and refractory hypotension are occasionally reported in overdoses of these agents.^{102,103} Fatalities are rare, even in massive ingestions of these drugs. The most common clinical presentation of phenothiazine overdose is neurotoxicity, manifesting as delirium, agitation, coma, seizures, and other antimuscarinic effects.

Haloperidol and droperidol are butyrophenone antipsychotic and antiemetic compounds available in the United States. Although these drugs share the potent dopamine receptor blocking properties of the phenothiazines, overdoses of these agents lack the prolonged sedation and antimuscarinic effects most often seen with phenothiazines. Torsades de pointes has been reported with the butyrophenones but usually follows large parenteral dosing.¹⁰⁴

Newer, atypical antipsychotics, such as quetiapine, olanzapine, risperidone, and ziprasidone, seem to have fewer effects on cardiac conduction. Most atypical antipsychotics have inhibitory functions at serotonin receptors, in addition to antimuscarinic and dopamine receptor blocking properties. Retrospective data and case reports have demonstrated the ability of some of these drugs to block fast sodium channels and potassium channels, resulting in QRS and Q-Tc prolongation, respectively. In general, these effects are much less common than with the older “typical” antipsychotic agents.

Antihistamines

Many H₁ receptor antagonists have been found to exert similar effects on the myocardial action potential as the class Ia antidysrhythmic compounds. The most commonly used medication in this class, diphenhydramine, has been shown to effectively block fast sodium channels at high concentrations.¹⁰⁵

In mild to moderate poisonings with these agents, patients most often exhibit a classic antimuscarinic syndrome, with sinus tachycardia, dry mouth, and confusion, often marked by hallucinations and psychotic behavior. The toxic syndrome may also include seizures, urinary retention, decreased gastric motility, and coma. Respiratory depression can occur in some severe cases, necessitating ventilator support.

In massive poisonings, antihistamines can impair fast sodium channel conduction, resulting in dysrhythmias and hypotension similar to that seen with other sodium channel blocking agents.^{105, 106} Dysrhythmias and cardiovascular collapse from these drugs are exacerbated by acidosis and, therefore, often occur after seizures, which frequently cause a sudden decline in the serum pH.^{105, 106}

Propoxyphene

Propoxyphene is an opioid analgesic found in combination with acetaminophen in Darvocet, and with salicylates in Darvon. Hepatic metabolism of propoxyphene produces an active metabolite known as norpropoxyphene. Both agents block fast sodium channels, causing QRS prolongation in toxic serum concentrations.¹⁰⁷ Overdoses of propoxyphene can result in hypotension and widening of the QRS complex, which can lead to ventricular dysrhythmias.¹⁰⁸ It is this membrane-stabilizing effect that is also thought to be responsible for the greater incidence of seizures from propoxyphene poisonings than from

other opioids. As with other sodium channel blocking agents, widening of the QRS complex with propoxyphene poisoning has been shown to respond to therapy with sodium bicarbonate (see later discussion).¹⁰⁹ Propoxyphene-induced seizures can be refractory to conventional anticonvulsants, such as phenytoin, necessitating use of benzodiazepines and phenobarbital for control.

Carbamazepine

Carbamazepine is an anticonvulsant with structural similarity to the cyclic antidepressants. In vitro, carbamazepine cardiotoxicity resembles that of the class Ia antiarrhythmics. However, carbamazepine rarely causes significant quinidine-like effects in poisoning, even with massive ingestions.^{110,111} Carbamazepine toxicity often results in mental status changes and occasionally respiratory depression.^{110,111} In addition, toxic carbamazepine concentrations may produce blockade of muscarinic receptors, resulting in the classic antimuscarinic syndrome with effects such as sinus tachycardia, dry mouth, and mydriasis.

Chloroquine

Chloroquine is a common antimalarial agent that often results in severe toxicity when taken in overdose. Chloroquine is structurally related to quinine and quinidine, and cardiotoxicity resulting from any of these agents can be indistinguishable.¹¹¹ The toxic to therapeutic ratio of chloroquine is low, and ingestions of as little as 300 mg by children have been fatal.¹¹² Seizures commonly and rapidly accompany the cardiotoxicity of this drug and appear to be unrelated to hypoxia.¹¹¹ A combination of intensive supportive care, intravenous boluses of benzodiazepines for convulsions, and vasopressor use for cardiovascular support has been shown to decrease mortality in animal models and human case reports of chloroquine poisoning.¹¹³

Management of Sodium Channel Blocking Drug Toxicity

As in the treatment of other cardiotoxic drug overdoses discussed in this chapter, the initial management of poisonings involving sodium channel blocking medications should begin with airway and circulatory support (Table 35-3). Any patient who is not breathing or in whom a patent airway is of question should receive endotracheal intubation and mechanical ventilation. Combative patients may require sedation and paralysis before an endotracheal tube can be placed.

Resuscitating the patient poisoned with sodium channel blocking drugs can be challenging. The hypotension resulting from massive ingestions of these agents is multifactorial and often refractory to intravenous fluid boluses. Vasopressors may be necessary in some situations, and vasopressor choice may be important. Although dopamine is employed with success in many cases of poisoning-related hypotension, it may be ineffective or even exacerbate the hypotension associated with cyclic antidepressants, phenothiazines, and other α -receptor blocking agents.¹¹⁴ Dopamine is the precursor of norepinephrine and requires uptake into the presynaptic terminals for activation; thus it may be ineffective with these agents, which block the catecholamine reuptake pump. At higher doses, the vasoconstrictive

Table 35–3. Outline of General Management of Sodium Channel Blocking Agent Toxicity

1. Stabilize airway.
2. Control breathing and hyperventilate patient if head injury is possible, or if cardiotoxicity is present and intravenous access is not established.
3. Resuscitate blood pressure and treat dysrhythmias.
 - a. Start intravenous normal saline or Ringer's lactate.
 - b. Normalize serum pH.
 - (1) Intravenous sodium bicarbonate
 - (2) Hyperventilation
 - c. Vasopressors
 - (1) Norepinephrine
 - (2) Phenylephrine
 - (3) Dopamine
 - d. Administer lidocaine for refractory ventricular dysrhythmias in cyclic antidepressant or class Ia antiarrhythmic poisoning.
4. Decontamination
 - a. Consider gastric lavage if less than 1 hour after massive poisoning.
 - b. Administer 1 g/kg oral activated charcoal

effects of dopamine are antagonized by the α -blocking effects of some of these drugs, leading to unopposed β -receptor stimulation of blood vessels and worsening of hypotension. For these reasons, vasopressors with more direct α -receptor stimulation, such as norepinephrine or phenylephrine, may be required for consistent blood pressure support.

The most helpful adjunct in the management of sodium channel blockade from drug poisoning has proved to be sodium bicarbonate. Sodium bicarbonate has been shown to be effective in raising the blood pressure and treating dysrhythmias associated with cyclic antidepressants, cocaine, flecainide, quinidine, chloroquine, and diphenhydramine.¹¹⁵⁻¹²¹ Sodium bicarbonate has been shown in both animal models and human cases of toxicity from these agents to increase blood pressure and improve conduction through the heart. Studies suggest that this is the result of the concomitant effects of both the bicarbonate and sodium components because they offer a synergistic benefit together when compared to each alone. Thus the beneficial effects are likely secondary to both an increase in the blood pH and an increase in the extracellular sodium concentration.

Although controlled studies do not exist to support the use of sodium bicarbonate for every drug in this category, its empirical administration to patients with evidence of toxicity from impaired sodium conduction seems prudent. The degree of alkalinization that one must achieve to be of benefit has not been well defined. Maintaining serum pH in normal ranges has been sufficient in our practice, but many authors recommend bolus injections of sodium bicarbonate to keep serum pH between 7.45 and 7.50. One common practice is the addition of 50 to 100 mmol sodium bicarbonate (1 to 2 ampules) to 1000 mL of 5% dextrose and water, titrating the infusion to an alkaline pH. This exercise may require frequent analyses of serum pH and sodium, and may lead to hyponatremia if not monitored closely. Intermittent boluses of sodium bicarbonate, at 1-2 meq/kg are equally effective. The bolus method is preferred by many toxicologists for the ability to more precisely titrate sodium bicarbonate doses to the effect of a narrowed QRS.

In some severe cases of sodium channel blocking drug toxicity, ventricular dysrhythmias may be refractory to the aforementioned management. Oxygenation should be maintained and resuscitative efforts continued as long as cardiac activity is present. Patients have survived neurologically intact after over an hour of advanced cardiac life support following massive cyclic antidepressant poisoning.¹²² Prolonged resuscitation may allow enough drug redistribution from cardiac receptors to restore conduction. The use of lidocaine has been effective in improving cardiac performance after overdose of membrane-stabilizing drugs,¹¹⁶ and can be administered in cases refractory to sodium bicarbonate.

Several therapeutic considerations should be addressed with regard to the antimuscarinic toxicity resulting from agents such as cyclic antidepressants, antihistamines, and phenothiazines. The antimuscarinic signs and symptoms that usually predominate are seldom life-threatening. Seizures from these agents, in the absence of severe hypotension or hypoxia, are most likely related to blockade of muscarinic receptors in the brain. They are usually self-limited and easily controlled with benzodiazepines or barbiturates. Sinus tachycardia produced by reduced vagal tone does not require specific treatment. Physostigmine, a short-acting carbamate cholinesterase inhibitor, can reverse the CNS toxicity and the sinus tachycardia associated with these agents, but may exacerbate impaired conduction throughout the heart, occasionally resulting in asystole.¹²³ For this reason, physostigmine is best reserved for cases with altered mental status in whom no cardiac conduction delays are present.

All patients with severe antimuscarinic signs and symptoms will need a urinary catheter if urinary retention occurs. Multiple doses of activated charcoal, and food and beverages, should be avoided in those individuals with evidence of impaired gastric motility. Soft restraints may be necessary and are usually adequate in individuals with agitation due to the CNS effects of these drugs. They are also usually preferred over pharmacologic restraints so as not to further impair the neurologic examination.

Gut decontamination may prevent absorption after ingestions of any of the agents discussed earlier. If benefit is to be derived from gastric decontamination, it should be undertaken soon after ingestion. The longer the delay, the more the drug escapes into the small intestine where most absorption occurs. Gastric decontamination more than 1 hour after ingestion may be of little benefit unless drugs that delay gastric emptying are involved in the poisoning. Large studies have found no effect on outcome when gastric decontamination is avoided altogether.¹²⁴ Syrup of ipecac is no longer recommended as a method of decontamination. Furthermore, gastric lavage is no longer routinely advocated, with the exception of life-threatening poisonings that present within 1 hour of ingestion.

Activated charcoal has been found to bind most cardiotoxic drugs and may be of benefit in limiting absorption. The timing of activated charcoal administration is also important, but charcoal administration may still be effective in binding a drug that has entered the duodenum. It is therefore rational to administer a dose of activated charcoal to most patients with a history or clinical evidence of ingesting a cardiotoxic substance. The recommended dose of activated charcoal is 1 g/kg, and patients may either drink the aqueous charcoal suspension (which has no taste) or have the dose administered through a nasogastric tube when intubated or uncooperative. Caution should be used

when using activated charcoal in obtunded patients or in those who are unable to protect their airway because this poses a risk of aspiration. Multiple doses of activated charcoal have been found to be of benefit in poisonings with agents such as theophylline and phenobarbital, but this therapy is not likely to benefit humans poisoned with any of the cardiotoxic agents listed in this chapter. In addition, those drugs that slow gastrointestinal motility may predispose the patient to charcoal bezoar formation when multiple doses are administered.¹²⁵

Extracorporeal removal of drugs using techniques such as hemodialysis or hemoperfusion has proved beneficial in overdoses of compounds such as theophylline, salicylates, and phenobarbital. Most other drugs, including those listed in this chapter, have not been found to be well removed by these modalities.

Illicit Drugs

Psychostimulant toxicity is a common cause of emergency department visits. Deaths have been described as a result of the multiorgan effects of these drugs. Although only cocaine and amphetamine derivatives are discussed here in detail, other agents such as ephedrine, pseudoephedrine, and phenylpropanolamine may cause similar clinical effects in toxic concentrations.

Cocaine

Cocaine is an alkaloid derived from the leaves of *Erythroxylon coca* and other trees indigenous to Peru and Bolivia. The alkaloid is dissolved in hydrochloric acid to form a water-soluble salt termed *cocaine hydrochloride* (chemical name, benzoyl-methylecgonine). Cocaine hydrochloride is sold as crystals, granules, or white powder. "Crack" (cocaine freebase) is the basic, nonsalt form that is created by the organic esterification of cocaine hydrochloride from a basic solution with ether. When crack is heated, it melts and forms a fat-soluble vapor that can be smoked and rapidly absorbed through the lungs. The name *crack* is derived from the popping sound made by the drug when it is heated. Therapeutically, cocaine is classified as an ester type of local anesthetic and currently limited to use as a mucosal anesthetic.

Pharmacology

Cocaine is well absorbed from the mucous membranes of the nose, lung, genitourinary, and gastrointestinal tract. Administration can occur through the intravenous, respiratory, intramuscular, and rectal routes. The method and dose of administration determine the onset of action. The "high" from intravenous administration of cocaine peaks within a few minutes after injection. Inhalation of the drug will produce effects within 1 to 3 minutes, but oral ingestion may delay symptoms up to 60 to 90 minutes. Plasma concentrations after intranasal use peak within 20 to 30 minutes and gradually decline over the next 60 minutes.¹²⁶

Cocaine is metabolized by nonenzymatic hydrolysis and liver esterases, including plasma cholinesterase. The two major metabolites include benzoylecgonine and ecgonine methyl ester, neither of which crosses the blood-brain barrier. Both of these compounds are water-soluble and are excreted in urine. Cocaine metabolites may be detected in urine up to 72 hours after an exposure, although heavy users may have positive urine screens

for up to 3 weeks.¹²⁷ When a user of cocaine also coingests ethanol, hepatic transesterification will create another pharmacologically active metabolite, cocaethylene. Cocaethylene is not on routine urine screens for cocaine metabolites.

Pathophysiology

The pharmacologic effects of cocaine in humans include the ability to stabilize membranes and block nerve conduction. The resulting effects on myocardial tissue cause blockade of fast sodium channels, leading to widening of the QRS complex with subsequent dysrhythmias. The sympathomimetic effects of cocaine are caused by impaired catecholamine reuptake and enhanced catecholamine release at nerve terminals.¹²⁶ The increased synaptic concentrations of neurotransmitters stimulate α - and β -receptors throughout the autonomic nervous system resulting in a cascade of clinical effects. Cocaine may also enhance the release of norepinephrine and dopamine in the CNS.¹²⁸ The unique ability of cocaine to inhibit nerve conduction while enhancing vasoconstriction is primarily responsible for its cardiovascular toxicity.¹²⁶

Cocaethylene is also a potent sodium channel blocking agent and appears to prolong the recovery time for the channel compared with cocaine.¹²⁹ In animal models, cocaine plus ethanol depressed myocardial contractility more than either agent given alone.^{130,131} Once formed, cocaethylene has a longer half-life than cocaine.

The mechanism of cocaine-induced myocardial ischemia is thought to be multifactorial. Cocaine increases myocardial oxygen demand while increasing heart rate and blood pressure. Usually, myocardial oxygen demand results in coronary vasodilation; however, cocaine taken by some routes can induce coronary vasospasm.¹³² Coronary artery thrombus formation has also been implicated as a cause of cocaine-induced myocardial ischemia. Thrombus formation leading to myocardial infarction has been associated with coronary artery vasospasm.¹³³ The vasospasm may damage the endothelium and cause release of vasoactive substances precipitating platelet aggregation. Cocaine may enhance this effect because in vitro studies have demonstrated that cocaine alone may directly stimulate platelet aggregation and platelet thromboxane production.¹³⁴ Cocaine activates platelets in whole blood by inducing the release of platelet granule contents and by promoting the binding of fibrinogen to the surface of the platelet.¹³⁴

Clinical Manifestations

The clinical effects of cocaine result from diffuse hyperadrenergic stimulation both centrally and peripherally. The peripheral sympathomimetic effects include tremor, mydriasis, urinary retention, and ileus. Adrenergic stimulation of the CNS leads to agitation, hallucinations, seizures, and coma.¹³⁵ Patients may experience psychosis, paranoia, and anxiety due to increased dopaminergic transmission.¹³⁶ Cerebrovascular complications from cocaine-induced vasospasm and a hyperadrenergic state include cerebral infarctions, transient ischemic attacks, and subarachnoid and intracranial hemorrhages.^{135,136}

Myocardial ischemia and infarction are well-documented complications of cocaine use. Ischemia of the myocardium does not require a massive exposure to cocaine and occurs commonly in the young adult with no history of cardiac risk factors. Symptoms of chest pain may be typical, atypical, or absent. A delay of several hours in the onset of chest discomfort may

occur after exposure to the drug.¹³⁷⁻¹³⁹ Electrocardiograms from patients with cocaine-associated chest pain may demonstrate a variety of abnormalities, including classic findings of myocardial injury such as ST segment elevation but may also be normal or have only nonspecific findings. A study of 42 cocaine users with chest pain and normal or nondiagnostic electrocardiograms documented 8 of these patients as having acute myocardial infarctions, defined by total creatinine kinase and myocardial isoenzyme levels.¹⁴⁰ Thus single or even serial electrocardiograms may not be useful in ruling out cocaine-induced ischemia.

Cocaine has been associated with a variety of dysrhythmias. Sinus tachycardia is common owing to the sympathomimetic effects. Atrial fibrillation, premature ventricular contractions, ventricular tachycardia, and ventricular fibrillation have all been described.¹⁴¹ Dysrhythmias may occur with or without underlying ischemia. Since cocaine can cause sodium channel blockade, this can lead to widening of the QRS complex and can precipitate associated dysrhythmias. Sodium channel blockade should be treated with sodium bicarbonate, as previously discussed.

Hypertension is also common with cocaine poisoning. The elevation in blood pressure combined with tachycardia may increase shear forces on the great vessels, resulting in aortic dissection,¹⁴² and coronary artery dissection.¹⁴³ The intestinal vasculature is susceptible to α -stimulating effects of catecholamines, and ischemic colitis has been described in adults¹⁴⁴ and in neonates after in utero exposure to cocaine.¹⁴⁵ The uteroplacental vasculature may also respond to cocaine exposure with diminished uterine blood flow after maternal cocaine use.¹⁴⁶

Extreme hyperthermia is often documented in cocaine overdose. Temperatures are frequently reported in excess of 106° F and are thought to result from a disturbance in thermoregulation due to excess dopaminergic stimulation, combined with excessive musculoskeletal activity and agitation.^{147,148} Although cocaine-induced hyperthermia may occur independent of seizure activity, it can be exacerbated by concomitant convulsions.¹⁴⁹ An acute rise in the central body temperature has also occurred after rupture of bags of cocaine ingested by body packers.¹⁵⁰

Rhabdomyolysis also contributes to the morbidity and mortality of cocaine poisoning. All routes of cocaine exposure have been associated with a rise in serum creatinine phosphokinase level from direct myotoxicity.¹⁵⁰⁻¹⁵² An association has been made between drug-induced hyperthermia and rhabdomyolysis, but observations suggest that cocaine can also induce rhabdomyolysis independently of hyperthermia.¹⁵⁰ Cocaine-induced rhabdomyolysis is associated with myoglobinuric renal failure.¹⁵² Cocaine is not known to be directly toxic to the renal tubules; however, the effects of cocaine on renal blood flow may exacerbate the effects of myoglobinuria.

Amphetamine Derivatives

Amphetamine derivatives, such as methamphetamine, are popular agents of abuse available as many different “designer” drugs in the phenylethylamine family (Table 35-4). Substitutions of the phenylethylene ring can result in many compounds with similar effects. The only approved uses of phenylethylamines in the United States at this time are for treatment of narcolepsy, attention deficit disorder, and short-term use for weight loss.

Amphetamines have been recognized for their stimulant properties for centuries and continue to be abused by various

Table 35-4. Designer Amphetamines

Chemical Name	Nickname
3,4-Methylenedioxymethamphetamine	MDMA, Adam, Ecstasy, XTC
3,4-Methylenedioxyethamphetamine	MDEA, Eve
3,4-Methylenedioxyamphetamine	MDA, Love Drug
4-Methyl-2,5-dimethoxyamphetamine	DOM/STP, Serenity, Tranquility

routes including intravenous and oral administration. “Ice” is a pure preparation of methamphetamine and is marketed in a solid form, hence its nickname. This preparation is volatile and can be smoked, resulting in rapid absorption and effect. This form of methamphetamine rapidly became one of the leading drugs of abuse in Hawaii and California in the 1980s.^{153,154} Illicit laboratories are able to produce large quantities of methamphetamines because of easy availability of most reagents.

Abuse of the phenylethylamines results in euphoria with increased self-confidence and well-being. Persistent use with repetitive doses over several days is common. During this “speed run,” the user may not sleep or eat owing to the stimulant and anorectic effects of the drug. Chronic use of amphetamines leads to tachyphylaxis, and increasing doses are usually required to maintain euphoria.

Pharmacology

The volume of distribution of amphetamines tends to be large, and the half-life ranges from 8 to 30 hours.¹⁵⁵ Elimination is primarily through hepatic transformation, but renal excretion results in significant elimination of certain members of the amphetamine family, such as methamphetamine.¹⁵⁶ Although acidification of the urine may enhance the excretion of some amphetamine derivatives, it may also exacerbate renal toxicity in the presence of rhabdomyolysis and is therefore not recommended.¹⁵⁷

Pathophysiology

The pharmacologic mechanisms of action of amphetamines are diverse but are thought to rely on indirect effects on catecholamine receptors. These compounds act by entering presynaptic neurons and stimulating the release of endogenous catecholamines such as norepinephrine and dopamine. Amphetamines also inhibit the reuptake of catecholamines and their breakdown by the monoamine oxidase enzyme system. These effects may last for hours, whereas those of cocaine may resolve within several minutes.¹⁵⁵

Increased catecholamine release results in stimulation of α - and β -receptors, both peripherally and centrally. Dopaminergic and serotonergic receptor stimulation may contribute to the behavioral disturbances and hyperthermic effects that are common with these poisonings.¹⁵⁸ The release of dopamine may be responsible for the pleasurable effects reported with these drugs. Although all members of the amphetamine family may produce a generalized hyperadrenergic state, the pattern of effects with these compounds differs with modification of the parent phenylethylamine molecule, resulting in different anorectic, cardiovascular, and hallucinogenic properties.¹⁵⁹

Clinical Manifestations

Physical findings in amphetamine poisoning are similar to those seen with other sympathomimetic drugs. The cardiovascular toxicity of amphetamines manifests most commonly as tachycardia and hypertension. Dysrhythmias are a common cause of death and can include ventricular tachycardia and ventricular fibrillation.¹⁶⁰ Hypertensive emergencies with intracranial hemorrhages and cerebrovascular accidents may be more common with amphetamine and methamphetamine than cocaine abuse.¹⁶¹ Acute myocardial ischemia, infarction, aortic dissection, and dilated cardiomyopathy are also known to occur in the setting of amphetamine use.¹⁶² Diffuse vascular spasm has also been reported with amphetamine poisoning, and may result in death.^{163,164}

CNS toxicity is the most common reason for amphetamine-poisoned patients to present to a hospital. Most victims are agitated, anxious, and can become volatile and violent. Tactile and visual hallucinations may contribute to patient agitation, and psychoses similar to paranoid schizophrenia are frequently observed in these patients. Mydriasis and diaphoresis are common. Seizures often complicate amphetamine poisoning.¹⁶⁴

As in acute cocaine intoxication, hyperthermia is well documented in amphetamine poisoning and is associated with increased morbidity and mortality. Hyperthermia may occur independent of seizures and has been associated with rhabdomyolysis, coagulopathy, renal failure, and death.¹⁶⁴⁻¹⁶⁶

Management

Successful treatment of sympathomimetic poisoning begins with aggressive supportive care. Management of airway, breathing, and circulation are initial priorities. Placement of the patient in a quiet setting may reduce the amount of stimulation and reduce patient agitation; however, the victim must be continuously monitored for potential complications. Vital signs should be obtained frequently and body temperature verified by rectal thermometer if hyperthermia is suspected. Rapid cooling measures should be instituted as soon as hyperthermia is discovered, and neuromuscular paralysis may be required in severe cases of hyperthermia.

Decontamination of the patient who ingested sympathomimetics or bags containing these drugs begins with the administration of activated charcoal as described earlier. Whole-bowel irrigation with an iso-osmotic, isoelectric lavage solution (e.g., Go-Lytely) may enhance the removal of bags from the gastrointestinal tract.¹⁶⁷ Due to the large volume of distribution of these agents, hemodialysis and hemoperfusion are not effective in their removal; however, hemodialysis may be required if acute renal failure develops as a complication of rhabdomyolysis.

Rapid and effective control of hypertension from sympathomimetic poisoning is imperative. The use of β -blockers to control the hypertension associated with sympathomimetics is controversial because these compounds may potentiate both coronary and peripheral vasoconstriction due to unopposed α -agonist activity.^{168,169} Case reports have suggested the use of labetalol as an alternative to nonselective β -blocking agents,¹⁷⁰ but labetalol is a more potent β than α antagonist. One study of patients given intranasal cocaine while undergoing angiography demonstrated that labetalol reduced the mean arterial pressure but had no effect on coronary artery vasoconstriction.¹⁷¹ Use of direct vasodilators such as nitroglycerin, nitroprusside, or phenolamine is optimal.^{172,173}

Cocaine or amphetamine-related chest pain must be considered to represent active myocardial ischemia. Therapy should initially include the application of oxygen and the reduction of central sympathomimetic effects with the liberal use of benzodiazepines. Nitroglycerin has been demonstrated to be effective in alleviating cocaine-induced vasoconstriction in diseased and nondiseased coronary arteries.¹⁷³ An antiplatelet drug such as aspirin may be administered because platelets are activated by cocaine. Heparin or thrombolytics may be considered when ischemia is refractory to more conservative management.

Treatment of sympathomimetic-induced dysrhythmias begins with the administration of benzodiazepines to sedate the patient and reduce catecholamine release.¹⁷⁴ Wide complex tachydysrhythmias from cocaine have been effectively treated by administering intravenous sodium bicarbonate.¹⁷⁵ Lidocaine may be considered for treatment of dysrhythmias secondary to ischemia or refractory to sodium bicarbonate but should be used with caution because it has potentiated cocaine-induced seizures and death in rats.¹⁷⁶

Benzodiazepines are the mainstay of treatment for CNS effects of sympathomimetic poisonings. These sedative-hypnotics have been demonstrated to reduce the lethality of both cocaine and amphetamines.^{174,177} Butyrophenones have also been effective in reducing the dopaminergic-based delirium associated with amphetamine use.¹⁷⁸ Butyrophenones must be administered cautiously to patients with either cocaine or amphetamine toxicity because most antipsychotic medications may lower seizure thresholds, alter temperature regulation, and cause acute dystonias.

Conclusion

Many drugs possess the ability to cause life-threatening cardiotoxicity in overdose. In this chapter we have outlined some of the most significant and most common agents in this regard, with emphasis on clinical presentation and management. Although primary resuscitative efforts in all disease states should focus on airway and circulation, the varied mechanisms of action of cardiotoxic compounds may require specific therapeutic interventions. Early consultation with a certified regional poison control center or a medical toxicologist may assist in the care of these patients.

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Anticoagulation: Antithrombin Therapy

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Hemostasis and the Coagulation Cascade
Antithrombins—Mechanism of Action
Unfractionated Heparin (UFH)
Low Molecular Weight Heparins (LMWH)

Synthetic Pentasaccharides (Fondaparinux and Idraparinux)
Direct Thrombin Inhibitors
Conclusions

DRUGS INTERFERING with blood coagulation are a mainstay of cardiovascular therapy. This therapeutic area is undergoing unprecedented change with the clinical introduction of newer drugs and intensive research into their role in the management of acute coronary syndromes (ACS) and percutaneous coronary intervention (PCI). These recent advances in antithrombin and antiplatelet therapy have led to significant improvement in patient outcomes. Although unfractionated heparin (UFH) alone has been the mainstay of antithrombin therapy for many years, studies with low molecular weight heparins (LMWHs), pentasaccharides, direct thrombin inhibitors (DTIs), and parenteral antiplatelet agents (glycoprotein IIb/IIIa inhibitors) have altered the landscape of therapy for patients having ACS and undergoing PCI.

Although improvements have been made in efficacy, this must be balanced with the need for safety. Both indirect and direct thrombin inhibitors have found an expanded role in PCI as recent trials have demonstrated their efficacy and safety.

Population-based surveys conducted in Europe during 1999–2001 demonstrated that more than 90% of patients with ACS receive aspirin upon hospital admission and that most (80%) also receive either UFH or LMWHs, with the proportions receiving these two forms of heparin approximately equal.^{1–3}

The Seventh American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic Therapy and the American College of Cardiology/American Heart Association/ Society for Cardiovascular Angiography and Interventions (ACC/AHA/SCAI) updated their recommendations for anticoagulation therapy in patients undergoing PCI in recent years and the European Society of Cardiology has also recently published its position paper on anticoagulants in heart disease.^{4–6}

The development of anticoagulant therapy in heart disease has added to the complexity of patient management for clinicians. The explosion of research has meant that both clinical

application of each drug and combination therapy has become increasingly intricate. The management of patients in the acute setting will continue to evolve.

Hemostasis and the Coagulation Cascade

When a blood vessel is damaged, the site of disruption is rapidly sealed to prevent blood loss. Hemostasis refers to the formation of a platelet and fibrin plug at the site of injury. This requires activation of platelets and coagulation at the site of injury. The clot is later dissolved by another protease reaction, fibrinolysis, which also prevents the vessel from being occluded by the clot during its formation. In order for the blood to stay fluid within the circulation, a delicate balance between the carefully regulated systems of coagulation and fibrinolysis is needed. Disturbances in either system will cause a tendency toward thrombosis or bleeding.⁷ Coagulation, as shown in [Figure 36-1](#), has often been represented as two independent pathways that converge to a common pathway, with thrombin generation as the end point of the cascade. This model gives a good representation of the processes observed in clinical coagulation laboratory tests. The prothrombin time measures the factors of the so-called extrinsic pathway, and activated partial thromboplastin time measures factors in the intrinsic pathway. However, this model has inadequacies relating to the *in vivo* hemostatic processes. For example, deficiencies of factor XII, high molecular weight kininogen (HK), or prekallikrein do not cause clinical bleeding, and others have shown that under normal circumstances, hemostasis is initiated by tissue factor (TF), a transmembrane glycoprotein.^{8,9} TF is a member of the class II cytokine receptor superfamily and functions both as the receptor and as the essential cofactor for factors (F) VII and VIIa. Assembly of the

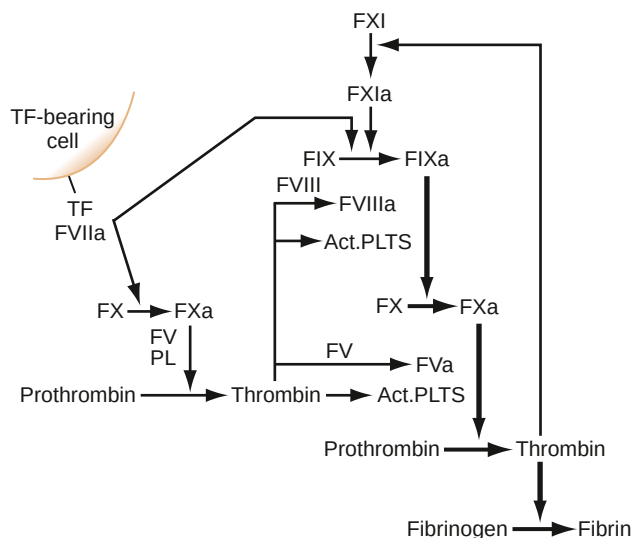


Figure 36-1. Coagulation cascade. Simplified schematic shows coagulation by activation of factor XII (intrinsic pathway) and factor VII/tissue factor (TF) (extrinsic pathway). F, factor; PLTS, platelets. Act, activated; PL, phospholipids

TF/FVIIa complex on cellular surfaces leads to the activation of FX and initiates coagulation. TF is constitutively expressed in cells surrounding blood vessels and large organs to form a hemostatic barrier. In addition to its role in hemostasis, the TF/FVIIa complex has been shown to elicit intracellular signaling resulting in the induction of various genes, thus explaining its role in various biologic functions, such as embryonic development, cell migration, inflammation, apoptosis, and angiogenesis.¹⁰⁻¹²

Cell-based Model of Coagulation

In this model, coagulation occurs in three overlapping phases: initiation, priming, and propagation.^{9,13,14} During the process of hemostasis, a break in the vessel wall brings plasma into contact with TF-bearing cells. FVII binds to TF and is rapidly activated by coagulation proteases and by noncoagulation proteases, depending on the cellular location of the TF.¹⁵⁻¹⁷ The FVIIa/TF complex then activates FX and FIX. The activated forms of these two proteins (IXa and Xa) play very different roles in subsequent coagulation reactions. FXa can activate plasma FV on the TF cell. If FXa diffuses from the protected environment of the cell surface from which it was activated, it can be rapidly inhibited by the TF pathway inhibitor (TFPI) or antithrombin (AT). However, the FXa that remains on the TF cell surface can combine with FVa to produce small amounts of thrombin (the enzyme responsible for clot formation). This thrombin, although not sufficient to cleave fibrinogen throughout a wound, nonetheless plays a critical role in amplifying the initial thrombin signal. The initial FVIIa/TF complex is subsequently inhibited by the action of the TFPI in complex with FXa.^{18,19} In contrast to FXa, FIXa is not inhibited by TFPI, and only slowly inhibited by AT. FIXa moves in the fluid phase from TF-bearing cells to nearby platelets at the injury site.

In the amplification phase (priming phase), low concentrations of thrombin activate platelets adhering to the injury site to release FV from their α -granules. Thrombin cleaves the partially activated FV to a fully active form. Thrombin also cleaves FVIII, releasing it from the von Willebrand factor. Such activated

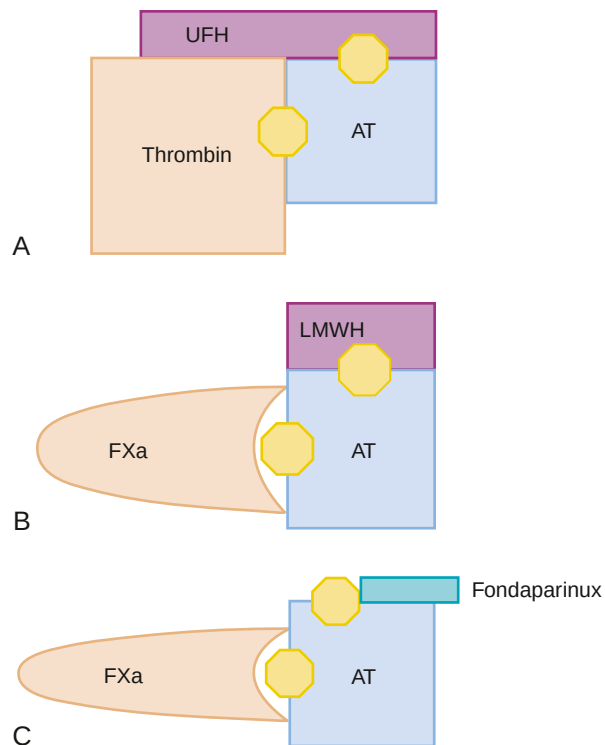


Figure 36-2. Mechanism of action of heparin derivatives.

A, Unfractionated heparin (UFH) possesses the pentasaccharide unit necessary for its interaction with antithrombin (AT). The UFH/AT complex is able to block the thrombin active site. **B**, Low-molecular-weight heparins (LMWHs) (short chains) do not bind to exosite 2 of thrombin, in contrast to the longer UFH chains. All LMWH/AT complexes can still bind to factor Xa (FXa). **C**, Synthetic pentasaccharides (fondaparinux and idraparinux), similar to LMWHs, bind and activate AT and allow AT to inhibit FXa efficiently. Hirudin and bivalirudin bind to thrombin via the active site and exosite 1, displacing thrombin from fibrin.

factors bind to platelet surfaces, which provide the backbone for thrombin generation that occurs during the propagation phase.²⁰

In the propagation phase, the phospholipid surface of activated platelets acts as a cofactor for the activation of the FVIIIa/FIXa complex and of the FVa/FXa complex, which accelerate the generation of FXa and thrombin, respectively. The burst of thrombin leads to the bulk cleavage of fibrinogen to fibrin. Soluble fibrin is finally stabilized by FXIIIa, also activated by thrombin, to form a fibrin network (i.e., a thrombus).

Arterial Thrombosis

Arterial thrombosis can occur from at least two main different mechanisms, endothelial erosion or plaque rupture.^{21,22} Plaque rupture results in the exposure of thrombogenic material (e.g., collagen and TF) to the circulation and subsequent activation of platelets and coagulation cascade. This, coupled with the simultaneous release of vasoactive substances, induces thrombus formation and vasoconstriction, which result in myocardial ischemia and ACS.

Antithrombins—Mechanism of Action

Thrombin has an active site and two exosites, one of which, exosite 1, binds to its fibrin substrate, orienting it toward the active site. Figure 36-2 displays the mechanisms of action of

the different thrombin inhibitors described below. The heparin derivatives in current use include UFH, LMWHs, and the synthetic pentasaccharide derivatives fondaparinux and idraparinux. These are all parenteral drugs that must be administered by intravenous (IV) or subcutaneous (SC) injection, and they are classified as indirect anticoagulants because they require a plasma cofactor (essentially AT) to exert their anticoagulant activity, while the DTIs (hirulog and hirudin) bind thrombin, essentially displacing it from fibrin.

Unfractionated Heparin

UFH was discovered almost 90 years ago and is the prototype of its derivatives. It is a natural product that can be isolated from beef lung or porcine intestinal mucosa. It consists of highly sulfated polysaccharide chains, with a mean of about 45 saccharide units. Only one third of the heparin chains possess a unique pentasaccharide sequence that exhibits high affinity for antithrombin (AT), and it is this fraction that is responsible for most of the anticoagulant activity of heparin.⁵

Pharmacokinetics, Metabolism, and Administration

UFH must be given parenterally either by continuous IV infusion or by SC injection. When given SC for treatment of thrombosis, higher doses of heparin than those administered by IV infusion are needed to overcome the fact that the bioavailability of heparin after SC injection is only about 30%.²¹ This is, however, highly variable among individuals.⁵ A number of plasma proteins compete with AT for heparin binding, thereby reducing its anticoagulant activity. The levels of these proteins vary among patients. This phenomenon contributes to the variable anticoagulant response to heparin and to the phenomenon of heparin resistance.²¹ Heparin is cleared through a combination of a rapid saturable phase and a slower first-order mechanism. Heparin binds to endothelial cells, platelets, and macrophage during the saturable phase. Once the cellular binding sites are saturated, heparin enters the circulation, from where it is cleared more slowly via the kidneys. The complex kinetics of heparin clearance render the anticoagulant response to UFH nonlinear at therapeutic doses, with both the peak activity and duration of effect increasing disproportionately with increasing doses.²¹

Dosing and Monitoring

Heparin can be given in fixed or weight-adjusted doses, and nomograms have been developed to aid with dosing.²² The doses of UFH recommended for the treatment of ACS are lower than those typically used to treat venous thromboembolism due to the lower thrombus burden in arterial thromboses. Due to the varying anticoagulant response of UFH among patients, UFH therapy is monitored and the dose is adjusted based on these results. The test most often used to monitor heparin is the activated partial thromboplastin time (aPTT). The activated clotting time (ACT) is used to monitor the higher doses of UFH given to patients undergoing PCI or cardiopulmonary bypass surgery.

An aPTT ratio between 1.5 and 2.5 (calculated by dividing the reported therapeutic aPTT range by the control value for the reagent) was associated with a reduced risk for recurrent VTE in a previous large retrospective registry.²³ Based on this study, an aPTT ratio of 1.5 to 2.5 was adopted as the therapeutic

range for UFH. Both the ACCP and the European Society of Cardiology agree that aPTT ratios should be adapted to the reagents used and that the use of a fixed aPTT target in seconds for any therapeutic indications of UFH should not be strictly applied. Despite these shortcomings, the aPTT is the most common method used for monitoring its anticoagulant response. The aPTT should be measured approximately 6 hours after the bolus dose of heparin, and the continuous IV dose should be adjusted according to the result. Various heparin dose-adjustment nomograms have been developed, but none is applicable to all aPTT reagents, and, for the reasons discussed above, the therapeutic range should be adapted to the responsiveness of the reagent used.

Side Effects

Bleeding is the major complication of heparin therapy. Other complications of heparin include heparin-induced thrombocytopenia (HIT) and osteoporosis. HIT is caused following the formation of heparin/platelet factor 4 (PF4) complexes. Antibodies are produced against the neoepitope on PF4 that binds to Fc receptors on the platelet, causing its activation.²⁴ Activated platelets are then removed from the circulation, which causes thrombocytopenia. Osteoporosis is a complication of long-term treatment with therapeutic doses of heparin and appears to be the result of heparin binding to osteoblasts with subsequent osteoclast activation.

Clinical Evidence

UFH has mainly been used in the management of patients with non-ST-segment elevation-ACS (NSTEMI-ACS), adjuvant therapy during PCI, and in the STEMI population (with or without fibrinolytic agents). In trials comparing the association of heparin plus aspirin versus aspirin alone in NSTEMI-ACS, a trend toward benefit was observed in favor of the heparin-aspirin combination, but at the cost of an increase in bleeding. Recurrence of events after interruption of UFH explains why this benefit is not maintained over time, unless the patient was revascularized before the interruption of UFH.²⁵ Adjunctive UFH use in the setting of STEMI, together with the use of fibrinolytic agents, has a narrow therapeutic window. The ISIS-3 and GISSI-2 trials examined its use with streptokinase and found no reduction in mortality at 35 days or 6 months with an increase in major bleeding. The evidence for the use of UFH with tissue plasminogen activator (tPA) was more favorable and it became standard therapy after the superiority of front-loaded tPA with UFH was demonstrated in the GUSTO-1 trial.²⁶ Intravenous UFH using a bolus of 60 U/kg (maximum 4000 U) followed by a maintenance infusion of 12 U/hr (maximum 1000 U) for 48 hours is recommended with tPA and other fibrin-specific fibrinolytic agents.⁵

UFH is the most commonly used anticoagulant during PCI. ACT monitoring is used in this case because the required level of anticoagulation is beyond the range that can be measured using aPTT. Randomized trials have shown UFH to reduce ischemic complications.^{27,28} UFH in a dose of 60 to 100 IU/kg and a target ACT between 250 and 350 seconds are recommended. A target of 200 seconds is advocated for UFH dosing in conjunction with glycoprotein (Gp) IIb/IIIa inhibitors.²⁹⁻³² After completion of PCI, UFH is not indicated because continued treatment does not reduce ischemic complications and is associated with a higher risk of bleeding.³³

Low Molecular Weight Heparin

In the early 1980s, LMWH was introduced as an alternative to UFH, first for the prevention of deep vein thrombosis (DVT) among postoperative patients.^{34,35} Four LMWHs have been studied in the setting of acute coronary syndromes, enoxaparin, reviparin, tinzaparin, and dalteparin. Enoxaparin and dalteparin have been approved by the FDA for use in cardiovascular disease, and enoxaparin is the most widely studied of the LMWHs.

The high bioavailability and minimal plasma protein binding of LMWH leads to a predictable dose-response, which obviates the need for plasma monitoring.³⁶ In addition, LMWH has been reported to have a lesser effect on platelet aggregation than UFH.³⁷ Other benefits of LMWH include a higher antifactor Xa:IIa ratio, less inhibition by platelet factor 4, and an inhibition in the early rise in von Willebrand factor.³⁸

Pharmacokinetics, Metabolism, and Administration

The LMWHs are most commonly administered SC, although an IV bolus has also been evaluated, most commonly in studies in the STEMI population. Enoxaparin is dosed according to body weight, with the most common dose used in ACS being 1 mg/kg every 12 hours. Following a single SC injection, enoxaparin has a peak plasma antifactor Xa activity within 3 to 6 hours.³⁹ One study demonstrated that 97.6% of patients had antifactor Xa activity above therapeutic range at the time of catheterization if enoxaparin was administered with 8 hours of planned PCI.⁴⁰ Enoxaparin is weakly metabolized in the liver. Renal clearance of active fragments represents about 10% of the administered dose, whereas about 40% of active and inactive fragments combined are excreted renally. Based on antifactor Xa activity, elimination half-life is 4.5 to 5 hours after a single dose and approximately 7 hours after repeated dosing.⁴¹

Clinical Evidence

Based on early experience with LMWHs,⁴²⁻⁴⁴ two pivotal trials examined the efficacy and safety of enoxaparin in patients with ACS. The ESSENCE trial evaluated enoxaparin in the setting of ACS.⁴⁵ They randomized more than 3000 patients to enoxaparin or UFH for at least 48 hours. At 14 days, the incidence of death, MI, or recurrent angina was significantly lower in patients randomized to enoxaparin than those receiving UFH (16.6% versus 19.8%, $p = 0.019$), and the outcomes remained significantly different at 30 days (19.8% versus 23.3%, $p = 0.016$). Although there was no significant difference in major bleeding (6.5% versus 7.0%, $p = \text{NS}$), the incidence of any bleeding event was significantly higher in the enoxaparin group (18.4% versus 14.2%, $p = 0.001$), primarily driven by an increase in injection-site ecchymosis. The TIMI 11B trial, which randomized nearly 4000 patients to either UFH or enoxaparin, again showed a statistically significant difference in ischemic outcomes favoring enoxaparin (12.4% versus 14.5%, $p = 0.048$) with no difference in major bleeding.⁴⁶

The SYNERGY trial randomized more than 10,000 patients having NSTEMI-ACS and high risk features undergoing an early invasive strategy to enoxaparin versus UFH.⁴⁷ More than half received a Gp IIb/IIIa inhibitor and two thirds received clopidogrel or ticlopidine. There was no significant difference in the incidence of death or nonfatal MI by 30 days between patients who received enoxaparin or UFH (14.0% versus 14.5%, $p = \text{NS}$).

In addition, the rates of acute complications, including abrupt closure, threatened abrupt closure, unsuccessful PCI, and emergency CABG surgery were not significantly different between the groups. There was, however, a significantly higher incidence of major bleeding (9.1% versus 7.6%, $p = 0.008$) in the enoxaparin group.

There have also been two large meta-analyses reported evaluating the role of enoxaparin in NSTEMI-ACS.^{48,49} Eikelboom and colleagues analyzed five trials involving more than 12,000 patients comparing UFH with LMWH. They reported no significant difference between LMWH and UFH in terms of 7-day incidence of a composite of death or recurrent MI (2.2% versus 2.3%, $p = 0.34$).⁴⁸ Petersen and colleagues evaluated six studies, including almost 22,000 patients randomized to either enoxaparin or UFH, and reported their results in 2004.⁴⁹ There was a significant difference favoring enoxaparin in terms of the 30-day incidence of a composite of death or recurrent MI (10.1% versus 11.0%, $p = 0.05$) with no difference in major bleeding (4.7% versus 4.5%, $p = \text{NS}$) at 7 days.

The ACC/AHA guidelines for the treatment of patients with NSTEMI, last updated in 2002, suggest that LMWHs are preferred over UFH in the absence of renal failure.⁶

Although enoxaparin gained a firm footing in the treatment of NSTEMI-ACS, it was not until 2001 that the first randomized trial evaluating its use as an adjunct to fibrinolytic administration for STEMI was reported. In the HART II trial, 400 consecutive patients with STEMI received aspirin and tissue tPA and were randomized to enoxaparin or UFH for at least 3 days in a non-inferiority design.⁵⁰ At 90 minutes, there was no significant difference in artery patency (80.1% versus 75.1%), and at 1 week, there was a trend toward a significant difference in reocclusion rates favoring enoxaparin (5.9% versus 9.8%, $p = 0.12$). There were no significant differences in in-hospital major bleeding (3.6% versus 3.0%) or death at 30 days (4.5% versus 5.0%).

The ASSENT-3 trial randomized more than 6000 patients with STEMI who were to undergo fibrinolytic therapy with tenecteplase to 1 of 3 regimens: full-dose tenecteplase plus enoxaparin, full-dose tenecteplase plus UFH, or half-dose tenecteplase plus low-dose UFH and a 12-hour infusion of abciximab. The composite incidence of 30-day mortality, in-hospital reinfarction, and refractory ischemia was significantly reduced with enoxaparin compared with UFH (11.4% versus 15.4%, $p = 0.0002$).⁵¹ When in-hospital major bleeding was added to the composite end point, the results still favored enoxaparin (13.7% versus 17.0%, $p = 0.0037$).

The EXTRACT-TIMI 25 study randomized more than 20,000 patients to enoxaparin or UFH following fibrinolytic therapy.⁵² The study reported a significant difference favoring enoxaparin in terms of a composite of death or nonfatal recurrent MI within 30 days (9.9% versus 12.0%, $p < 0.001$) and nonfatal reinfarction alone (3.0% versus 4.5%, $p < 0.001$), with a trend toward decreased mortality (6.9% versus 7.5%, $p = 0.11$). However, major bleeding at 30 days was significantly higher (2.1% versus 1.4%, $p < 0.001$).

Guidelines published in 2004 for the management of patients with STEMI, before the publication of the results of the EXTRACT-TIMI 25 study, suggest LMWH might be considered as an ancillary therapy among patients undergoing fibrinolytic therapy provided they are less than 75 years old and do not have underlying renal dysfunction.⁵³

Synthetic Pentasaccharides (Fondaparinux and Idraparinux)

A synthetic analogue of the antithrombin-binding pentasaccharide sequence found in UFH and LMWH, fondaparinux binds antithrombin and enhances its reactivity with factor Xa.⁵⁴

Pharmacokinetics, Metabolism, and Administration

Fondaparinux shares all the pharmacologic and biologic advantages of LMWHs over UFH, but in comparison with LMWHs, fondaparinux selectively inhibits FXa, without specific inhibition of thrombin (it is too short to bridge antithrombin to thrombin). As a synthetic molecule, fondaparinux is highly standardized and has no antigenic properties. A derivative of fondaparinux, termed idraparinux, is a synthetic, long-acting, highly sulfated analogue of fondaparinux, with prolonged a half-life.

In plasma, fondaparinux binds to antithrombin, and there is no detectable binding to other plasma proteins (a finding that explains why it produces a more predictable anticoagulant response than heparin). With excellent bioavailability after SC injection and a plasma half-life of about 17 hours, fondaparinux can be administered SC once daily and produces a predictable anticoagulant response and exhibits linear pharmacokinetics when given in doses ranging from 2 to 8 mg.⁵⁵ The drug is excreted unchanged in the urine. Consequently, dose adjustments are necessary in patients with renal insufficiency, and fondaparinux should not be used in those with renal failure.

The specific anti-Xa activity of fondaparinux is about sevenfold higher than that of LMWHs. Fondaparinux does not bind to platelets or PF4. Because it does not induce the formation of heparin/PF4, complexes that serve as the antigenic target for the antibodies that cause HIT, HIT is unlikely to occur with fondaparinux. However, fondaparinux also fails to interact with protamine sulfate, the antidote for heparin. If uncontrolled bleeding occurs with fondaparinux, a procoagulant such as recombinant factor VIIa may be effective.⁵⁶ However, recombinant factor VIIa is not available in all hospitals, and the drug is expensive and can cause thrombotic complications.

Like fondaparinux, idraparinux is a selective indirect FXa inhibitor.⁵⁷ Idraparinux binds antithrombin with such high affinity (more than tenfold higher than that of fondaparinux) that its plasma half-life of 130 hours is similar to that of antithrombin. The anti-FXa activity and inhibition of thrombin generation of idraparinux are dose-dependent.

Fondaparinux is given SC once daily in fixed doses. A dose of 2.5 mg is used in patients with NSTEMI and STEMI and for thromboprophylaxis in medical and orthopedic surgery patients. A dose of 7.5 mg is used for treatment of VTE. Because of the long half-life, idraparinux can be given SC once a week.⁵⁷

Fondaparinux and idraparinux have little or no effect on routine tests of coagulation, such as the aPTT or ACT.⁵⁸ These tests are therefore unsuitable to monitor the clinical use of these drugs. If monitoring is required, their anticoagulant effect can be measured with anti-Xa assays.

Besides bleeding, side effects of fondaparinux and idraparinux are largely unknown. In contrast to UFH or LMWHs, fondaparinux does not cause HIT and has actually been used successfully to treat HIT. Although data are lacking, in vitro and in vivo studies suggest that fondaparinux may have less effect on bone than UFH or LMWHs.^{59,60}

Clinical Evidence

Fondaparinux has been studied for venous thromboprophylaxis, treatment of venous thromboembolism and in the treatment of acute coronary syndromes. For thromboprophylaxis, four large phase 3 trials comparing fondaparinux with enoxaparin in patients undergoing major orthopedic surgery, and in general medical and surgical patients, have been performed.⁶¹⁻⁶⁴ In these trials, fondaparinux was found to reduce the risk of venous thromboembolism by approximately 55% compared with enoxaparin. Major bleeding occurred more frequently in the fondaparinux-treated group ($p = 0.008$), but the incidence of bleeding leading to death or reoperation, or occurring in a critical organ, was not significantly different between the two groups. It is possible that the increase in major bleeding with fondaparinux relative to enoxaparin reflects the timing of therapy following surgery (6 hours with fondaparinux versus 12 to 24 hours with enoxaparin).

Fondaparinux also has been evaluated for the initial treatment of established venous thromboembolism in two phase III clinical trials. In the MATISSE DVT trial,⁶⁵ 2205 patients with DVT were randomized, in a blinded fashion, to receive either fondaparinux or enoxaparin for 5 days followed by a minimum 3-month course of treatment with an oral vitamin K antagonist. At 3 months, the rates of recurrent symptomatic venous thromboembolism with fondaparinux or enoxaparin were 3.9% and 4.1%, respectively, whereas major bleeding rates were 1.1% and 1.2%, respectively. None of these differences was statistically significant.

In the open-label MATISSE PE trial,⁶⁶ 2213 patients with PE were randomized to receive either fondaparinux or unfractionated heparin (by continuous infusion) for 5 days followed by a minimum 3-month course of therapy with an oral vitamin K antagonist. At 3 months, the rates of recurrent symptomatic venous thromboembolism occurring after therapy with fondaparinux or unfractionated heparin were 3.8% and 5.0%, respectively, whereas major bleeding rates were 1.3% and 1.1%, respectively. Based on these two trials, fondaparinux appears to be at least as effective and safe as LMWH or UFH for the initial treatment of venous thromboembolism.

In ACS, fondaparinux was first evaluated in two dose-finding phase 2 trials in NSTEMI-ACS and two phase 2 elective PCI studies.⁶⁷⁻⁷⁰ These studies identified the lowest dose of 2.5 mg SC once daily to be the safest, with at least similar efficacy as higher dosages.

The OASIS-5 trial randomized 20,078 patients with NSTEMI-ACS to SC fondaparinux 2.5 mg daily versus SC enoxaparin 1 mg/kg body weight twice daily for a mean of 6 days.⁷¹ The prespecified primary end point was death, MI, or refractory ischemia at 9 days. This end point was reached in 5.8% with fondaparinux compared with 5.7% with enoxaparin, which satisfied the prespecified criterion for noninferiority ($p = 0.007$). Major bleeds were halved with fondaparinux compared with enoxaparin (2.2% vs 4.1%, $p < 0.001$), with lower rates of bleeding complications at the access site (3.3 versus 8.1%, $p < 0.001$). Major bleeding was an independent predictor of long-term mortality, which was lower with fondaparinux (5.8% versus 6.5% at 6 months, $p = 0.05$). At 6 months, the composite outcome of death, MI, or strokes was also significantly reduced (11.3% versus 12.5%, $p = 0.007$). Overall, the trial demonstrated that fondaparinux was equivalent to enoxaparin in terms of efficacy but with a substantially lower rate of major bleeding, which

translated into a significantly lower long-term mortality and morbidity.

The OASIS-6 trial evaluated the effect of fondaparinux, given for up to 8 days, compared with standard adjuvant anticoagulant treatment in 12,092 patients with STEMI.⁷² The trial had a complicated design with two strata: 5658 patients were randomized to fondaparinux versus the placebo and 6434 patients were randomized to fondaparinux versus UFH. Both strata contained subgroups with and without reperfusion treatments and also with the use of different types of reperfusion (i.e., streptokinase [73% of thrombolysis], urokinase, tPA agents, and primary PCI). In the overall population, the end point of death or reinfarction at 30 days was significantly reduced from 11.2% in the control group to 9.7% in the fondaparinux group ($p = 0.008$). The benefit was, however, only seen in stratum I with 11.2% versus 14.0% ($p < 0.001$) in the fondaparinux versus placebo groups, respectively. In contrast, there were no significant differences in stratum II (8.3% versus 8.7% in the fondaparinux and UFH groups, respectively). In the 3768 patients treated with primary PCI, who all were in stratum II, there was no benefit and actually a trend toward harm of fondaparinux, with a 30-day rate of death or MI of 6.1% with fondaparinux versus 5.1% in the UFH group ($p = 0.19$). There was a higher rate of guiding catheter thrombosis (22 versus 0, $p < 0.001$) and more coronary complications (270 versus 225, $p = 0.04$) with fondaparinux. There was a trend toward fewer severe bleeds with fondaparinux combining both strata, and, interestingly, severe bleeds were even less common with fondaparinux than with placebo in stratum I patients. It appears from these results that in acute STEMI without indication for UFH, fondaparinux is more effective and as safe as no anticoagulant treatment regardless of whether any reperfusion treatment is used or not. Secondly, in STEMI patients treated with thrombolysis, fondaparinux is at least as effective and as safe as UFH, although at present a claim of superiority is doubtful. In STEMI patients treated with primary PCI, fondaparinux used as the only anticoagulant seems associated with a risk of harm, based on an increased rate of coronary complications. This risk seems avoidable by pretreatment with UFH before PCI.

Idraparinux

This drug has been developed for long-term anticoagulation. The AMADEUS trial enrolled patients with AF at high risk of stroke with an indication for vitamin K antagonists. Patients were randomized to receive idraparinux 2.5 mg once weekly SC or VKAs (goal INR 2-3) for 6 to 24 months. This trial has been prematurely interrupted for safety reasons (unpublished results).

Direct Thrombin Inhibitors

Direct thrombin inhibitors (DTIs) are derivatives of hirudin, a polypeptide first isolated from the salivary glands of the medicinal leech, *Hirudo medicinalis*.⁷³ They are bivalent molecules that are capable of binding the active site and fibrin-binding site of thrombin. Rather than catalyzing the production of endogenous thrombin inhibitors, DTIs bind directly to thrombin and inhibit its interaction with substrate, thereby preventing fibrin formation, thrombin-mediated activation of the coagulation cascade and thrombin-induced platelet aggregation.⁷⁴ Although indirect thrombin inhibitors such as heparin and LMWH lead to the inactivation of only circulating thrombin, because of their

mechanism of action, DTIs are capable of inactivating clot-bound heparin as well. Importantly, in comparison to heparin derivatives, HIT has not been reported in patients receiving bivalirudin.

Two hirudin preparations are available, desirudin and lepirudin (65 amino acids), each of which is approved for use in thrombosis associated with HIT.⁷⁴ Bivalirudin is a synthetic derivative of hirudin (20 amino acids) and is approved for use as an alternative to heparin in patients undergoing PCI. Lepirudin and desirudin are irreversible inhibitors of thrombin. Antidesirudin and antilepirudin antibodies have been described among patients receiving these agents, leading to decreased clearance and a lower dose requirement.⁷⁵ There are three consequences of the smaller size and synthetic nature of bivalirudin: (1) immunogenicity has not been reported; (2) it can be cleaved by thrombin, thus restoring thrombin activity; and (3) it binds reversibly.

Although some early clinical studies evaluated the use of hirudin among patients with ACS, a narrow therapeutic index has limited its use.⁷⁶ The following discussion, therefore, will be limited to bivalirudin because it is the only DTI approved by the FDA for use in percutaneous coronary intervention and in the setting of acute coronary syndromes.

Pharmacokinetics, Metabolism, and Administration

Bivalirudin is administered parenterally. It is most frequently administered as a weight-based bolus (usually 0.75 mg/kg) followed by an infusion (usually 1.75 mg/kg/hr) through the completion of PCI. Its peak plasma concentration after a 15-minute bolus infusion occurs within 5 minutes of the completion of the infusion, and its half-life is approximately 25 minutes. Elimination of bivalirudin is via a combination of renal excretion and proteolytic cleavage, both by endogenous proteases and thrombin itself. Therefore, in patients with renal impairment, bivalirudin has a lower renal clearance and a longer half-life. The aPTT should be monitored more carefully among patients with kidney disease.

Clinical Evidence

Despite the use of heparin, the rate of ischemic and hemorrhagic complications during the early balloon angioplasty era coupled with a need for an antithrombotic strategy among patients with a history of HIT led to the introduction of bivalirudin.

The viability of bivalirudin as an alternative to heparin in patients undergoing balloon angioplasty was first reported by Topol and colleagues in a dose-escalation study that evaluated the efficacy of bivalirudin in patients undergoing elective coronary balloon angioplasty.⁷⁷ In a nonrandomized trial, patients receiving the bivalirudin had rates of abrupt vessel closure (6.2% among all patients, 3.9% among patients receiving the two highest doses of bivalirudin) similar to that previously reported with heparin (6% to 8%).⁷⁸⁻⁸⁰

Among patients with STEMI undergoing fibrinolysis, the HERO-2 trial randomized more than 17,000 patients to bivalirudin or heparin. Mortality at 30 days was not statistically different (10.8% versus 10.9%, $p = \text{NS}$), but bivalirudin was associated with a lower incidence of reinfarction within 96 hours (1.6% versus 2.3%, $p = 0.001$) that was countered by a small but significant increase in moderate (1.4% versus 1.1%, $p = 0.05$) and severe (0.7% versus 0.5%, $p = 0.07$) hemorrhagic outcomes.⁸¹

The REPLACE-2 trial randomized more than 6000 patients undergoing urgent or elective PCI to unfractionated heparin plus planned Gp IIb/IIIa blockade or bivalirudin plus provisional

Gp IIb/IIIa blockade.⁸² Bivalirudin was not inferior in terms of the composite primary outcome of the 30-day incidence of death, MI, urgent repeat revascularization or in-hospital major bleeding (9.2% versus 10.0%, $p = \text{NS}$); however, in-hospital major bleeding was significantly less common (2.4% versus 4.1%, $p < 0.001$). At 1 year, there was no significant difference in mortality (1.9% versus 2.5%, $p = \text{NS}$) between the groups.⁸³

The aforementioned studies evaluated patients undergoing urgent or elective PCI, but most excluded patients with ACS scheduled to undergo coronary angiography and subsequent PCI.

The ACUITY trial randomized almost 14,000 patients with NSTEMI-ACS and planned early invasive strategy to three arms: UFH or enoxaparin plus Gp IIb/IIIa blockade, bivalirudin plus Gp IIb/IIIa blockade, or bivalirudin monotherapy with provisional Gp IIb/IIIa blockade at the discretion of the treating physician.⁸⁴ There were three primary 30-day end points: (1) a composite ischemia end point (death from any cause, MI, or unplanned revascularization), (2) major bleeding, and (3) a composite of the ischemia end point plus major bleeding. There was no significant difference in any of the three primary end points among patients who received a heparin product plus Gp IIb/IIIa blockade compared with those who received bivalirudin plus Gp IIb/IIIa blockade (7.7%, 5.3%, and 11.8%, respectively, among patients receiving bivalirudin plus Gp IIb/IIIa blockade versus 7.3%, 5.7%, and 11.7%, respectively, among patients receiving heparin plus Gp IIb/IIIa blockade, all $p = \text{NS}$). Compared with those who received a heparin product plus Gp IIb/IIIa blockade, bivalirudin alone was associated with a noninferior rate of ischemic outcomes (7.8% versus 7.3%, $p = \text{NS}$) but was associated with significantly reduced major bleeding (3.0% versus 5.7%, $p < 0.001$) and the composite ischemic and hemorrhagic outcome (10.1% versus 11.7%, $p = 0.02$). A subsequent subgroup analysis of patients who underwent PCI in the ACUITY trial (nearly 8000 patients) reported similar findings.⁸⁵

The joint American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions guidelines for patients undergoing PCI, last updated in 2005 before the publication of the ACUITY trial, gives bivalirudin a Class I recommendation among patients with a history of HIT and a Class IIa recommendation among low-risk patients. Guidelines for patients with STEMI give bivalirudin a Class IIa recommendation among patients undergoing fibrinolytic therapy with streptokinase.⁸⁶

Conclusions

Antithrombin therapy in the treatment of cardiovascular disease has rapidly evolved over the past decade. This evolution has arisen from extensive randomized controlled trials that have explored the numerous clinical applications of therapy in terms of both efficacy and safety. The largest body of evidence has been obtained with LMWH and, more specifically, enoxaparin, showing superiority or at least equivalence to UFH in ACS patients undergoing currently recommended early invasive strategy. Enoxaparin use has been shown to be simple and safe without the need for monitoring or dose adjustment when combined with Gp IIb/IIIa receptor inhibitors. However, biologic monitoring (anti-Xa measurement) may be needed in special situations such as prolonged treatments in obese patients (BMI >30)

or those with renal insufficiency (creatinine clearance <60 mL/min) when accumulation of the drug is likely to occur.

From the results of the recent OASIS-5 and OASIS-6 trials, fondaparinux has demonstrated positive effects on both efficacy and safety. However, despite these encouraging results, many cardiologists have voiced uncertainty about using the drug routinely instead of UFH or enoxaparin in ACS patients because of concerns about catheter thrombosis in patients undergoing PCI. The need for combining UFH with fondaparinux to overcome this potential detrimental side effect is a limitation that needs further investigation.

Bivalirudin has been shown to be as effective and safe as heparin plus a Gp IIb/IIIa inhibitor for ACS patients rapidly managed in the catheterization laboratory. However, it remains to be seen whether bivalirudin can replace selective procedural abciximab use in the catheterization laboratory in high-risk ACS patients with positive troponin undergoing PCI. The practicality and benefit of bivalirudin in ACS patients may be more for the low-risk patients having rapid access to the catheterization laboratory. Patients who require a prolonged upstream treatment (>24 hours) may not be ideal candidates given the cost of bivalirudin and the lack of data.

There is no doubt that safety has become a critical issue as outlined by recent randomized studies providing evidence that severe bleeding and transfusion are associated with poorer prognosis, increase in mortality, and cost. Fondaparinux and bivalirudin represent an opportunity to improve safety. The three new anticoagulants, enoxaparin, fondaparinux, and bivalirudin, have demonstrated improvements in comparison to UFH that will certainly lead to changes in recommendations of anticoagulation in ACS.

At present, therapy is targeted in patients having ACS either with or without PCI. The reduction in morbidity and mortality in this population over recent years has stemmed from not only the advances of antithrombin therapy but also from the combination of improved primary and secondary prevention. This spectrum of care ranges from health care promotion and lifestyle changes to advancements in antiplatelet therapy, techniques in PCI, and risk factor modification. For continued improvements in patient care, all these areas need to be addressed along with an ongoing interest in the development of newer agent and therapies. These advancements should not only concentrate on efficacy but equal importance should be placed on improving safety.

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Antiplatelet Therapy

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CHAPTER

37

The Platelet and Acute Coronary Syndromes
Antiplatelet Therapy for Unstable Angina and Non-STEMI
Antiplatelets in ST segment elevation Myocardial Infarction

Antiplatelet Therapy and Bleeding Complications
Conclusions and Future Directions

OVER THE last 2 decades, clinical management and outcomes of patients having acute coronary syndromes (ACS) have progressed dramatically. The better understanding of the role of the platelet in the pathophysiology of the acute coronary syndrome has been the fundamental pillar for that progress. The development and availability of effective pharmacologic agents and the advance of coronary revascularization procedures have been the tools by which the basic science paradigm shift was translated into reductions in morbidity and mortality of patients having unstable angina (UA), non-ST segment (NSTEMI) and ST-segment myocardial infarction (STEMI).

The Platelet and Acute Coronary Syndromes

Plaque rupture and luminal thrombus formation are the sentinel events that convert the atherosclerotic disease process from a slowly progressive condition causing insidious luminal obstruction to an acute coronary event that may lead to clinical deterioration and possible death. Plaque rupture is a term that describes the development of a gap in the fibrous cap exposing its collagen and the underlying lipid-rich core to flowing blood.¹ This event results in activation of the circulating platelets, which in turn initiates a sequence of events involving the activated platelet: adhesion, aggregation, and secretion (Fig. 37-1).

Platelet activation occurs via multiple stimuli including adenosine diphosphate (ADP) and thromboxane A₂, but collagen and thrombin are the two most potent platelet activators. Once collagen is available for binding, platelet adhesion and activation depend on two major collagen receptors located on the platelet membrane: the integrin glycoprotein Ia/IIa ($\alpha_2\beta_1$) and glycoprotein VI. Both of these receptors generate activation signals that enhance platelet thrombus formation. Thrombin is also a potent stimulus for platelet activation by binding and cleaving platelet protease activated receptors (PAR), PAR₁, and PAR₄. This process forms a tethered-ligand that acts to initiate transmembrane signaling, also leading to platelet activation.²⁻⁴

Once activated, platelet adhesion occurs when platelet glycoprotein Ib-IX-V binds to tissue von Willebrand factor (vWF).⁵ At least one other receptor that participates in platelet adhesion includes the platelet receptor Ia/IIa, which binds to collagen

fibrils.⁶ Platelet aggregation soon follows and is primarily mediated by the glycoprotein IIb/IIIa complex ($\alpha_{IIb}\beta_3$). Glycoprotein IIb/IIIa adhesion proteins are found on platelets and megakaryocytes. They are the most abundant glycoprotein found on the platelet surface with approximately 80,000 copies. The glycoprotein IIb/IIIa complex requires platelet activation, which causes a conformational change in the receptor thereby becoming a high-affinity fibrinogen binding receptor. Fibrinogen bridges activated platelets forming a platelet plug. The cytosolic portion of the glycoprotein IIb/IIIa complex stimulates actin rearrangement resulting in platelet spreading, aggregation, and clot retraction. Glycoprotein IIb/IIIa receptor antagonists are powerful antiplatelet drugs and will be discussed in detail later in this chapter.²⁻⁴

Activated platelets secrete substances from their granules, which stimulate further activation and aggregation. These mediators include, but are not limited to, adenosine diphosphate (ADP), thromboxane A₂, fibrinogen, fibronectin, and thrombospondin. There are at least two receptors that bind ADP: P2Y₁₂ and P2Y₁. The thienopyridine drugs prasugrel, clopidogrel, and ticlopidine block the P2Y₁₂ receptor. Thromboxane A₂ is an arachidonic-acid metabolite and a strong platelet stimulator. The production of thromboxane A₂ depends on the cyclo-oxygenase pathway, which is irreversibly inhibited by acetyl salicylic acid or aspirin (see Fig. 37-1).²⁻⁴ It should be noted that the aforementioned steps of adhesion, aggregation, and secretion do not occur in a stepwise fashion, but are presented that way for simplicity. In reality, these processes occur simultaneously and much work is still needed to better define targets for future antiplatelet drugs.

Antiplatelet Therapy for Unstable Angina and Non-STEMI

As previously described, the first step in the process of coronary thrombus formation involves platelet activation and aggregation. Therefore antiplatelet therapy is the cornerstone of treatment in UA and NSTEMI. Numerous clinical trials have established that appropriate antiplatelet therapy in UA and NSTEMI reduces mortality and other ischemic events. When antiplatelet therapy is used in the coronary care unit (CCU), it is imperative that physicians ensure their patients are receiving these agents at

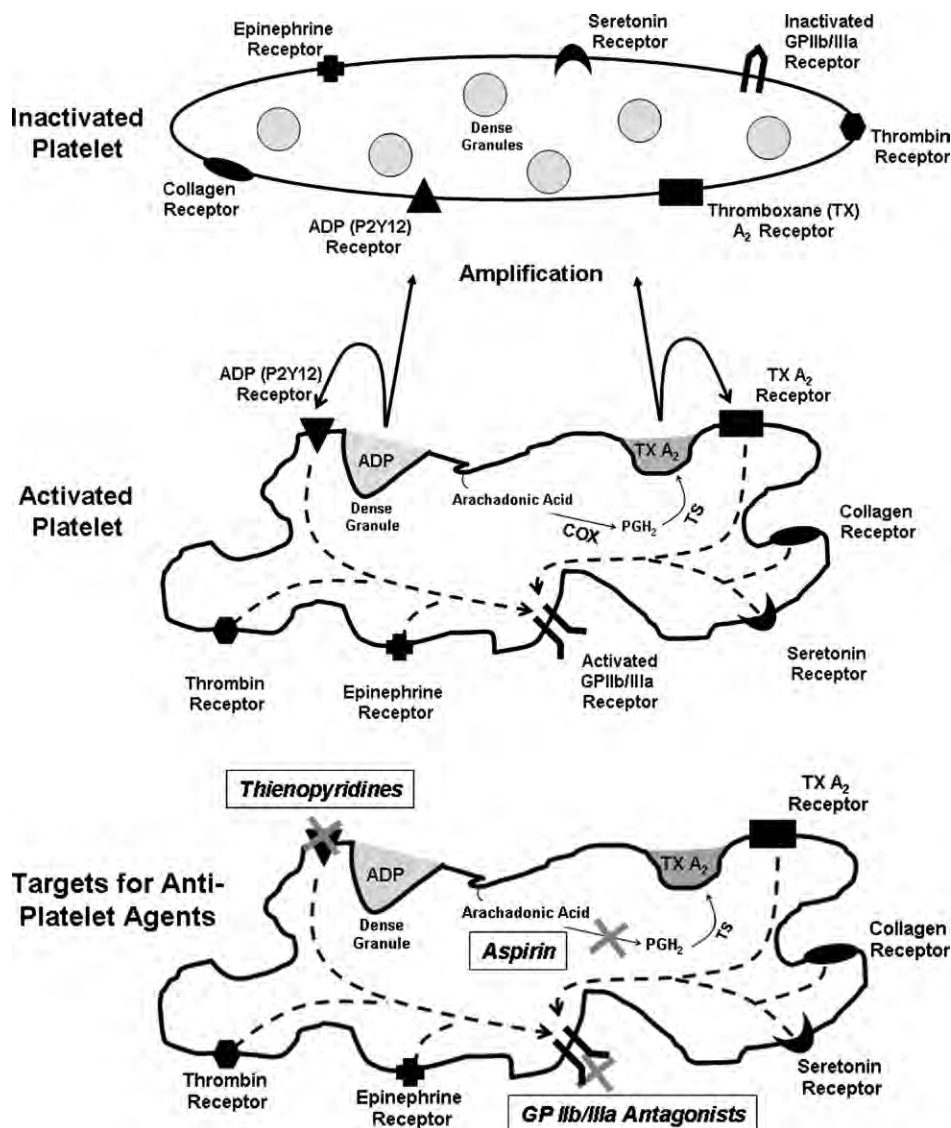


Figure 37-1. In the inactive state, the platelet is rich with membrane receptors and contains dense granules (*top panel*). When the membrane receptors are stimulated, the platelet is activated (*middle panel*), leading to morphologic changes and a cascade of events, which result in deformational change and activation of the final common pathway of platelet activation: the glycoprotein (GP) IIb/IIIa receptor complex. Activation of that receptor leads to binding of fibrinogen, aggregation of platelets, and formation of a platelet-rich thrombus. The *bottom panel* shows the sites of action of the most commonly used platelet inhibitors in clinical practice. Aspirin inhibits the cyclooxygenase enzyme and reduces formation of thromboxane A₂ (TXA₂), thienopyridines irreversibly inhibit the P2Y₁₂ receptor, and GP IIb/IIIa inhibitors inhibit the activated IIb/IIIa receptor. ADP, adenosine diphosphate; PGH₂, prostaglandin H₂.

the appropriate dosages and cautiously watch for side effects, namely bleeding and hematologic abnormalities.

Acetyl Salicylic Acid (ASA or Aspirin)

The importance of effective and early use of aspirin in acute coronary syndromes has been a well-established management strategy for decades. Fortunately, the awareness of this fact among the public and health care professionals encountering these patients is very high. In many instances, patients reach for aspirin as they are calling emergency medical services for acute onset chest pain. The dispatchers receiving the calls instruct the patient to use aspirin if they have it available and the paramedics immediately provide it upon arrival to the scene. For those who

did not receive it, almost all patients with chest pain are given aspirin in the emergency department.

When aspirin is given acutely as a tablet, it should be chewed to achieve rapid platelet inhibition within approximately 20 minutes. Aspirin blocks the production of thromboxane A₂ by irreversibly acetylating a serine residue on cyclo-oxygenase 1. This prevents the conversion of arachidonic acid to prostaglandin-H₂, a precursor of thromboxane A₂. Thromboxane A₂ causes vasoconstriction and platelet aggregation.⁷ Unless there is a well-documented severe allergic reaction, all patients with acute coronary syndrome should be treated with aspirin.

The benefit of aspirin in unstable angina has been demonstrated in several trials. In the Veterans Administration Cooperative

Trial, 1266 men with unstable angina were randomized to receive either aspirin or placebo. The primary end points were death and myocardial infarction (MI). The incidence of death or acute MI was reduced by 51% in the aspirin group (5.0% versus 10.1%, $p = 0.0005$). Examined individually, both nonfatal acute MI and death were dramatically reduced by more than 50% in the aspirin group, although the reduction in death did not quite reach the level of statistical significance (3.4% versus 6.9%, $p = 0.005$ for acute MI and 1.6% versus 3.3%, $p = 0.054$).⁸ Further conformation for the benefit of aspirin was provided in the Canadian multicenter trial where 555 unstable angina patients were randomized to aspirin, sulfinpyrazone, both, or neither. In those randomized to aspirin, there was a significant risk reduction of 51% in combined end points of death and nonfatal MI ($p = 0.008$).⁹ Individual end points of both death and nonfatal myocardial infarction reached statistical significance. Sulfinpyrazone showed no clinical benefit in this trial. Further trials in patients with unstable angina continued to demonstrate a significant reduction in event rates in those receiving aspirin therapy.¹⁰

Despite the extensive body of literature describing the benefits of aspirin, little is known about the most effective dose. As little as 30 mg/day chronically can completely inhibit serum TXB₂ production,¹¹ and many studies suggest equal benefit with doses less than 150 mg daily compared to higher doses when taken long-term (Fig. 37-2).¹² For instance, in 3131 patients with minor stroke or CVA, 30 mg of aspirin daily was just as effective as 283 mg daily in preventing death from vascular causes, nonfatal stroke, or nonfatal myocardial infarction.¹³ Many large, blinded, controlled trials in addition to several meta-analyses of placebo-controlled trials have evaluated the optimal aspirin dose in treating patients with nearly every clinical manifestation of atherosclerosis including stroke, transient ischemic attack (TIA), percutaneous coronary and peripheral interventions, carotid endarterectomy, and myocardial infarctions. In all of these trials, there is no relationship between increasing aspirin dosage and improved clinical efficacy¹² (Table 37-1, see Fig. 37-2).

Although only 30 mg/day of aspirin is needed to inactivate thromboxane production, the rapidity of platelet inactivation should also be considered in the context of ACS. In a small study involving 18 healthy volunteers, chewing 162 mg and 324 mg of aspirin resulted in maximal inhibition of TXA₂ within 15 minutes. This was not seen with the 81 mg dose.²⁴ When comparing 162 mg aspirin with 325 mg aspirin, both doses seem equally effective in lowering mortality in patients with an STEMI, however, recent data suggests that the 162 mg dose is associated with fewer episodes of bleeding. This was noted in a recent study where acute mortality and bleeding risk was evaluated in fibrinolytic-treated STEMI patients. Data was obtained from the GUSTO I and GUSTO III trials. After adjustment, aspirin dose (162 mg versus 325 mg) was not associated with 24-hour, 7-day, or 30-day mortality rates. There was also no noted difference in MI between the two groups. However, in-hospital moderate/severe bleeding occurred in 9.3% of those treated with 325 mg versus 12.2% among those receiving 162 mg ($p < 0.001$). After adjustment, 325 mg was associated with a significant increase in moderate/severe bleeding (OR, 1.14; 95% CI, 1.05 to 1.24; $p = 0.003$).²⁵

To assess the effect of aspirin dosage on number and severity of bleeding episodes, data from 31 trials including

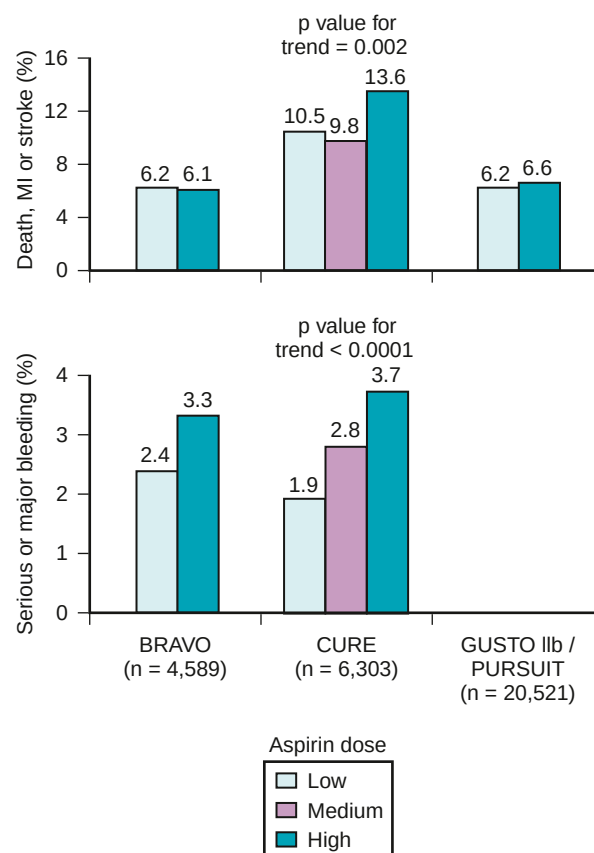


Figure 37-2. Efficacy and safety of various aspirin doses in acute coronary syndrome. In the control arms of three large randomized trials examining the role of various antiplatelet agents in which aspirin was the sole antiplatelet agent, there was no evidence of any reduction in major ischemic events with increasing doses of aspirin (top graph). There is a clear trend, however, toward increasing bleeding complications with increasing aspirin dose (bottom graph). The definitions of the composite efficacy end points and the definitions of major or serious bleeding varied among the trials. MI, myocardial infarction. (Data from Campbell CL, Smyth S, Montalescot G, et al: Aspirin dose for the prevention of cardiovascular disease: a systematic review. *JAMA* 2007;297:2018-2024; figure courtesy of Charles Campbell, MD, University of Kentucky.)

192,036 patients was analyzed. The dosage of aspirin was compared with bleeding complications and these data were divided into several categories, including major bleeding, minor bleeding, gastrointestinal, stroke, fatal/life-threatening, and total bleeding episodes. In all of the aforementioned categories, aspirin doses higher than 100 mg/day were associated with significantly more events.²⁶

The ACC/AHA guidelines for treatment of UA/NSTEMI give aspirin a class IA recommendation for immediate and indefinite use in this patient population.²⁷ According to these recommendations, 162 to 325 mg should be administered once ACS is suspected. In patients who do not receive a stent, the first dose should be followed by 75 to 162 mg/day indefinitely. The same daily aspirin dose is recommended in patients who receive stents except during months following stent placement where the aspirin dose should be higher. In patients receiving a bare metal stent, 162 to 325 mg/day is recommended

Table 37–1. The Effect of Different Doses of Aspirin on Clinical Outcomes

Source	Study Population	Clinical End Point	Mean Follow-Up	Aspirin Dosages (Number of Patients)	Event Rate
1. UK-TIA Trial ¹⁴	TIA or minor stroke	Vascular death, MI or major stroke	4 yr	Placebo (N = 814) 300 mg daily (N = 806) 600 mg q12h (N = 815)	22.9% 20.1% 19.9%
2. Dutch TIA Trial ¹³	TIA or minor stroke	Vascular death, MI or stroke	2.6 yr	30 mg daily (N = 1555) 283 mg daily (N = 1576)	14.7% 15.2%
3. Taylor et al ¹⁵	Scheduled for CEA	Death, MI or stroke	3 mo	81 mg or 325 mg daily (N = 1417) 325 mg or 650 mg q12h (N = 1432)	6.2% 8.4%
4. Cottbus reinfarction study ¹⁶	Following acute MI	Death or reinfarction	2 yr	30 mg daily (N = 179) 60 mg daily (N = 245) 1000 mg daily (N = 277)	7.3/6.7% * 8.7/8.2% * 11.2/15.9%
5. Husted et al ¹⁷	Acute MI	Cardiac death or MI	3 mo	Placebo (N = 97) 100 mg daily (N = 99) 1000 mg daily (N = 97)	20.6% 15.1% 23.7%
6. Lee et al ¹⁸	TIA, RIND, or ischemic stroke	TIA, stroke or MI	24 mo	100 mg daily (N = 145) 300 mg daily (N = 138)	7.5% 10.8%
7. Minar et al ¹⁹	Peripheral angioplasty	Death	24 mo	100 mg daily (N = 109) 1000 mg daily (N = 107)	12.3% 13.4%
8. O'Connor et al ²⁰	Following lytic Rx for acute MI	Death	In hospital	81 mg daily (N = 79) 325 mg daily (N = 83)	1.3% 4.8%
9. Peters et al ²¹	Non-STEMI ACS	Cardiovascular death, MI or stroke	9 mo	75-100 mg daily (N = 2695) 101-199 mg daily (N = 1525) 200-325 mg daily (N = 2071)	10.5% 9.8% 13.6%
10. Topol et al ²²	Recent MI, TIA, stroke or >1 vascular bed	Death, MI or stroke	1 yr	75-162 mg daily (N = 2410) 162-325 mg daily (N = 2179)	6.2% 6.1%
11. Quinn et al ²³	ACS	Death, MI or stroke	Discharge to 6 mo	≤150 mg daily (N = 6128) >150 mg daily (N = 14341)	6.2% 6.6%

*Reinfarction was significantly reduced in patients receiving 30-60 mg of ASA versus those receiving 1000 mg (p <0.01).

1-8: prospective trials, 9-11: retrospective observational results from the ASA alone arms of trials

Abbreviations: TIA, transient ischemic attack; CEA, carotid endarterectomy; RIND, reversible ischemic neurologic deficit; MI, myocardial infarction; ACE, ASA carotid endarterectomy.

for the first month after stenting. In patients who receive a drug eluting stent, 162 to 325 mg/day for 3 to 6 months is recommended.

Adenosine Diphosphate Receptor Antagonists

The adenosine diphosphate (ADP) receptor antagonists include ticlopidine, clopidogrel, and prasugrel. Both ticlopidine and clopidogrel are effective adjuvants to aspirin therapy in acute coronary syndrome. Prasugrel has just been approved for use in the US and clopidogrel is used more commonly than ticlopidine because of a more favorable side-effect profile and a shorter time to onset of platelet inhibition.

Clopidogrel

The introduction of clopidogrel to the field of ACS management has had a dramatic effect on the algorithms of therapy used all over the world. Clopidogrel has been found to be as effective, if not more effective, than aspirin when used in secondary

prevention of vascular events. This was demonstrated in the CAPRIE trial where 19,185 patients with recent ischemic stroke, recent MI, or symptomatic peripheral arterial disease were randomized to aspirin (325 mg) or clopidogrel (75 mg) and followed for 1 to 3 years. Patients assigned to receive clopidogrel had a statistically significant relative-risk reduction in the composite outcome of ischemic stroke, MI, or vascular death when compared with aspirin.²⁸ There was no significant difference in side effects between the two treatment groups.

The typical daily dose of clopidogrel is 75 mg daily. In circumstances when rapid platelet inhibition is desired such as ACS, a loading dose of clopidogrel at 300 or 600 mg can be given and has demonstrated additional antiplatelet aggregation properties when compared with aspirin alone.^{29,30}

When added to aspirin in patients with UA/NSTEMI, clopidogrel offers additional reduction in vascular events and death, as established in the CURE study.³¹ The study randomized 12,562 patients having an NSTEMI (defined by clinical symptoms plus

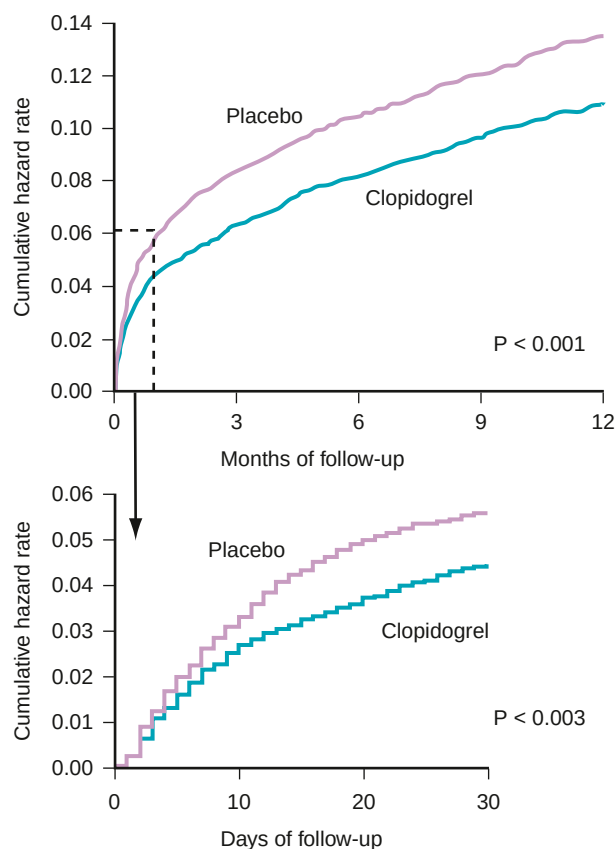


Figure 37-3. Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial. Compared with placebo, the addition of clopidogrel to aspirin and other standard therapeutics used to treat patients with acute coronary syndrome resulted in a statistically significant reduction in major adverse cardiovascular events over a 9 months follow up period (upper graph). The differences between the groups were evident within the first 30 days (bottom graph). (Data from Yusuf S, Zhao F, Mehta SR, et al: Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;345:494-502.)

elevated cardiac enzymes or electrocardiographic changes) to receive aspirin plus clopidogrel versus aspirin plus a placebo. The study was designed to examine two primary outcomes: the first was a composite of cardiovascular death, MI, or stroke and the second consisted of the first primary outcome plus refractory ischemia. At 9 months, patients receiving aspirin plus clopidogrel had a statistically significant reduction in the first primary outcome (9.3% versus 11.4%, $p < 0.001$) (Fig. 37-3). Similarly, clopidogrel was associated with a statistically significant reduction in the second primary outcome (16.5% versus 18.8%, $p < 0.001$).³¹

Several observations solidified the role of clopidogrel in management of this patient population. The benefit appeared within 24 hours of presentation and was seen irrespective of the baseline risk stratification.³² Additionally, the continuation of clopidogrel after hospitalization in this group of patients further reduced subsequent ischemic vascular events (cardiovascular death, MI, or stroke). Moreover, the reduction in vascular events was independent of concomitant use of antiplatelet and antithrombotic medication, antihypertensives, lipid lowering

therapy, or coronary intervention.³³ However, a statistically significant increase in bleeding (based on the CURE definition) was seen in patients on dual antiplatelet therapy.³¹

With most patients with NSTEMI or severe UA being referred to coronary angiography and revascularization early in the course of their admission to the CCU, it is important to clearly define the value of clopidogrel therapy in patients undergoing PCI. The PCI CURE substudy tested the hypothesis that treatment with clopidogrel plus aspirin, before PCI would reduce post-procedure ischemic complications. Additionally, this trial evaluated the efficacy of long-term clopidogrel use along with aspirin in further reducing vascular complications after PCI. Patients were pretreated with aspirin and either clopidogrel or placebo for a median of 6 days before PCI. After stenting, more than 80% of patients were started on open label ticlopidine or clopidogrel for 4 weeks, and then resumed taking placebo or clopidogrel for an additional 8 months. In the clopidogrel arm, the primary outcome of death, MI, or urgent target vessel revascularization within 30 days was significantly reduced (4.5% versus 6.4% in the aspirin alone arm, $p = 0.03$). In patients receiving clopidogrel for at least 8 months, there were fewer events of cardiovascular death, MI, or revascularization from any cause ($p = 0.03$).³⁴

A limitation of PCI CURE was that patients were treated with clopidogrel for an average of 6 days before PCI. With the more rapid and early invasive strategies for managing NSTEMI and UA patients in the United States, this pretreatment duration is logistically unrealistic. The CREDO trial assessed the utility of clopidogrel loading less than 24 hours before PCI. In this trial, 2116 patients undergoing elective PCI for symptomatic coronary artery disease were randomized to receive clopidogrel 300 mg loading dose or placebo 3 to 24 hours before PCI. Subsequent to PCI, all patients received clopidogrel for an additional 28 days. From day 29 to 12 months, those individuals in the control group received a placebo while those loaded on clopidogrel received an additional 75 mg/day of clopidogrel for 12 months. At 28 days only a nonsignificant trend toward benefit was found with pretreatment with a loading dose compared with no pretreatment and no loading dose. However, in a post hoc analysis, patients who received the clopidogrel loading dose between 6 to 24 hours before PCI had a nearly significant 38.6% relative risk reduction in the composite of death, MI, or urgent target vessel revascularization ($p = 0.051$).³⁵ Further examination of this data revealed that a statistically significant reduction in death, MI, or urgent target vessel revascularization does not actually occur with the 300 mg loading dose unless it is given at least 15 hours before PCI.³⁶

The 600 mg dose has recently been found to inhibit platelets more rapidly and effectively than the 300 mg dose.³⁷⁻³⁹ Clinically, this may translate into fewer short-term ischemic events after PCI. Recently, Cuisset and colleagues demonstrated that patients who received the 600 mg loading dose of clopidogrel before PCI for an NSTEMI had fewer subsequent ischemic events (defined as cardiovascular death, acute or subacute stent thrombosis, recurrent ACS, and stroke) within 1 month, when compared to those receiving a 300 mg loading dose (5% versus 12%; $P = 0.02$).³⁸ These findings were subsequently confirmed in another trial: the ARMYDA-2. In that study, 255 patients scheduled for PCI were randomized to either a 300 mg or 600 mg loading dose of clopidogrel 4 to 8 hours before the procedure. The primary end point was 30-day death, MI, or target

vessel revascularization. Levels of troponin, CK, and CK-MB were measured at baseline, 8 and 24 hours after the intervention. The primary end point was reached in 4% of patients receiving 600 mg and 12% in patients receiving 300 mg clopidogrel ($p = 0.041$). The benefit of the higher loading dose was due to a reduction in periprocedural MI. There was also a significant reduction in peak values of troponin, CK, and CK-MB ($P = 0.038$).⁴⁰

The AHA/ACC guidelines for management of ACS give clopidogrel a class IA indication in patients who cannot take aspirin. If an early invasive strategy is taken, a preprocedural load and maintenance dose of clopidogrel should be given (IA). If an early noninvasive approach is taken, clopidogrel is recommended for at least 1 month (IA) and for up to 1 year if possible (IB). If no intervention is performed and the patient has recurrent symptoms, heart failure, or rhythm disturbances, clopidogrel load and daily maintenance dose can be added to current therapy (IA).²⁷

Ticlopidine

Ticlopidine is given at 250 mg twice daily with platelet inhibition starting within 24 to 48 hours. Ticlopidine is an effective antiplatelet agent in ACS patients and clearly demonstrated a reduction compared with placebo in nonfatal MI and combined end point of vascular death and nonfatal MI.⁴¹ The reduction in nonfatal MI and death was confirmed in a follow-up substudy in patients with angina at rest and with electrocardiographic changes who received the same dose of ticlopidine for 6 months.⁴²

Ticlopidine is prescribed less frequently than clopidogrel because of side effects, including nausea, vomiting, and diarrhea, but the most serious side effects are hematologic. Neutropenia was reported in 2.4% of patients with severe neutropenia in 0.8%. Even more concerning are the rare reported incidences of thrombotic thrombocytopenia purpura (TTP) associated with ticlopidine use.⁴³

The superior safety profile of clopidogrel over ticlopidine was demonstrated in three comparative studies between ticlopidine and clopidogrel in the post-PCI population. The reduced bleeding complications were achieved with no compromise in efficacy of reducing ischemic complications. In the larger randomized trial, 1020 patients were randomized after coronary stenting to a 28-day regimen of either (1) 300-mg clopidogrel loading dose followed by 75 mg daily; (2) 75 mg daily of clopidogrel; or (3) 250 mg twice daily ticlopidine. All patients received 325 mg of aspirin daily. The primary end point included any of the following: major peripheral or bleeding complications, neutropenia, thrombocytopenia, or early discontinuation of study drug. This occurred in 9.1% of the ticlopidine group compared with 4.6% in the combined clopidogrel group (relative risk 0.50; 95% CI 0.31 to 0.81; $p = 0.005$). Ischemic complications (cardiac death, MI, and target lesion revascularization) were low and comparable between treatment groups (0.9% with ticlopidine, 1.5% with 75 mg/day clopidogrel, 1.2% with the clopidogrel loading dose; $p = \text{NS}$ for all comparisons).⁴⁴

These results were supported in two separate studies. In the first, clopidogrel 75 mg daily or ticlopidine 500 mg daily was initiated just after stent placement in 700 patients. All patients were taking aspirin 100 mg. Therapy was continued for 4 weeks. A primary composite end point of ischemic events within 30 days of stent placement (cardiac death, urgent target vessel revascularization, angiographically documented thrombotic stent occlusion or nonfatal MI) was rare and not significantly different between both groups. Primary noncardiac end points

defined as noncardiac death, stroke, severe peripheral vascular or hemorrhagic events, or any events causing discontinuation of the study drug occurred in 16 patients taking clopidogrel and 33 patients taking ticlopidine ($p = 0.01$).⁴⁵ Further confirmation that clopidogrel was as effective as ticlopidine in patients receiving intracoronary stents occurred when 30-day event rates were measured in 500 patients receiving coronary stents that were treated with aspirin and clopidogrel (300 mg loading then 75 mg/day for 14 days) to 827 patients with coronary stents treated with aspirin and ticlopidine (500 mg loading dose and 250 mg twice daily for 14 days). Mortality was 0.4% in clopidogrel patients versus 1.1% in ticlopidine patients; nonfatal MI occurred in 0% versus 0.5%, stent thrombosis in 0.2% versus 0.7%, bypass surgery or repeat angioplasty in 0.4% versus 0.5%, and any event occurred in 0.8% versus 1.6% of patients, respectively ($p = \text{NS}$).⁴⁶

Prasugrel

The newest of the ADP receptor antagonists, prasugrel has recently been approved by the FDA for use in the US. Phase 3 clinical trials suggest it is a more potent platelet inhibitor that may add a new weapon for the treatment of ACS. The loading dose of prasugrel (60 mg) appears more potent than the commonly used 600 mg of clopidogrel. Similarly, the maintenance dose of prasugrel (10 mg) maintains a higher degree of platelet inhibition than a daily dose of 150 mg of clopidogrel.⁴⁷

The largest clinical investigation to date to examine prasugrel was the TIMI-38 or the TRITON trial.⁴⁸ In that study, 13,608 patients with moderate to high risk ACS scheduled for PCI were randomized to receive prasugrel (a 60-mg loading dose and a 10-mg daily maintenance dose) or clopidogrel (a 300-mg loading dose and a 75-mg daily maintenance dose) for 6 to 15 months. All patients received aspirin in addition to thienopyridine therapy. The primary efficacy end point was a composite of cardiovascular death, nonfatal MI, or nonfatal stroke, whereas the key safety end point was major bleeding. There was a statistically significant 19% reduction in the primary end point in the prasugrel group (9.9% versus 12.1%, hazard ratio for prasugrel versus clopidogrel, 0.81; 95% confidence interval [CI], 0.73 to 0.90; $p < 0.001$). The use of prasugrel was also associated with significant reduction in other ischemic complications, such as MI and urgent target-vessel revascularization. Interestingly, there was a significant reduction in stent thrombosis as well (1.1% versus 2.4%, $p < 0.001$).⁴⁸ However, there was a significant concern about the bleeding complications encountered in the TIMI-38 trial. Among patients receiving prasugrel and aspirin, there was a significant increase in the rate of major bleeding complications compared with those receiving clopidogrel (2.4% versus 1.8%, hazard ratio 1.32; 95% CI, 1.03 to 1.68, $p = 0.03$). Even more concerning, a similar statistically significant increase was noted in fatal bleeding (0.4% versus 0.1%; $p = 0.002$).⁴⁸ These findings represent a dilemma for prescribing physicians seeking a balance between improved efficacy, but without an increase in the risk of serious complications.

Glycoprotein IIb/IIIa Receptor Antagonists

Platelet aggregation depends on the glycoprotein IIb/IIIa receptor located on the surface of platelets. Often called the final common pathway, the IIb/IIIa receptor on the activated platelet undergoes a conformational change that allows binding of fibrinogen and vWF, which in turn cross-links with IIb/IIIa receptors on other activated platelets promoting platelet aggregation.

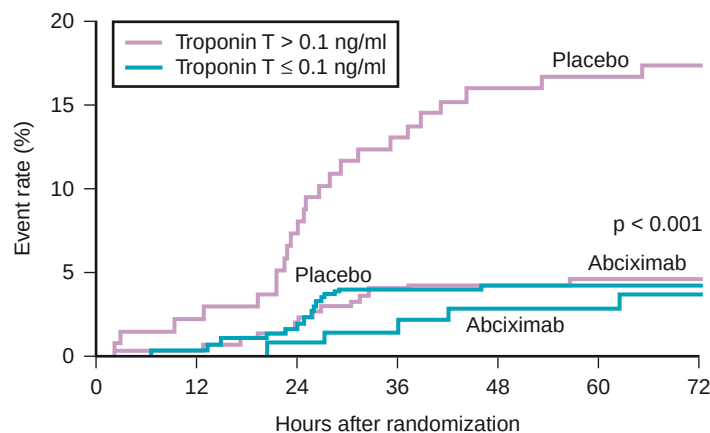


Figure 37-4. Benefit of glycoprotein IIb/IIIa inhibitors and value of troponin in identifying high-risk acute coronary syndrome. In the c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) trial, high-risk acute coronary syndrome patients received abciximab for 18 to 24 hours before percutaneous coronary intervention and only for 1 hour after the procedure. Major adverse cardiac events at 30 days were significantly reduced in the abciximab arm, primarily owing to a reduction in myocardial infarction. The reduction in events conferred by abciximab therapy was significantly more apparent in patients with troponin elevation on presentation (*red line graph*). Although there was a reduction in events with abciximab in the troponin-negative patients (*blue line graph*), that difference was not statistically significant. Differences between abciximab and placebo were noticed within the first 24 hours (i.e., before percutaneous coronary intervention), indicating that the reduction in ischemic events was driven by the intense platelet inhibition. (Data from *Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE Study*. *Lancet* 1997;349:1429-1435.)

The glycoprotein IIb/IIIa receptor antagonists were initially approved as adjunctive pharmacologic agents that reduce the ischemic complications of PCI, particularly in patients at high risk of abrupt closure in the present era. The significant success of these agents in reducing abrupt closure and periprocedural myonecrosis established the importance of aggressive platelet inhibition in reducing ischemic complications. It was only natural that these agents be tested in other clinical situations in which the activated platelets play the fundamental role, namely in acute coronary syndromes. The intravenous IIb/IIIa receptor antagonists available for use in the United States include abciximab, eptifibatide, and tirofiban.

Abciximab

Abciximab was the prototype of all intravenous IIb/IIIa receptor antagonists. It is a chimeric human-murine monoclonal antibody that irreversibly binds to the IIb/IIIa receptor. Abciximab also cross reacts with the $\alpha_v\beta_3$ (vitronectin) receptor.⁴⁹ It has a plasma half-life of approximately 30 minutes and is cleared through the reticulo-endothelial system, but once bound to the platelet it remains nearly irreversibly bound and maintains some IIb/IIIa blockade for up to 10 to 14 days. The dose of abciximab approved for use in conjunction with other antithrombotics in the setting of PCI is a bolus of 0.25 mg/kg 10 to 60 minutes before intervention, and then given as an infusion of 0.125 μ g/kg/min (10 μ g/min maximum) for 12 hours.

Numerous landmark trials have established the value of abciximab as an adjunct to heparin for anticoagulation during PCI. Those trials included both stable and unstable patients.⁵⁰⁻⁵³ In those trials, the benefit of abciximab in reducing major adverse ischemic end points at 30 days (primarily periprocedural MI and urgent revascularization) was achieved with the use of the bolus and a 12-hour infusion regimen. However, in the earlier randomized trial, CAPTURE, abciximab was used in a different regimen, which resulted in some interesting observations.⁵⁴ In

this trial, 1266 patients with high risk ACS (refractory UA and/or NSTEMI) were randomized to a placebo or abciximab given for 18 to 24 hours before intervention and continuing for 1 hour after the procedure. The primary end point (death, MI, or urgent intervention within 30 days of enrollment) was significantly reduced in the abciximab group (11.3% versus 15.9%, $p = 0.012$). The observed difference was mainly because of the reduction in MI (4.1% versus 8.2% in favor of the abciximab group, $p = 0.002$). Interestingly, the benefit of intense antiplatelet therapy was observed within 24 hours, even before revascularization was attempted (Fig. 37-4). Further analysis of the CAPTURE study demonstrated the benefit of intense and early platelet inhibition by abciximab was mostly observed in patients having elevated serum troponin levels (see Fig. 37-3).⁵⁵

In contrast to the aforementioned studies, the GUSTO IV-ACS study evaluated the efficacy of abciximab therapy in patients with chest pain who were troponin positive or had 0.5 mm of ST depression and were not undergoing early revascularization. Somewhat surprisingly, there was no reduction in death or MI at 30 days in patients with ACS receiving abciximab as a bolus plus 24 to 48 hour infusion after presentation. In fact, at 48 hours, a higher rate of mortality was seen in patients receiving abciximab.⁵⁶ This observation (excess mortality with abciximab therapy) remained true after 1 year follow-up in patients having a low troponin or elevated c-reactive protein.⁵⁷ The reason for this excess mortality is unclear. One possibility is that subtherapeutic dosing or insufficient platelet inhibition by IIb/IIIa inhibitors may actually be harmful in patients with higher levels of inflammation.⁵⁸ The antiplatelet effects of abciximab become unpredictable and tend to diminish with time. This was found in a small pharmacodynamic study in 100 patients where platelet function was tested using a rapid platelet function assay (VerifyNow) immediately after an abciximab bolus, 8 hours into a 12-hour abciximab infusion, and 13 to 26 hours after the bolus. After the bolus, abciximab achieved 95% platelet inhibition.

At 8 hours platelet inhibition had decreased to $88 \pm 9\%$ with 13 patients achieving less than 80% inhibition. Between 13 and 26 hours (mean 19), platelet inhibition had dropped to a mean of $71 \pm 14\%$.⁵⁹ This failure to sustain an adequate degree of platelet inhibition may explain the excess mortality in patients receiving 24 to 48 hours of abciximab infusion in the GUSTO IV-ACS study.

In the current era of routine use of thienopyridines and aspirin to treat ACS patients, the question has been raised as to the role of IIb/IIIa antagonists in patients already receiving dual antiplatelet therapy. This question was examined in two clinical trials addressing the role of abciximab with PCI in low- and high-risk patients: ISAR REACT and ISAR REACT II. In ISAR REACT, 2159 patients undergoing elective PCI were randomized to receive abciximab or placebo. All patients received clopidogrel 600 mg 2 hours before the procedure and the composite end point was death, MI, or target vessel revascularization within 30 days. The primary end point was achieved in 4% of patients in both groups, suggesting that abciximab provided no additional benefit in low- to intermediate-risk patients undergoing elective PCI who are pretreated with clopidogrel.⁶⁰ Maximum antiplatelet therapy is desired in patients with ACS undergoing PCI because platelet aggregates can cause microemboli, leading to periprocedural MI and sudden cardiac death. Therefore the benefit of abciximab, when added to clopidogrel, may only be demonstrated in patients having an unstable plaque, as opposed to more stable atherosclerotic disease as seen in the patients studied in ISAR REACT. This hypothesis was tested in the ISAR REACT II trial, which randomized 2022 patients having acute coronary syndromes to receive abciximab or a placebo—after all patients were pretreated with heparin, aspirin, and 600 mg of clopidogrel. Again, the composite end point was death, myocardial infarction, or target vessel revascularization. The target end point was reached in 8.9% of the abciximab group and 11.9% of the placebo group (relative risk 0.75, 95% CI, 0.58 to 0.97; $p = 0.03$). The patients who benefited from abciximab had an elevated troponin, suggesting that abciximab is beneficial only in high-risk patients who already demonstrate evidence of active atherothrombotic disease with distal embolization.

Eptifibatide

Eptifibatide is a cyclic heptapeptide competitive inhibitor of platelet glycoprotein IIb/IIIa. Eptifibatide binding to the IIb/IIIa receptor is reversible and the drug's efficacy is dependent on maintaining a high serum concentration, which allows a steady state of IIb/IIIa receptor blockade. In patients with acute coronary syndrome, eptifibatide is given as a bolus of 180 $\mu\text{g}/\text{kg}$ followed by a continuous infusion of 2 $\mu\text{g}/\text{kg}/\text{min}$. In patients with a creatinine clearance less than 50 mL/minute, the continuous infusion is given as 1 $\mu\text{g}/\text{kg}/\text{min}$. High levels of platelet inhibition occurs within 1 hour, with platelet function normalizing 4 to 8 hours after discontinuation. It is secreted primarily in urine.

The benefit of eptifibatide in patients with acute coronary syndrome was established in the PURSUIT trial. This randomized placebo-controlled trial included 10,948 ACS patients without STEMI. Most patients received aspirin and heparin, and were then randomized to receive a placebo or eptifibatide (intravenous bolus of 180 $\mu\text{g}/\text{kg}$ followed by an infusion at 1.3 or 2.0 $\mu\text{g}/\text{kg}/\text{min}$). The duration of therapy extended to 72 hours (or 96 if intervention occurred later in the hospitalization) or until the

patient left the hospital. The primary end point was a composite of death and nonfatal MI at 30 days. In the eptifibatide group, there was a 1.5% absolute reduction in the incidence of the primary end point (14.2% versus 15.7%, $p = 0.04$), with this effect occurring in most major subgroups.^{43,61} Further investigation of the PURSUIT cohort reveals that eptifibatide reduced the rates of death and MI in patients before and after PCI, in stented and nonstented patients and those who did not undergo PCI, though the reduction in primary events appears greater in patients who had an early PCI.⁶²

Tirofiban

Tirofiban is a small, nonpeptide mimetic of the RGD (Arg-Gly-Asp) sequence of fibrinogen and is another reversible antagonist of the platelet glycoprotein IIb/IIIa receptor. Tirofiban is cleared renally and platelet function returns to normal 4 to 8 hours after discontinuation. In acute coronary syndrome patients, the initial infusion rate is 0.4 $\mu\text{g}/\text{kg}/\text{min}$ for 30 minutes and then continued at 0.1 $\mu\text{g}/\text{kg}/\text{min}$ for 12 to 24 hours after angioplasty.

The RESTORE trial was one of the first randomized, double-blind, placebo-controlled trials examining the role of tirofiban in 2139 patients undergoing PCI within 72 hours of presentation with ACS. Patients were randomized to receive tirofiban or placebo, while both groups were treated with heparin and aspirin. Tirofiban was administered as a bolus of 10 $\mu\text{g}/\text{kg}$ over 30 minutes followed by a 36-hour infusion of 0.15 $\mu\text{g}/\text{kg}/\text{min}$. At 30 days, the primary composite end point (all-cause death, MI, actual or threatened abrupt closure of the target vessel, and surgical or percutaneous revascularization for recurrent ischemia) was reduced from 12.2% in the placebo group to 10.3% in the tirofiban group (16% relative risk reduction, $p = 0.16$). There was a significant relative risk reduction in ischemic events at the 2- and 7-day mark after PCI (38% and 27%, $p = 0.005$ and $p = 0.02$, respectively) because of a reduction in nonfatal MI and the need for repeat angioplasty. However, based on the fact that the study did not meet the 30-day primary end point, tirofiban was not approved for use as an adjunctive agent for PCI.

The role of tirofiban in management of ACS was established in two subsequent studies: a comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina (PRISM) and inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction (PRISM-Plus).^{63,64} In PRISM, 3232 patients with UA or NSTEMI already receiving aspirin received either heparin or tirofiban for 48 hours. In PRISM-Plus, 1915 patients with UA or NSTEMI were randomized to receive tirofiban, heparin, or tirofiban plus heparin for a mean of 71.3 ± 20 hours. The primary composite end point in both studies included death, MI, or refractory ischemia. In PRISM, patients were randomized to either tirofiban alone or heparin alone with patients assigned to tirofiban receiving a loading dose of 0.6 $\mu\text{g}/\text{kg}/\text{min}$ for 30 minutes, followed by 0.15 $\mu\text{g}/\text{kg}/\text{min}$ for 47.5 hours. Angiography and revascularization were typically performed after 48 hours in both studies. In PRISM, the composite end point was 32% lower with tirofiban at 48 hours (3.8% versus 5.6% with heparin; risk ratio 0.67; $p = 0.01$). However, at 30 days the composite end point was the similar in both groups (15.9% in the tirofiban group versus 17.1% in the heparin group, $P = 0.34$). In PRISM-Plus, the frequency of the composite end point at 7 days was lower among patients receiving tirofiban plus heparin than those receiving heparin alone (12.9% versus 17.9%; risk ratio 0.68; $p = 0.004$). The

significantly improved outcomes in the tirofiban plus heparin arm were preserved at 30 days (18.5% versus 22.3%, $p = 0.03$) and at 6 months (27.7% versus 32.1%, $p = 0.02$). Importantly, the third arm of randomization in the study (those receiving tirofiban without heparin) was stopped prematurely because of an excess mortality at 7 days (4.6% compared with 1.1% for patients treated with heparin alone).

Although effective as a class, data suggests that clinical outcomes from the glycoprotein IIb/IIIa receptor blockade may differ between drugs. This was demonstrated in the comparison of two glycoprotein IIb/IIIa inhibitors, tirofiban and abciximab, for the prevention of ischemic events with PCI (TARGET) study.⁶⁵ In TARGET patients received either tirofiban or abciximab before undergoing PCI with stenting. The end point was a composite of death, nonfatal MI, or urgent target vessel revascularization at 30 days. The primary end point occurred more frequently in the tirofiban group than the abciximab group (7.6% versus 6.0%; $p = 0.04$). Each component of the composite end point had similar results (hazard ratio for death, 1.21; hazard ratio for MI, 1.27; and hazard ratio for urgent target vessel revascularization, 1.26), and the difference in the incidence of MI between the tirofiban group and the abciximab group was significant (6.9% versus 5.4%, $p = 0.04$).

The ACC/AHA guidelines for management of patients with UA or NSTEMI who are allocated to an early invasive strategy endorse the use of glycoprotein IIb/IIIa inhibitors, which can be given in addition to aspirin before diagnostic angiography (IA). However, abciximab should be used only if there will be no appreciable delay in angiography and PCI will likely be performed. Otherwise, eptifibatide or tirofiban should be used. If an initial conservative approach is chosen and the patient develops chest pain, heart failure, or arrhythmias, then tirofiban or eptifibatide should be used in addition to aspirin before angiography (IA). Furthermore, if patients are already receiving aspirin, clopidogrel, and an anticoagulant and have a return of ischemic discomfort, it is reasonable to add a glycoprotein IIb/IIIa antagonist before angiography (IIa). For patients undergoing an early invasive strategy, patients can be started on both clopidogrel and glycoprotein IIb/IIIa inhibitors before angiography (IIa). Again, abciximab should be used only if there is no appreciable delay in angiography and PCI is likely to be performed. Additionally, if there is an early conservative approach, it is reasonable to add tirofiban or eptifibatide to oral antiplatelet therapy (IIb).⁷⁷

Antiplatelets in ST Segment Elevation Myocardial Infarction

The paramount importance of early reperfusion in acute ST segment elevation MI as the primary goal of therapy has been well established.⁶⁶ The preferred mechanism by which such reperfusion is achieved has shifted over the years from thrombolytic therapy to primary angioplasty.^{1,67} In either case, patients having acute STEMI usually arrive at the coronary care unit with therapy already administered, either in the emergency room or in the catheterization laboratory.

Although the purpose of antiplatelet therapy in and of itself is not to achieve initial reperfusion in patients with STEMI, there is ample evidence that various antiplatelet agents can play a significant role as adjunctive therapies to improve outcome of the reperfusion therapy.

Although effective in dissolving arterial thrombi, fibrinolytic agents can activate thrombin and promote platelet aggregation, potentially leading to rethrombosis. This procoagulant activity has been demonstrated in several studies. Fibrinopeptide A levels, when used as a measure of thrombin activity, significantly increased after the infusion of both streptokinase and tissue plasminogen activator (tPA) in patients having acute STEMI.⁶⁸ The increased thrombin is thought to be due to upstream activation of coagulation factors because prothrombin levels are also elevated in patients receiving tPA.⁶⁹ More direct evidence of platelet activation with thrombolysis is demonstrated by assessing thromboxane biosynthesis in patients receiving streptokinase after having a STEMI. Major enzymatic metabolites of thromboxane A₂, urinary 2, 3-dinor-thromboxane B₂ and plasma 11-dehydro-thromboxane B₂, were markedly increased in patients that received intravenous streptokinase when compared with patients not receiving thrombolytic therapy. Platelets are the main source of thromboxane A₂, suggesting marked platelet activation after the infusion.⁷⁰ Thus the addition of effective antiplatelet therapy may not lead to patency, but can have a role in preserving the patency of the infarct-related artery that is prone to platelet activation and reocclusion.

Similarly, there is ample evidence for the benefits of antiplatelet agents in the context of PCI. The benefits of adjunctive antiplatelets have been seen in the form of improved flow, reduced embolization, reduced infarct size, and/or improve clinical outcomes.

Aspirin

The benefit of aspirin in the treatment of STEMI was clearly demonstrated in the ISIS-2 trial, in which more than 17,000 patients were randomized to receive an intravenous infusion of streptokinase, 1 month of 160 mg aspirin, both, or neither within 24 hours of a suspected acute MI. Vascular death was significantly reduced in patients receiving aspirin compared with a placebo (9.4% versus 11.8%, $2p < 0.0001$). The reduction in mortality in those receiving aspirin was very similar to patients receiving streptokinase compared with a placebo infusion (9.2% versus 12%, $2p < 0.0001$) (see Fig. 37-5). However, the greatest reduction in mortality occurred when aspirin and streptokinase were used in combination.⁷¹

Aspirin therapy is also proven to prevent reocclusion and recurrent ischemia after thrombolysis. In a meta-analysis of 32 studies that included angiographic assessment after receiving thrombolytic therapy (heparin plus streptokinase or heparin plus recombinant tissue type of plasminogen activator), patients receiving aspirin had a significantly lower rate of reocclusion compared with those who did not receive it (11% versus 25% $p < 0.001$).⁷²

A large meta-analysis of 287 studies including 135,000 patients (approximately 10% with acute STEMI), found antiplatelet therapy (mainly aspirin) resulted in a significant protective value in patients with acute STEMI. After a loading dose of 150 mg during the acute phase, lower doses of 75 to 150 mg daily were found to be effective maintenance therapy. The absolute risk reduction of having a major vascular event (MI, stroke, or vascular death) among patients with acute MI was 38 per 1000 patients treated (or 10.4% in the aspirin-treated group versus 14.2% in the control group; $p < 0.0001$). The absolute risk reduction in patients on antiplatelet therapy (mostly aspirin) compared with the control groups was 13 events per 1000 patients.⁷³

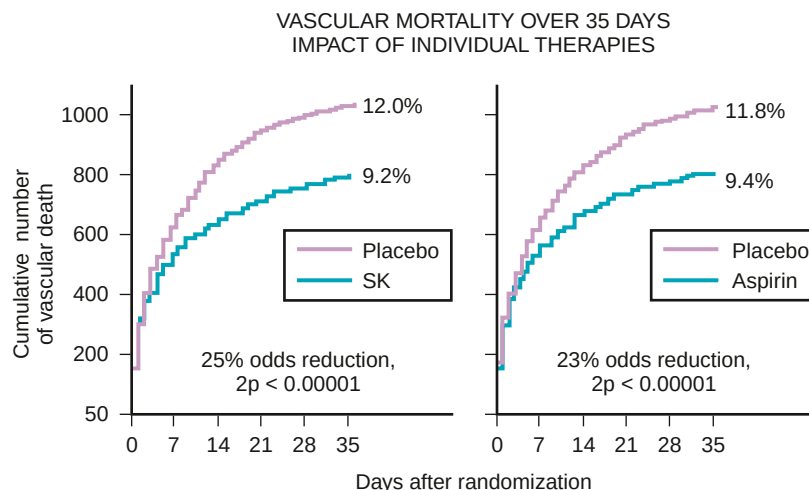


Figure 37-5. In the Second International Study of Infarct Survival (ISIS-2) trial, patients with suspected acute myocardial infarction were randomly assigned in a 2×2 factorial design to receive aspirin versus placebo and streptokinase (SK) versus placebo. A 23% relative reduction in mortality was achieved with aspirin therapy alone, which was almost identical to that achieved with thrombolytic therapy. Patients randomly assigned to aspirin and SK (data not shown) had the best outcomes in this trial. (Data from *Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Lancet 1988;2:349-360.*)

Given the significant mortality benefit demonstrated with aspirin administration, all patients having an STEMI should receive 162 to 325 mg of aspirin, preferably nonenteric coated and in chewable form for faster onset of action. Subsequently, they should continue taking a daily aspirin indefinitely. These recommendations are designated as class IA recommendations by the ACC/AHA guidelines for treatment of STEMI.¹

ADP Receptor Antagonists

Ticlopidine and clopidogrel are considered reasonable alternatives to aspirin in the minority of patients with STEMI who are unable to tolerate aspirin.¹ More importantly, these agents offer additional benefits when used in addition to aspirin in STEMI patients. The benefits of these thienopyridines can be seen in the early phase as adjuvants to the reperfusion strategy (primary angioplasty or thrombolytic therapy) and also as long-term maintenance therapy for more effective prevention of recurrent infarction and other ischemic vascular events.

Two trials have evaluated the role of clopidogrel in addition to aspirin compared with aspirin alone in medically treated STEMI patients: CLARITY-TIMI 28 and COMMIT trials. In CLARITY-TIMI 28, 3491 patients under 75 years of age, with a recent (12 hours) STEMI received a loading dose of clopidogrel (300 mg), then 75 mg daily or a matching placebo after receiving fibrinolytic therapy. All patients received aspirin, and heparin was given when for fibrin-specific thrombolytic agents were used. The composite end point included an occluded infarct-related artery on angiography, death, or recurrent MI before angiography. At the time of angiography, there was a 41% reduction in the incidence of an occluded infarct-related artery in the clopidogrel-treated patients (11.7% versus 18.4% in the aspirin only group, $p < 0.001$). Addition of clopidogrel also resulted in a 30% reduction in recurrent MI (from 3.6% to 2.5%; $p = 0.08$). Similar trends were seen at 30 days.⁷⁴

The COMMIT study included greater than 45,000 patients with an acute MI (87% with ST segment elevation and 6% with

left bundle branch block) not undergoing PCI, who received clopidogrel (75 mg) daily ($n = 22,961$) or a placebo ($n = 22,891$) in addition to aspirin (162 mg) daily until discharge or for up to 28 days (mean therapy of 14.9 days). No loading dose of clopidogrel was given and approximately half of the patients received fibrinolytic therapy before or shortly after enrollment. The primary end point of death alone was significantly reduced in all patients receiving clopidogrel compared with the placebo (1726 events in the clopidogrel group versus 1845 in the placebo group, corresponding to a significant 7% proportional reduction) (Fig. 37-6). Those receiving clopidogrel also had a significant 14% proportional reduction in the risk of reinfarction. There was a nonsignificant 14% proportional reduction in the risk of stroke. Furthermore, when specifically examining those receiving fibrinolytic therapy, there was a significant 11% proportional reduction in events in the fibrinolytic group that received clopidogrel compared with those receiving a placebo.⁷⁵

The combination of clopidogrel and aspirin has been prescribed by clinicians for STEMI patients undergoing primary and rescue PCI for several years. Initially, the rationale was based on extrapolation of the data from the NSTEMI trials demonstrating a reduction in the composite of death, MI, and target vessel revascularization.^{31,35} In addition, the widespread use of stents eventually leads to the near-immediate beginning of dual antiplatelet therapy in those patients. More recently, direct evidence of benefit of clopidogrel in the treatment of STEMI patients emerged from two clinical trials: the PCI-CLARITY trial and the TRITON or TIMI-38 trial.^{48,76}

In PCI-CLARITY, 863 patients undergoing PCI received aspirin and either a clopidogrel 300-mg loading dose, then 75 mg once daily or a placebo initiated with fibrinolysis and given until coronary angiography was performed (2 to 8 days after initiation of the study drug). Open-label clopidogrel with the 300-mg loading dose was recommended for those undergoing coronary stenting. The primary end point was the composite of cardiovascular death, recurrent MI, or stroke from PCI to

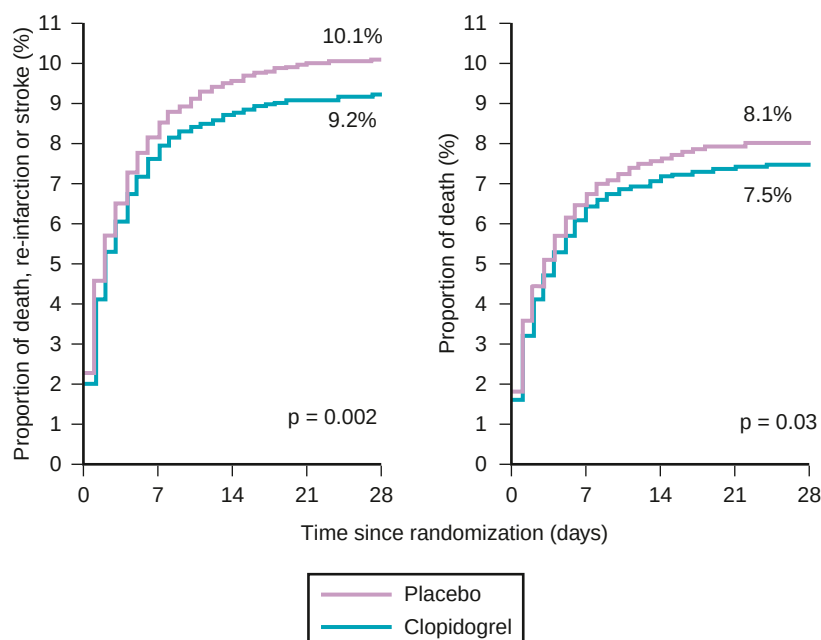


Figure 37-6. The Clopidogrel and Metoprolol in Myocardial Infarction (COMMIT) trial showed that addition of clopidogrel to standard, mostly noninterventional therapy for acute ST segment elevation myocardial infarction results in a significant reduction in the primary end point, all-cause mortality before hospital discharge (*right graph*), and in the composite end point of proportional death, reinfarction, and stroke during the same time period (*left graph*). (Data from Chen ZM, Jiang LX, Chen YP, et al: Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet* 2005;366:1607-1621.)

30 days after randomization. Secondary outcomes included MI or stroke before PCI and the aforementioned composite from randomization to 30 days. Pretreatment with clopidogrel significantly reduced the incidence of cardiovascular death, MI, or stroke following PCI (3.6% versus 6.2%; $p = 0.008$). Pretreatment with clopidogrel also reduced the incidence of MI or stroke before PCI (4.0% versus 6.2%; $p = 0.03$), and there was a highly significant reduction in cardiovascular death, MI, or stroke from randomization through 30 days (7.5% versus 12.0%; $p = 0.001$).

In TRITON, patients having STEMI were not excluded and eventually represented 3534 of 13,608 patients included in the study. Patients scheduled for PCI received prasugrel (a 60-mg loading dose and a 10-mg daily maintenance dose) or clopidogrel (a 300-mg loading dose and a 75-mg daily maintenance dose) for 6 to 15 months. As previously discussed, the study as a whole achieved its primary efficacy end point: a statistically significant reduction in the composite of cardiovascular death, nonfatal MI, or stroke. In the STEMI subgroup, the results were similar with a significant reduction in the primary end point in the prasugrel arm (hazard ratio 0.79; 95% CI, 0.65 to 0.97; $p = 0.02$).

When used as the only antiplatelet agent, ADP receptor antagonists have demonstrated reduction in future vascular events in patients after myocardial infarction. A cumulative review of three studies compared the rate of vascular events (nonfatal MI, nonfatal stroke, and vascular death) in patients receiving at least 1 month of aspirin or ticlopidine, and demonstrated an odds reduction of 10% favoring ticlopidine.⁷⁷

The benefit of ticlopidine in secondary prevention after acute MI was also demonstrated in the STAMI trial, which compared ticlopidine 500 mg/day to aspirin 160 mg/day in 1470 patients after thrombolytic therapy for acute MI. The primary end points

evaluated in STAMI were the first occurrence of fatal and nonfatal MI, fatal and nonfatal stroke, angina with evidence of myocardial ischemia, vascular death, and all cause death within 6 months. There was no significant difference in the number of primary end points between the two groups, and patients taking ticlopidine had fewer nonfatal MI (2.4% versus 1.1%; $p = 0.049$).⁷⁸ Because of safety concerns associated with ticlopidine, clopidogrel is a more attractive option.

Early and sustained use of thienopyridine inhibitors can also have a major role in secondary prevention (i.e., reducing death, reinfarction, and other ischemic vascular events). The CAPRIE trial compared aspirin to clopidogrel in more than 19,000 patients with atherosclerotic vascular disease, including nearly 6,000 patients with recent myocardial infarction (35 days before randomization). After a mean follow-up of 1.9 years, there was no significant difference in stroke, MI, or other vascular death between patients treated with aspirin and those receiving clopidogrel. When other subgroups including patients with recent stroke and peripheral arterial disease were included in the evaluation, patients treated with clopidogrel had a statistically significant greater than 8% relative risk reduction in annual risk of ischemic stroke, MI, or vascular death compared with aspirin.²⁸

Patients with prior MI, ischemic stroke, or peripheral vascular disease were found to have further reduction in recurrent events when clopidogrel was administered in addition (not as a substitute) to aspirin. This was recently demonstrated in a subgroup of 9478 patients from the CHARISMA trial. With a median follow-up of 27.6 months, the rate of cardiovascular death, MI, or stroke was significantly lower when clopidogrel was added to aspirin compared with a placebo plus aspirin: 7.3% versus 8.8% (hazard ratio 0.83, 95% CI 0.72 to 0.96, $p = 0.01$). Hospitalizations for ischemia were also significantly decreased,

11.4% versus 13.2% (hazard ratio 0.86, 95% CI 0.76 to 0.96, $p = 0.008$).⁷⁹

Thienopyridines, specifically clopidogrel, currently has both Class I and Class II recommendations based on the ACC/AHA 2004 guidelines for treatment of STEMI and the 2007 update. A thienopyridine, preferably clopidogrel, should be taken in all patients who cannot take aspirin (Class I). Clopidogrel should be continued for at least 1 month after bare metal stent implantation, several months after drug-eluting stent implantation, and for at least 12 months in patients who are not at high risk for bleeding (Class I). Clopidogrel 75 mg should be added to aspirin therapy in patients with an STEMI regardless of whether they undergo reperfusion therapy with thrombolytics or receive no reperfusion therapy (Class IB). If CABG is planned, clopidogrel should be withheld for at least 5 days (Class IB). In patients less than 75 years of age who receive fibrinolytic therapy or who do not receive reperfusion therapy, it is reasonable to administer an oral loading dose of clopidogrel—300 mg (Class IIA). Long-term maintenance therapy (e.g., 1 year) of clopidogrel, 75 mg daily, is reasonable in STEMI patients regardless of whether they undergo reperfusion therapy with fibrinolytic therapy or do not receive reperfusion therapy.^{1,80}

Glycoprotein IIb/IIIa Inhibitors

Glycoprotein IIb/IIIa inhibitors can be used as adjunctive agents for the primary reperfusion therapy selected to manage an acute STEMI; be that thrombolysis or primary PCI. Most clinical investigations assessing the benefit of IIb/IIIa inhibitors in these situations examined the prototype agent abciximab, with few studies using eptifibatide and tirofiban.

IIb/IIIa Inhibitors and Thrombolytic Therapy

A significant body of literature addresses the role of glycoprotein IIb/IIIa inhibitors when used as adjuvants to thrombolytic therapy. One of the earliest studies was the TIMI 14 trial whereby 888 patients with an STEMI presenting less than 12 hours from symptom onset were treated with full dose (100 mg) of accelerated-dose alteplase (control), full dose abciximab (bolus plus infusion), abciximab in combination with reduced dose alteplase (20 to 65 mg), or abciximab in combination with reduced dose streptokinase (500,000 U to 1.5 MU). The most impressive TIMI 3 flow results were observed in the abciximab plus reduced-dose (50 mg) alteplase: 77% versus 62%; for the full-dose alteplase control group, $p = 0.02$.⁸¹

The initially encouraging results led a series of trials investigating the use of abciximab in conjunction with fibrinolytic therapy: SPEED, ENTIRE-TIMI 23, ASSENT-3, and GUSTO V trials.⁸²⁻⁸⁵ In the ENTIRE-TIMI 23 trial, 483 STEMI patients received full-dose tenecteplase or half-dose tenecteplase plus abciximab. A second randomization to unfractionated heparin or enoxaparin was performed, although doses of both heparin and enoxaparin were lower in the abciximab arm. Compared with those receiving full-dose tenecteplase, patients receiving tenecteplase-abciximab combination therapy had comparable TIMI 3 flow rates at 60 minutes and more complete ST segment resolution at 180 minutes regardless of the type of heparin used. Furthermore, there was a reduction in the rate of recurrent MI, but there were more episodes of increased bleeding. More importantly, the 30-day results demonstrated a significant reduction in combined death and MI in patients receiving full-dose tenecteplase and enoxaparin compared with

unfractionated heparin, and that became the most significant finding of the trial.⁸³

In the ASSENT-3 trial, 6095 patients with an acute STEMI were randomized to one of three regimens: full-dose tenecteplase + enoxaparin for 7 days, full-dose tenecteplase + unfractionated heparin for 48 hours, or half-dose tenecteplase + unfractionated heparin + 12-hour infusion of abciximab. The end points were 30-day mortality, in-hospital reinfarction, or in-hospital refractory ischemia. Safety end points included intracranial hemorrhage or in-hospital major bleeding. There was a significant reduction in the primary end point with enoxaparin and abciximab therapy when compared with conventional full-dose tenecteplase + heparin (11.4% with enoxaparin, 11.1% with abciximab, and 15.4% with full-dose tenecteplase, $p = 0.0002$). The benefits of enoxaparin and abciximab were primarily driven by the reduction in reinfarctions and in refractory ischemia. There was a higher rate of bleeding complications in the abciximab group and a nonsignificant increase in major bleeding complications in the enoxaparin group. There was no statistically significant reduction mortality at the 30-day and the 1-year time points.^{78,84}

The largest trial assessing the efficacy of abciximab with fibrinolytic therapy was the GUSTO V trial, in which 16,588 patients having STEMI within 6 hours were randomized to standard-dose reteplase or half-dose reteplase plus full-dose abciximab. The primary end point was 30-day mortality. The secondary end point was development of MI complications including, but not limited to, reinfarction and recurrent ischemia. At 30 days, there was no difference between the groups in the primary end point (5.9% in the reteplase group versus 5.6% in the combined reteplase and abciximab group, $p = 0.43$). However, there was a significant reduction in the number of MI complications in the group receiving combination therapy ($p < 0.0001$). The reduction in secondary end point with the combined therapy was associated with an increase in nonintracranial bleeding episodes.⁸⁵ The lack of any survival benefit with the combination therapy was also noted at 1 year.⁸⁶

A meta-analysis of the aforementioned studies (ASSENT III, ENTIRE-TIMI 23, and GUSTO V) concluded that the combination of abciximab and thrombolytic therapy had no significant reduction on short-term (30 day) or long-term (6 to 12 month) mortality. Combination therapy did cause a significant reduction in 30-day reinfarction rates. Additionally, the incidence of intracranial bleeding was not different in patients receiving abciximab and thrombolytics, but there was an increased risk of major bleeding complications with combination therapy.⁸⁷

Eptifibatide has also been studied in combination therapy with thrombolytics in patients with an acute STEMI. The INTRO AMI trial evaluated the benefit of adding eptifibatide to tPA versus tPA alone in patients with an STEMI. Similar to the abciximab trials, the incidence of death at 30 days was similar among patients receiving tPA and different regimens of an eptifibatide/tPA combination.⁸⁸

Facilitated PCI (the use of glycoprotein IIb/IIIa inhibitors with or without reduced-dose fibrinolytic therapy followed by PCI) was recently addressed in the 2007 ACC/AHA document on guidelines for management of STEMI and was given a class IIB recommendation. Per these guidelines, facilitated PCI using regimens other than full-dose fibrinolytic therapy might be considered as a reperfusion strategy when all of the following conditions are present: (1) patients are considered at high

risk, (2) PCI is not immediately available within 90 minutes, and (3) bleeding risk is low (young age, absence of poorly controlled hypertension, normal body weight). However, full-dose fibrinolytic therapy followed by planned PCI may be harmful and has a class III indication.⁸⁰

IIB/IIIA Inhibitors and Primary PCI

The use of glycoprotein IIB/IIIA inhibitors in patients undergoing nonemergent PCI has been well studied in numerous randomized trials.^{51,52,54,89} Several lessons were learned from those trials that were used in the subsequent use of those agents during primary PCI. With increasing baseline risk, the advantage of these agents in reducing ischemic complications becomes more robust.^{54,60,90} Other important lessons that came from earlier IIB/IIIA inhibitor trials include modifications in practice that have been shown to reduce bleeding complications, such as weight adjustment of the heparin dose and early removal of femoral access sheaths.

Abciximab is the most well-studied glycoprotein IIB/IIIA inhibitor used in patients receiving primary PCI. The RAPPORT trial was one of the first trials evaluating the potential benefit of abciximab in patients with an STEMI undergoing PCI, in which patients were randomized to receive abciximab ($n = 241$) or a placebo ($n = 242$). There was no difference in the primary efficacy end point of death, reinfarction, or any target vessel revascularization at 6 months. However, abciximab significantly reduced the prespecified end points of death, reinfarction, or urgent target vessel revascularization at 7 days (9.9% versus 3.3%, $p = 0.003$), 30 days (11.2% versus 5.8%, $p = 0.03$), and 6 months (17.8% versus 11.6%, $p = 0.05$). In patients receiving abciximab, at 7 days there was a significant reduction in death or reinfarction: 4.7% versus 1.4%, $p = 0.047$. Additionally, the need for unplanned urgent stenting was reduced by 42% in the abciximab group (20.4% versus 11.9%, $p = 0.008$).⁹¹

The ISAR-2, ADMIRAL, and ACE trials were subsequent trials similar in design and end results.⁹²⁻⁹⁴ In these trials, patients undergoing primary PCI with stenting were randomized to abciximab or placebo. The composite clinical end point was death, reinfarction, and target lesion revascularization, with stroke being included in the ACE trial. In all trials, there was a significant reduction in 30-day ischemic events in patients receiving abciximab after PCI. This benefit was demonstrated up to 6 months in some trials, but none of these trials was individually powered to detect a mortality benefit. In ISAR-2 the composite end point was reached in 5.0% of the abciximab group and 10.5% of the control group ($p = 0.038$). There was no statistically significant difference in the composite end point at 1 year.⁹² In ADMIRAL, the composite end point was reached in 6.0% of the patients in the abciximab group versus 14.6% in the placebo group ($p = 0.01$). At 6 months, the corresponding figures were 7.4% and 15.9% ($p = 0.02$).⁹³ The reduction in the primary end point caused by abciximab use was similar in the ACE trial (4.5% and 10.5%, respectively; $p = 0.023$). Additionally, the composite of 6-month death and reinfarction was lower in the abciximab group than in the placebo group (5.5% and 13.5%, respectively; $p = 0.006$).⁹⁴

The CADILLAC trial was the largest clinical investigation evaluating the role of abciximab in patients undergoing primary PCI.⁹⁵ This trial randomized 2082 patients in a 2-by-2 factorial design whereby patients were allocated to PTCA alone (518 patients), PTCA plus abciximab therapy (528), stenting alone

(512), or stenting plus abciximab therapy (524). The primary end point was death, reinfarction, disabling stroke, and ischemia-driven target vessel revascularization. At 6 months the primary end point was achieved in 20.0% of patients after PTCA, 16.5% after PTCA plus abciximab, 11.5% after stenting, and 10.2% after stenting plus abciximab ($p < 0.001$). The benefit observed with abciximab in CADILLAC was due entirely to differences in the rates of urgent target-vessel revascularization. There were no significant differences in the rates of death, stroke, or reinfarction.⁹⁵ The lack of benefit of abciximab in reducing ischemic events in CADILLAC may have been driven by the relatively low risk of the patient population in this particular study, which was evidenced by the very low mortality (approximately 2%) and reinfarction (approximately 0.8%), irrespective of therapy.

Despite the lack of a 30-day mortality benefit in any of these individual trials, the meta-analysis of De Luca and colleagues that included randomized comparisons of abciximab versus a placebo in both primary and facilitated PCI, demonstrated a statistically significant reduction in 30-day (2.4% versus 3.4%, $p = 0.047$) and 6-month (4.4% versus 6.2%, $p = 0.01$) mortality with abciximab use.⁸⁷ The benefit of abciximab was offset by a significant increase in the risk of bleeding when abciximab therapy was combined with fibrinolysis. However, the risk of bleeding was not increased when abciximab was used with primary PCI (i.e., when no thrombolytic therapy was administered). This led to a statistically significant reduction in adverse ischemic events that was not offset by the bleeding complications (Fig. 37-7). More recently, a large prospective randomized controlled clinical trial (FINESSE) was designed to further define and establish the benefit of abciximab in acute management of STEMI patients.⁹⁶ In that trial, 2452 patients were randomized to one of three treatment arms: primary PCI with abciximab administered in the catheterization laboratory facilitated PCI with abciximab administered before arrival in the catheterization laboratory, and facilitated PCI with abciximab and half-dose reteplase administered before arrival in the catheterization laboratory. The primary end point of the trial was a composite of all-cause mortality, readmission for heart failure, ventricular fibrillation, or cardiogenic shock. At 90 days, there was no difference in efficacy between the treatment arms: the primary end point was met in 10.7%, 10.5%, and 9.8%, respectively ($p = \text{NS}$). There were no differences in rates of death or any of the individual components of the primary end point. The rate of TIMI major bleeding was highest in the facilitated PCI group (4.8%), which was significantly higher than the 2.6% in those receiving primary PCI with abciximab in the catheterization laboratory ($p = 0.025$). There was also a strong trend toward increased intracranial hemorrhage through discharge or day 7 of treatment. Although the full report of the trial results is still not published, it does appear that it provides more evidence against the use of the combination of IIB/IIIA inhibitors and thrombolytic agents. It also raises questions about the importance of early administration of abciximab and seems to suggest that there is no clear clinical benefit from early compared to catheterization laboratory administration of abciximab for primary PCI.

There is significantly less data on the benefit of small molecule IIB/IIIA inhibitors in primary PCI. Many laboratories have been using eptifibatide as a cheaper substitute for abciximab in the context of primary PCI, although the data supporting that approach have been very scarce and not well controlled.^{97,98} More recently, two publications lent some credence to this

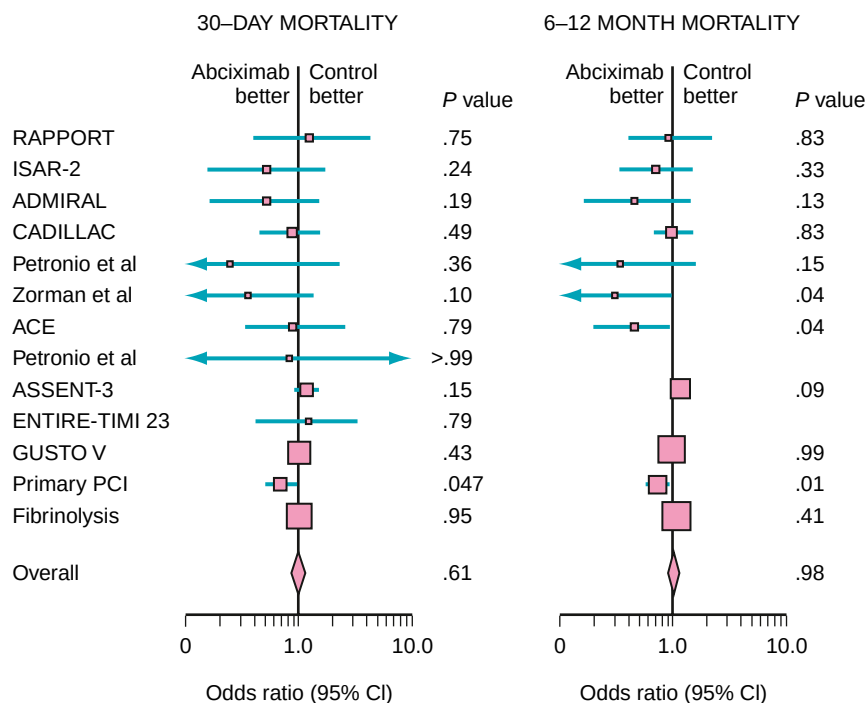


Figure 37-7. In a meta-analysis of 11 randomized trials comparing abciximab with placebo as an adjunct to mechanical or pharmacologic reperfusion of ST segment elevation myocardial infarction, abciximab was associated with a significant reduction in short-term (30 days) mortality (*left plot*) and long-term (6 to 12 months) mortality (*right plot*) in patients undergoing primary PCI, but not in patients treated with fibrinolysis or in all trials combined. (Data from De Luca G, Suryapranata H, Stone GW, et al: *Abciximab as adjunctive therapy to reperfusion in acute ST-segment elevation myocardial infarction: a meta-analysis of randomized trials*. *JAMA* 2005;293:1759-1765.)

approach by demonstrating noninferior outcomes with eptifibatide compared with abciximab. In a retrospective analysis of hospital outcomes from a statewide database of primary PCI over 4 years, 3541 patients who underwent primary PCI for STEMI were treated with abciximab ($n = 729$) or with eptifibatide ($n = 2,812$). There was no difference in the incidence of hospital death (4.1% versus 3.5%, $p = 0.39$), recurrent MI (0.8% versus 1.2%, $p = 0.42$), or stroke (0.7% versus 0.6%, $p = 0.80$). As for safety measures, there was no difference in the need for blood transfusion (12.4% versus 11.7%, $p = 0.61$), but the incidence of gastrointestinal bleeding was significantly higher with abciximab (4.8% versus 2.8%, $p = 0.01$). Even with parsimonious risk-adjusted models, no significant difference between abciximab and eptifibatide in efficacy and safety measures could be identified.⁹⁹ In a more recent smaller but prospective and randomized trial, 400 STEMI patients were randomized to a double bolus plus 24-hour infusion of eptifibatide or a single bolus plus 12-hour infusion of abciximab. All patients received aspirin, clopidogrel, and heparin or enoxaparin. Because of the small number of randomized patients, the primary end point was the surrogate of ST resolution 1 hour post-PCI. Using this end point, the eptifibatide strategy was noninferior compared with abciximab. In addition, in-hospital events, including death, reinfarction, heart failure, and target vessel revascularization were similar between the two groups. Major and minor bleeding rates were not different between the two strategies, although the 24-hour infusion of eptifibatide may have contributed to an increased bleeding risk in the eptifibatide strategy.¹⁰⁰

Some evidence of benefit of tirofiban in primary PCI was also demonstrated in a small study of 100 patients, in whom large

bolus-dose tirofiban was compared with abciximab. Because of the small size, the study used the surrogate primary end point of change in the infarct-zone wall motion between the initial and 30-day follow-up echocardiograms. Secondary end points included before and after TIMI grade flow, TIMI grade myocardial perfusion, and corrected TIMI frame count. In all primary and secondary end points, there was no statistically significant differences between the abciximab and tirofiban patients.¹⁰¹ More recently, a prospective randomized trial was conducted to evaluate the potential of high dose tirofiban as an adjunct to primary PCI. The MULTISTRATEGY trial was a multicenter, open-label, 2×2 factorial trial of 745 patients having STEMI or new left bundle branch block who were then randomized in a 2×2 factorial design to high-dose bolus tirofiban versus abciximab and a sirolimus-eluting stent versus a bare metal stent implantation. For drug comparison, the primary end point was a 50% ST segment elevation resolution at 90 minutes post-PCI, with a prespecified noninferiority margin of 9% difference (relative risk, 0.89). The results demonstrated an ST segment resolution of 83.6% of patients in the abciximab group versus 85.3% in the high-dose tirofiban group (relative risk 1.02; 97.5% CI, 0.96 to 1.09; $p < 0.001$ for noninferiority). Ischemic and hemorrhagic outcomes were similar in the tirofiban and abciximab groups,¹⁰² although the small size of the study does not definitively rule out a possibility of increased risk of bleeding with high-dose tirofiban.

Despite the aforementioned studies suggesting that all currently used IIB/IIIa inhibitors have comparable benefits when used in primary PCI for STEMI, abciximab has the most evidence supporting its use. Adequately powered comparative trials

would be prohibitively large and expensive to conduct. It is likely that these small prospective trials and retrospective reports from large databases maybe the only data to guide clinicians in this area.¹⁰³ Per the ACC/AHA 2004 guidelines, abciximab should be given as early as possible before primary PCI (Class IIa). Eptifibatide and tirofiban can also be considered before PCI as an alternative to abciximab, but these agents receive a Class IIb indication because of the paucity of data.¹

Antiplatelet Therapy and Bleeding Complications

With dramatic progress in reducing mortality and ischemic complications in patients with acute coronary syndromes, more attention is focused on the increased risk of complications of modern therapy. Potent antiplatelet therapies are by default associated with a risk of bleeding. It is the balance between the reduction in ischemic complications and the incidence and severity of bleeding complications that determines the value and clinical utility of a specific antiplatelet agent. This becomes more of an issue when antiplatelet therapy is used in addition to other antithrombotics and/or fibrinolytic agents. In the CCU, acute coronary syndrome patients in whom one or more of all these agents are used, symptoms and signs of bleeding should be monitored diligently.

The literature on bleeding complications related to antiplatelets, antithrombotics, and/or interventional procedures is quite extensive. However, it is plagued by the lack of uniform methodology in assessing and reporting bleeding complications, which makes it difficult to compare efficacy and safety of each of the agents and/or procedures.

Aspirin

It has been well established that aspirin increases the risk of gastrointestinal hemorrhage; however, this appears to occur with chronic use and not acute therapy. In a meta-analysis of 66,000 patients on chronic aspirin therapy, gastrointestinal hemorrhage occurred in 2.47% of patients taking aspirin compared with 1.42% taking a placebo (odds ratio 1.68; 95% CI 1.51 to 1.88); the number needed to harm was 106 (82 to 140) based on an average of 28 months of therapy.¹⁰⁴ Importantly, however, as demonstrated in the ISIS-2 trial, when used alone in patients with acute MI, aspirin was not associated with an increase in intracerebral hemorrhage or bleeding requiring transfusion.⁷⁰ Nonetheless, it should be emphasized that acute MI patients are rarely treated with aspirin alone.

As previously discussed in this chapter, numerous investigations have demonstrated an increased risk of bleeding with larger doses of aspirin with no clear reduction in ischemic events (see Table 37-1, see Fig. 37-2).^{12,26}

Clopidogrel

Not surprisingly, the combination of aspirin and clopidogrel has been found to increase the likelihood of bleeding. In CURE, major bleeding occurred more frequently in patients receiving clopidogrel compared with a placebo (3.7% versus 2.7%; relative risk, 1.38; $p = 0.001$). There were no increased episodes of life-threatening bleeding requiring surgical intervention or hemorrhagic stroke. The most common cause of bleeding was gastrointestinal hemorrhage and bleeding at arterial puncture sites.³¹

The heightened risk of bleeding becomes a significant issue when and if patients are transferred for surgical revascularization soon after admission with the diagnosis of ACS. At least in the United States, such transfers are usually done within one or a few days and the effect of clopidogrel administered at the time of admission cannot be reversed. Clopidogrel has been found to increase the risk of bleeding in patients undergoing coronary bypass surgery if taken within 5 days of surgery. This was initially demonstrated in CURE, whereby 910 patients who stopped taking clopidogrel at least 5 days before bypass surgery had no increase in bleeding complications (4.4% in patients taking clopidogrel and 5.3% for those taking placebo). However, if clopidogrel was stopped less than 5 days before surgery, the likelihood for bleeding was higher within 7 days after bypass surgery (9.6% clopidogrel versus 6.3% placebo; relative risk, 1.53; $p = 0.06$).

These observations were subsequently confirmed in other studies. When 59 patients received clopidogrel within 7 days of bypass surgery were compared with 165 patients who did not receive clopidogrel, there was a significant increase in chest tube output, blood, platelet, and fresh frozen plasma transfusions, and reoperation.¹⁰⁵ These outcomes were supported in a similar study that subdivided patients into three groups: those receiving clopidogrel within 4 days of bypass surgery, 5 to 8 days of bypass surgery, greater than 8 days, or never. The group receiving clopidogrel within 4 days had greater chest tube losses and more transfusions.¹⁰⁶ Therefore the AHA/ACC guidelines recommend that CABG surgery be postponed, if possible, for at least 5 days after administration of clopidogrel. On clinical grounds, this is not always feasible and many patients still undergo bypass surgery with this 5-day period.¹⁰⁷ It is therefore imperative that there is full communication, understanding, and preparation among the medical and surgical teams caring for such patients in the operating room and the postoperative intensive care unit.

Glycoprotein IIb/IIIa inhibitors

Glycoprotein IIb/IIIa inhibitors have also demonstrated an increased risk of bleeding, although the incidence and severity of such bleeding complications varied from one study to another. In EPILOG, abciximab with standard dose heparin was found to increase minor TIMI bleeding.⁵² However, when using weight-adjusted dosing, in addition to early removal of arterial access sheaths, the increased bleeding risk was eliminated. Based on the lessons learned from EPILOG, heparin dosing and sheath management with abciximab use changed. In ISAR-REACT 2, whereby NSTEMI patients were randomized to receive a 600-mg clopidogrel load, heparin, and either abciximab or placebo, there were no differences in the two groups in neither major nor minor bleeding,⁹⁰ and in the meta-analysis by De Luca and colleagues, abciximab use in management of acute STEMI was not associated with an increased risk of bleeding unless combined with thrombolytic therapy.⁸⁷ Like abciximab, the incidence of bleeding with eptifibatide varied depending on the study. In PUR-SUIT, patients receiving eptifibatide had an increased incidence of bleeding and required more blood transfusions.⁹¹ This is in contrast to IMPACT II where an increased bleeding risk was not established,⁶¹ although this difference was most likely because of the smaller eptifibatide bolus in IMPACT II.

Certain patient populations including women, the elderly, and those with acute renal insufficiency have an increased risk for

bleeding with glycoprotein IIb/IIIa inhibitor therapy. Observations from the CRUSADE registry demonstrated that women treated with glycoprotein IIb/IIIa inhibitors had higher rates of major bleeding compared with men (15.7% versus 7.3%, $p < 0.0001$). Furthermore, when compared with men, women more frequently received excess glycoprotein IIb/IIIa inhibitors (46.4% versus 17.2%, $p < 0.0001$; adjusted OR 3.81, 95% CI 3.39 to 4.27). This excess dosing caused more bleeding in women (OR 1.72, 95% CI 1.30 to 2.28) and men (OR 1.27, 95% CI 0.97 to 1.66); however, bleeding risk attributable to dosing was much higher in women (25.0% versus 4.4%).¹⁰⁸

Elderly patients are also at a higher risk for bleeding. Octogenarians are traditionally excluded from clinical trials assessing the efficacy of glycoprotein IIb/IIIa inhibitors, but are commonly prescribed one of these agents in the context of high-risk ACS and/or high-risk PCI. In a retrospective analysis of 459 patients who received glycoprotein IIb/IIIa inhibitors, the risk of bleeding was increased, with vascular access and gastrointestinal tract representing the most common sources. Events were not always related to a prior history of peptic ulcer disease and/or peripheral vascular disease in this patient population.¹⁰⁹

Patients with renal insufficiency are also known to be at an increased risk of bleeding complications and in-hospital mortality when undergoing PCI. This bleeding risk is increased further with glycoprotein IIb/IIIa inhibitors. In 4158 patients undergoing PCI, use of abciximab showed a trend towards major bleeding in patients with renal insufficiency (OR, 1.18; $p = 0.06$). There was not a significant increase in minor bleeding (OR, 1.01; $p = 0.94$).¹¹⁰ In a smaller retrospective analysis, patients with acute coronary syndrome and renal insufficiency who received any glycoprotein IIb/IIIa inhibitor had an increased risk of major bleeding ($p < 0.001$).¹¹¹

The bleeding complications associated with CABG and glycoprotein IIb/IIIa inhibitor use has been studied far less. Only one such study exists, examining abciximab administration before urgent CABG surgery and the need for platelet transfusions nearly reached statistical significance ($p = 0.059$) but there was no increase in major blood loss or transfusions. However, surgical re-exploration for bleeding occurred in 3% of patients not receiving abciximab compared with 12% who did.¹¹²

Conclusions and Future Directions

Acute arterial thrombosis is one of the world's primary causes of mortality today and antiplatelet agents remain the cornerstone of therapy to treat and prevent these events. Over the last 40 years, through hundreds of trials involving nearly a half-million patients, the benefits of antiplatelet therapies have been identified and the risks highlighted. However, despite their history of such extensive investigation, many unknowns remain. Even with aspirin, a drug that has been available for more than 100 years, there is still debate as to the best dose and a thorough understanding of the actual mechanism behind its surprising clinic benefit remains allusive.

As great as past advances have been in the application of platelet inhibitors to clinical practice, it appears that we have just begun to scratch the surface. The field is poised to advance dramatically over the next 5 to 10 years. A number of new P2Y₁₂ ADP antagonists are in phase 3 testing. Multiple platelet thrombin receptor antagonists are also entering large-scale clinical trials. In addition, agents targeting platelet receptors for novel agonists such

as serotonin, collagen, and thromboxane A₂ are entering clinical testing. At the same time, our knowledge of the biology and physiology of platelets continues to expand and with it will come a number of new agents that target yet unidentified platelet-centered processes that contribute to atherothrombotic disease.

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Inotropic and Vasoactive Agents in the Cardiac Intensive Care Unit

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CHAPTER 38

Sympathomimetic Agents
Phosphodiesterase Inhibitors
Calcium-Sensitizing Agents

Other Parenteral Inotropes
Vasodilators

INOTROPIC AND vasoactive agents often play an important role in the management of hemodynamic instability in the intensive care setting. In this chapter, we discuss the relevant pharmacology and clinical indications for the parenteral inotropic, vasodilator, and vasoconstrictor agents most frequently used in the cardiac intensive care unit.

These agents are used to correct or stabilize hemodynamic function and, therefore, in many cases their proper selection and dosing requires hemodynamic information based on a pulmonary artery catheter, an intra-arterial pressure monitor, and electrocardiographic monitoring (Table 38-1). However, the use of a pulmonary artery catheter did not show benefit in either acute decompensated heart failure patients in the ESCAPE trial¹ or a recent meta-analysis of 13 randomized trials including more than 5000 critically ill patients.² This lack of benefit may result from the absence of effective strategies to use in combination with pulmonary artery catheter information. These studies also demonstrated no increase in mortality or hospitalization associated with pulmonary artery catheter use. Based on the available data, there is no indication for routine use of a pulmonary artery catheter in patients hospitalized with acute decompensated heart failure. Nevertheless, a pulmonary artery catheter may provide valuable information and help guide therapy in specific situations (e.g., patients in whom congestion does not resolve after initial therapy, or in whom the presence of congestion is unclear or associated with worsening renal function).

Sympathomimetic Agents

Dopamine

Dopamine is the immediate precursor of epinephrine and norepinephrine. It has both cardiac and vascular sites of action, depending in part on the dose used^{3,4} (Table 38-2). At low doses (i.e., 1 to 3 $\mu\text{g/kg/min}$), dopamine directly activates dopaminergic receptors in the kidney and splanchnic arteries, thereby causing vasodilation of these beds. The resultant increase in renal blood flow leads to increased urine output and sodium excretion. At moderate doses (i.e., 3 to 8 $\mu\text{g/kg/min}$), dopamine is a weak partial agonist at myocardial β_1 -receptors and causes the release of norepinephrine from sympathetic nerve terminals in the myocardium and vasculature. The direct stimulation of myocardial β -adrenergic receptors exerts positive chronotropic and inotropic effects. The increased release of norepinephrine from nerve terminals (a tyramine-like effect) also contributes to

myocardial stimulation, but in addition may exert a mild vasoconstrictor effect due to stimulation of vascular α -adrenergic receptors. At high doses of dopamine (i.e., 5 to 20 $\mu\text{g/kg/min}$), the effect of peripheral α -adrenergic stimulation predominates, resulting in vasoconstriction in all vascular beds and leading to increases in mean arterial pressure and systemic vascular resistance. At high doses, the vasoconstrictor effect overshadows the dopaminergic vasodilator effects, so that renal blood flow decreases and urine output may decline. However, in patients with acute decompensated heart failure the dose required for improving systemic and renal hemodynamics may be higher (on the order of 4 to 6 $\mu\text{g/kg/min}$) than the usual “low dose” range, leading to the suggestion that severe heart failure may impair the renal effects of dopamine.⁵

Table 38-1. Intravenous Drug Selection in Patients with Elevated Left Heart Filling Pressures and a Reduced Cardiac Output

SVR	Low CO		
	High PCWP		
	HIGH	NORMAL	LOW
Initial Agents	Nitroprusside Nitroglycerin Nesiritide	Nitroprusside Milrinone Dobutamine/ Nitroprusside	Dobutamine Dopamine

Table 38-2. Receptor Activities of Several Sympathomimetic Agents

	Myocardial	Vascular		Dopaminergic
	β_1/β_2	α_1	β_2	
Dobutamine	+++	++	++	0
Dopamine (low dose)	0	0	0	+++
Dopamine (high dose)	+++	+++	0	+++
Isoproterenol	+++	0	+++	0
Norepinephrine	+++	+++	+	0

Given its varying actions, there are several potential uses for dopamine in the cardiac intensive care unit. In patients with decompensated heart failure, dopamine is frequently used at low infusion rates to improve renal function by increasing renal blood flow.^{6,7} Increased water and sodium excretion results in a decrease in right and left ventricular filling pressures. Low dose dopamine is frequently combined with one or more other inotropic (e.g., dobutamine) or vasodilator (e.g., nitroprusside) agents.⁸

In patients with severe compromise of the arterial pressure or frank cardiogenic shock, higher doses of dopamine are used to increase systemic vascular resistance. At these higher doses, the increased left ventricular afterload is partially offset by the positive inotropic action. In addition, when it is necessary to use vasoconstrictor doses of dopamine to manage systemic hypotension in the setting of myocardial failure, it is often useful to add dobutamine to augment the level of positive inotropic support beyond that provided by dopamine alone. When used alone at vasoconstrictor doses in patients with left ventricular failure, dopamine may increase both left and right heart filling pressures⁹ (Fig. 38-1 and Table 38-3). This effect reflects increased left and right ventricular afterload and increased peripheral venoconstriction, the latter causing increased return of venous blood to the heart. To counteract these actions, high dose dopamine is sometimes combined with vasodilators (e.g., nitroglycerin).¹⁰

The inotropic responses to dopamine may be attenuated because of desensitization of the β -adrenergic pathway and depletion of myocardial catecholamine stores, both of which are common in patients with advanced heart failure.^{11,12} Although generally well tolerated at low doses, higher infusion rates of dopamine may result in unwanted sinus tachycardia and/or arrhythmias (supraventricular and ventricular). Other adverse effects of dopamine include digital gangrene in patients with underlying peripheral arterial disease, tissue necrosis at sites of infiltration, and nausea at high doses. Local infiltration may be counteracted by the local injection of the α -adrenergic antagonist phentolamine.

Dobutamine

Dobutamine is a direct-acting synthetic sympathomimetic amine that stimulates β_1 -, β_2 -, and α -adrenergic receptors (see Table 38-2). Clinically, it is available as a racemic mixture in which the (+) enantiomer is both a β_1 - and β_2 -adrenergic receptor agonist and an α -adrenergic receptor competitive antagonist, and the (–) enantiomer is a potent β_1 -adrenergic receptor agonist and an α -adrenergic receptor partial agonist.^{13,14} The net effect of this pharmacologic profile is that dobutamine causes a relatively selective stimulation of β_1 -adrenergic receptors, and accordingly, dobutamine's primary cardiovascular effect is to increase cardiac output by increasing myocardial contractility. This positive inotropic effect is associated with relatively little increase in heart rate. The drug causes modest decreases in left ventricular filling pressure and systemic vascular resistance due to a combination of direct vascular effects and the withdrawal of sympathetic tone¹⁵ (see Table 38-3). Dobutamine also directly improves left ventricular relaxation (positive lusitropic effect) via stimulation of myocardial β -adrenergic receptors.¹⁶ Dobutamine has no effect on dopaminergic receptors and therefore no direct renal vasodilator effect. However, renal blood flow often increases with dobutamine in proportion to the increase in cardiac output.

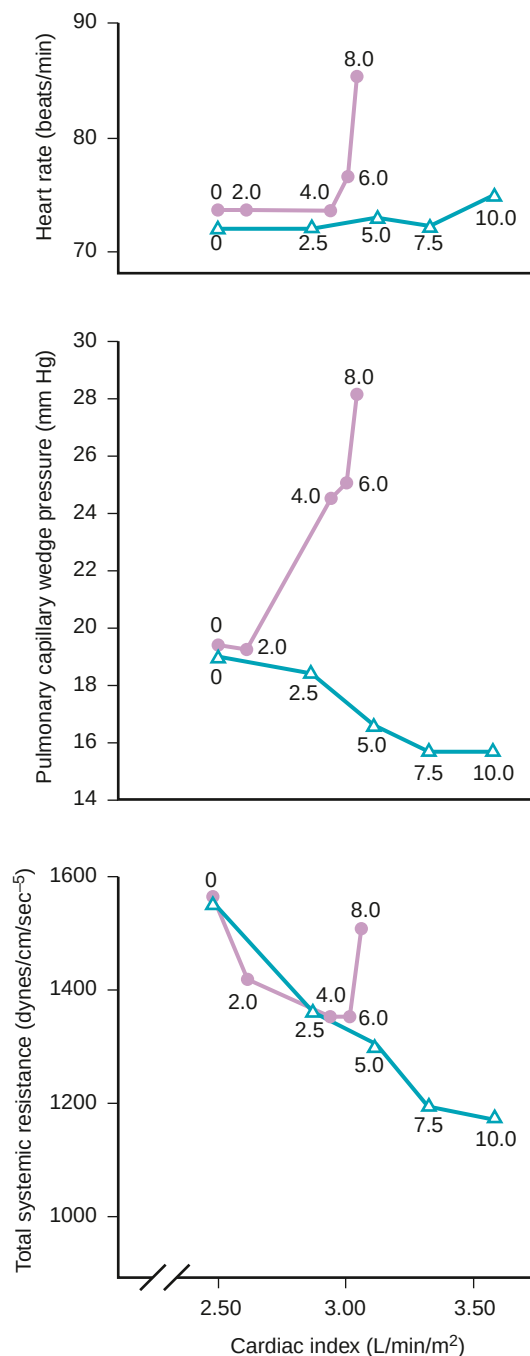


Figure 38-1. Comparative effects of dopamine (●) and dobutamine (Δ) on heart rate, pulmonary capillary wedge pressure, and total systemic resistance in patients with moderate to severe heart failure. Each agent was titrated over the doses shown. These data illustrate that dopamine, when given alone at vasoconstrictor doses to patients with severe heart failure, increases left heart filling pressures. (Adapted from Leier CV: Regional blood flow responses to vasodilators and inotropes in congestive heart failure. *Am J Cardiol* 1988;62:86E.)

Dobutamine is a valuable agent for the initial management of patients with acute or chronic systolic heart failure characterized by a low cardiac output.¹⁷ It is often initiated at an infusion rate of 2 $\mu\text{g/kg/min}$ (without a loading dose) and titrated upward by 1 to 2 $\mu\text{g/kg/min}$ every 15 to 30 minutes until the hemodynamic

Table 38-3. Comparative Hemodynamic Effects of Commonly Used Positive Inotropic Agents

	+ dP/dt	PCWP	SVR	CO
Dobutamine	↑↑	↓	↓	↑
Dopamine (low dose)	↔	↔	↓	↔↑
Dopamine (high dose)	↑↑	↑	↑↑	↑↔↓
Milrinone	↑	↓↓	↓↓	↑↑
Levosimendan	↑	↓↓	↓↓	↑

goal is reached or a dose-limiting event, such as unacceptable tachycardia or arrhythmias, occurs. Maximum effects are usually achieved at a dose of 10 to 15 $\mu\text{g/kg/min}$, although higher infusion rates may occasionally be used. In patients with more severe decompensation, and presumably greater β -adrenergic receptor downregulation, dobutamine can be started at 5 $\mu\text{g/kg/min}$. If the maximum tolerated infusion rate of dobutamine does not result in a sufficient increase in cardiac index, a second drug (e.g., milrinone) may be added.^{8,18} In patients with elevated systemic vascular resistance and/or left heart filling pressures, the co-administration of a vasodilator such as nitroprusside or nitroglycerin may be required. In patients who remain hypotensive on dobutamine, consideration should be given to the addition of a pressor dose of dopamine and/or the use of mechanical circulatory support.

Other clinical situations in which dobutamine is effective include cardiogenic shock complicating acute myocardial infarction, low cardiac output following cardiopulmonary bypass, and as a “bridge” to cardiac transplantation.¹⁹ There is some evidence that short-term or intermittent infusions of dobutamine can result in sustained improvement in hemodynamics and functional status for days or weeks after the infusion is stopped.²⁰⁻²² However, there are limited clinical data to suggest that the intermittent use of dobutamine either has no effect on outcomes²³ or may increase mortality.²⁴ As a result, the administration of dobutamine should be limited to the inpatient setting.

Dobutamine may increase heart rate, thereby limiting the dose that can be infused. However, in some patients with very depressed cardiac output the improvement in hemodynamic function may cause a withdrawal of sympathetic tone such that heart rate falls. Hypotension is uncommon, but can occur in patients who are hypovolemic. Arrhythmias, including supra-ventricular and ventricular tachycardia, may limit the dose. Likewise, myocardial ischemia secondary to increased myocardial oxygen consumption may occur. Some patients with chronic severe heart failure may be tolerant to dobutamine, or tolerance to dobutamine may develop after several days of a continuous infusion.²⁵ In this situation, the addition or substitution of a phosphodiesterase inhibitor may be helpful. Hypersensitivity myocarditis has also been reported with chronic infusions of dobutamine and should be suspected if a patient develops worsening hemodynamics or peripheral eosinophilia.

Isoproterenol

A synthetic sympathomimetic structurally related to epinephrine, isoproterenol is a nonselective β -adrenergic receptor agonist with little or no effect on α -receptors (see Table 38-2).

Its cardiovascular effects include increased myocardial contractility, heart rate, and atrioventricular conduction due to stimulation of myocardial β_1 - and β_2 -adrenergic receptors, and vasodilation of skeletal muscle and pulmonary vasculature due to stimulation of vascular β_2 -adrenergic receptors. Isoproterenol increases cardiac output and lowers both systemic and pulmonary vascular resistance.

Because of its propensity to increase heart rate, isoproterenol has relatively limited applications in the cardiac intensive care unit. However, isoproterenol may be useful in the management of torsades de pointes that is refractory to magnesium,²⁶ inotropic and chronotropic support immediately following cardiac transplant,²⁷ and treatment of pulmonary hypertension secondary to acute pulmonary embolism.²⁸ Isoproterenol is usually administered as a continuous infusion at 0.5 to 5 $\mu\text{g/min}$. The dose of isoproterenol may be limited by tachycardia, increased myocardial oxygen consumption leading to ischemia, and atrial or ventricular arrhythmias.

Epinephrine

Like isoproterenol, epinephrine stimulates β_1 - and β_2 -adrenergic receptors in the myocardium, thereby causing marked positive chronotropic and inotropic responses. Unlike isoproterenol, it also has potent agonist effects at vascular α -adrenergic receptors causing increased arterial and venous constriction. Because of this latter effect, epinephrine (like high-dose dopamine and norepinephrine) plays little role in the acute management of heart failure, except when complicated by severe hypotension. Epinephrine may be useful for the treatment of low cardiac output, with or without bradycardia, immediately following cardiopulmonary bypass or cardiac transplantation.²⁹ Continuous infusions may be started at a low dose (0.5 to 1 $\mu\text{g/min}$), and titrated upwards to 10 $\mu\text{g/min}$, as needed. The use of epinephrine may be limited by tachycardia, arrhythmias, increased myocardial oxygen consumption leading to ischemia, and oliguria from renal vasoconstriction.

In the setting of cardiac arrest, epinephrine may be used as per the Advanced Cardiac Life Support (ACLS) protocol (1 mg intravenous push or via endotracheal tube every 3 to 5 minutes) to manage ventricular fibrillation, pulseless ventricular tachycardia, asystole, or pulseless electrical activity.³⁰ Epinephrine may also be infused at 2 to 10 $\mu\text{g/min}$ to manage symptomatic bradycardia that is unresponsive to atropine, while awaiting placement of an external or temporary transvenous pacemaker.

Norepinephrine

The myocardial and peripheral vascular effects of this endogenous catecholamine are similar to those of epinephrine except that norepinephrine causes little stimulation of vascular β_2 -adrenergic receptors and therefore causes more intense vasoconstriction (see Table 38-2). Norepinephrine may be used to provide temporary circulatory support in the setting of hemodynamically significant hypotension (e.g., following cardiac surgery or with cardiogenic shock complicating acute myocardial infarction or pulmonary embolism). Norepinephrine is titrated to improve blood pressure at doses of 2 to 10 $\mu\text{g/min}$. As with epinephrine, the use of norepinephrine in the cardiac intensive care unit may be limited by arrhythmias, myocardial ischemia, renal impairment, or tissue necrosis at the site of local infiltration. If extravasation occurs, phentolamine 5 to 10 mg may be infiltrated into the affected area.

Phosphodiesterase Inhibitors

The breakdown of cAMP is mediated by a membrane-bound enzyme, phosphodiesterase (PDE). In myocardium and vascular smooth muscle, the predominant isoform of this enzyme, termed type III, is inhibited by the type-III selective PDE inhibitors milrinone and inamrinone, leading to an increase in intracellular cAMP concentrations. In the myocardium, intracellular cAMP increases both contractility and the rate of relaxation (positive lusitropic effect). PDE III inhibitors are also potent vasodilators in the systemic and pulmonary vasculature.³¹⁻³³

In patients with acute decompensated heart failure, type III PDE inhibitors increase cardiac output by increasing stroke volume. Balanced arterial and venous dilation cause decreases in right atrial, pulmonary artery, pulmonary capillary wedge, and mean arterial pressures. Because PDE inhibitors exert both positive inotropic and vasodilator actions, their net hemodynamic effects differ from those of dobutamine and nitroprusside. Thus, for a comparable increase in cardiac output, the PDE inhibitor milrinone decreases systemic vascular resistance and left ventricular filling pressure to a greater extent than dobutamine³⁴ (Fig. 38-2; see Table 38-3). Conversely, for a comparable decrease in arterial blood pressure, milrinone increases cardiac output to a greater extent than nitroprusside³⁵ (Table 38-4).

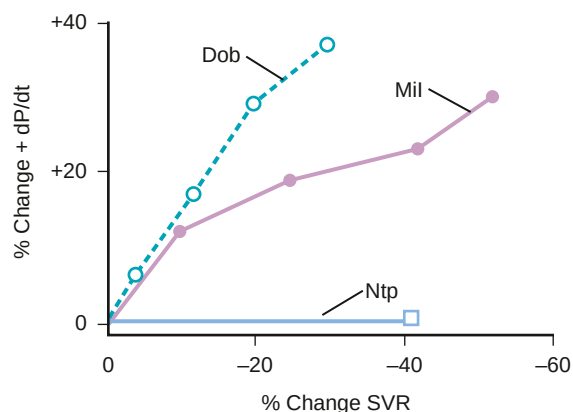


Figure 38-2. The relative effects of dobutamine (Dob), milrinone (Mil), and nitroprusside (Ntp) on left ventricular contractility, as reflected by peak $+dP/dt$, and systemic vascular resistance (SVR) in patients with severe heart failure. (From Colucci WS, Wright RF, Jaski BE, et al: Milrinone and dobutamine in severe heart failure: differing hemodynamic effects and individual patient responsiveness. *Circulation* 1986;73:III-175.)

Table 38-4. Comparative Hemodynamic Effects of Intravenous Vasodilators

	PCWP	SVR	CO
Nitroprusside	↓↓	↓↓	↑
Nitroglycerin	↓↓	↔↓	↑↔↓
Milrinone	↓↓	↓↓	↑↑
Hydralazine	↓	↓↓	↔↑
ACE Inhibitor	↓↓	↓↓	↑
Nesiritide	↓↓	↓↓	↑

PDE inhibitors are used for the treatment of heart failure characterized by low cardiac output, high filling pressures, and elevated or normal systemic vascular resistance. They may also be useful in the management of low cardiac output following cardiopulmonary bypass and as a bridge to mechanical support or cardiac transplant,³⁶ especially in patients tolerant of β -adrenergic agonists. Chronic infusions of milrinone at home have also been used for palliative care in selected patients with end-stage heart failure. The positive inotropic effects of these drugs are additive to those of digoxin and may be synergistic with those of sympathomimetics such as dobutamine^{37,38} (Fig. 38-3).

Milrinone

In patients with heart failure, milrinone is administered as a 25 to 50 $\mu\text{g/kg}$ intravenous bolus over 10 minutes followed by a constant infusion at 0.25 to 0.75 $\mu\text{g/kg/min}$. Lower infusion rates without a bolus may be used in patients with low baseline blood pressure. If a lower bolus dose (i.e., 25 $\mu\text{g/kg}$) is used to initiate therapy and the response is not adequate, a second bolus of 25 $\mu\text{g/kg}$ may be given before increasing the infusion rate. The dose of milrinone tolerated may be limited by tachycardia or tachyarrhythmias. In addition, relatively volume-depleted patients may not tolerate its vasodilator effects and will experience symptomatic hypotension that may necessitate stopping the drug. Thrombocytopenia is rarely seen with milrinone (less than 0.5%). Milrinone has a half-life of 30 to 60 minutes in patients with heart failure. It can be used alone or in combination with other agents (e.g., dobutamine or nitroprusside).

The routine use of milrinone was assessed in a study of 900 patients admitted to the hospital with an exacerbation of heart failure. In this setting, a 48-hour infusion did not reduce the subsequent need for hospitalization and was associated with an increased risk of arrhythmias and sustained hypotension.³⁹

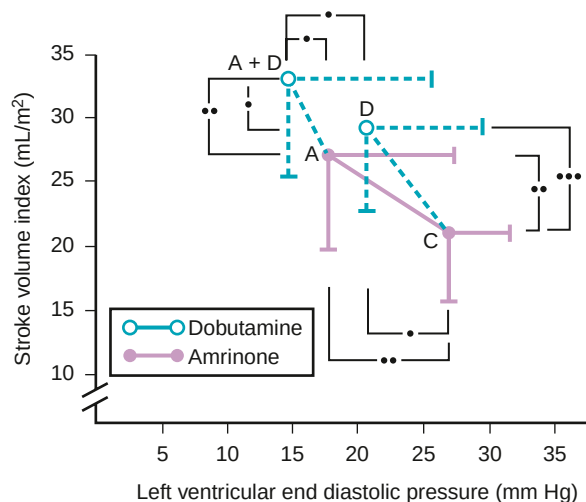


Figure 38-3. Hemodynamic effects of dobutamine (D), amrinone (A), and the combination (A + D) in patients with moderate to severe heart failure. As shown here, the additive effect of the two agents may exceed the effect of either agent alone. C, hemodynamics during the control periods (Adapted from Gage J, Rutman H, Lucido D, LeJemtel TH: Additive effects of dobutamine and amrinone on myocardial contractility and ventricular performance in patients with severe heart failure. *Circulation* 1986;74:367.)

It is important to note that patients requiring inotropic support (with shock or severe hypotension) were excluded from this study. Thus, milrinone, like dobutamine, should be reserved for the short-term management of patients with symptomatic hemodynamic compromise that is not responsive to diuretics and vasodilators. Patients with pulmonary hypertension secondary to chronically elevated left heart filling pressures may be particularly responsive to milrinone.

Inamrinone

Inamrinone is administered as an intravenous bolus of 0.5 to 0.75 mg/kg over 2 to 3 minutes, followed by a continuous infusion at 5 to 10 µg/kg/min titrated to hemodynamic goals. The major dose-limiting effects of inamrinone are similar to milrinone, and include tachycardia, atrial or ventricular arrhythmias, and hypotension. The latter effect is most likely to occur in patients who are hypovolemic. Thrombocytopenia, which is seldom severe, occurs in 2% to 3% of patients. This effect is dose-dependent, occurring with higher doses and/or more prolonged infusions, and appears to be due to decreased platelet survival.⁴⁰ Other adverse effects include liver function abnormalities, headache, and nausea.

Calcium-Sensitizing Agents

Positive inotropic agents, such as dobutamine and milrinone, act by increasing myocyte calcium influx, and therefore may be associated with increased arrhythmias. An alternative approach that may avoid such complications is to enhance myocardial response to a given concentration of calcium with a class of agents referred to as “calcium sensitizers.”⁴¹ Several calcium sensitizers have been studied in heart failure and acute coronary syndromes and most have additional effects such as phosphodiesterase inhibition that may contribute significantly to their clinical profile.

Levosimendan

Levosimendan, the most widely studied calcium sensitizer,⁴² increases myocardial contractility by increasing myofilament sensitivity to calcium. Levosimendan is also a potent vasodilator due to activation of adenosine triphosphate-dependent potassium channels in vascular smooth muscle cells, leading to decreases in both preload and afterload. In patients with severe heart failure, levosimendan increases cardiac output and reduces pulmonary capillary wedge pressure and systemic vascular resistance (see Table 38-3).^{43,44}

The effects of levosimendan are dose-dependent at infusion rates ranging from 0.05 to 0.6 µg/kg/min, with higher incidence of side effects (headache, nausea, and hypotension) at rates above 0.2 µg/kg/min.⁴⁵ Levosimendan is completely metabolized before excretion. Approximately 5% is converted to a highly active metabolite, OR-1896, that exhibits hemodynamic effects similar to those of levosimendan and has an elimination half-life of 75 to 80 hours (compared with 1 hour for levosimendan itself). Because of the long half-life of this active metabolite, hemodynamic effects last for up to 7 to 9 days after discontinuation of a 24-hour infusion of levosimendan.⁴³

Several clinical trials have evaluated the efficacy of levosimendan in patients with acute decompensated heart failure, in comparison with placebo⁴⁶ or dobutamine,^{47,48} and its use is approved in several European and South American countries.

The data from these trials suggest short-term symptomatic benefit with levosimendan in patients with acute decompensated heart failure, but no impact on survival compared with placebo. Levosimendan may be useful in other situations, such as the perioperative and postoperative setting, acute coronary syndromes, and cardiogenic and septic shock.⁴² In addition to positive inotropic effects, levosimendan exerts dose-dependent lusitropic effects in failing hearts.⁴⁹

Other Parenteral Inotropes

Digoxin

Although digoxin can be given intravenously, it is seldom used as a positive inotropic agent in the acute management of heart failure. Digoxin may be useful for the control of a rapid ventricular rate in patients with or without heart failure complicated by atrial fibrillation or atrial flutter.

Vasodilators

For many patients with acute decompensated heart failure characterized hemodynamically by low cardiac output, high filling pressures and elevated systemic vascular resistance and/or clinically by symptomatic congestion with normal or elevated blood pressure, a parenteral vasodilator is the initial agent of choice. As discussed later, intravenous vasodilators can be used alone or in combination with a positive inotropic agent (see Table 38-1).

Nitroprusside

Nitroprusside is a sodium salt consisting of ferricyanide and nitric acid. Its reduction by intracellular glutathione leads to the local production of nitric oxide, which mediates the drug's potent vasodilator effect.⁵⁰ The onset of action is rapid, in 1 to 2 minutes, making it an ideal agent for use in urgent situations which require rapid dose titration and a predictable hemodynamic effect. Nitroprusside is both an arterial and venous dilator and, therefore, it reduces both filling pressures and vascular resistance (systemic and pulmonary). Stroke volume and cardiac output increase, and pulmonary artery, pulmonary capillary wedge, and right atrial pressures decrease (Fig. 38-4). In patients with heart failure, heart rate is generally unchanged or may fall because of reflex sympathetic withdrawal.⁵¹

There are several indications for the use of nitroprusside in the cardiac intensive care unit.⁵² One indication is acute decompensated heart failure manifested by low cardiac output, elevated filling pressures, high systemic vascular resistance, and a systolic blood pressure adequate to maintain vital organ perfusion, usually greater than or equal to 90 mm Hg. This hemodynamic picture is often seen with heart failure in the setting of acute myocardial infarction, acute mitral or aortic regurgitation, and fulminant myocarditis. In acute myocardial infarction, nitroprusside may be particularly useful if the infarction is complicated by significant hypertension, mitral regurgitation secondary to papillary muscle rupture, or rupture of the ventricular septum.⁵³ Acute valvular regurgitation secondary to endocarditis, aortic dissection, or ruptured chordae is another situation in which nitroprusside may be used effectively, often as a “bridge” to more definitive therapy (e.g., valve replacement or repair).⁵⁴ A recent study showed increased cardiac output with nitroprusside administration in patients with severe aortic stenosis and left ventricular dysfunction occurring with severe heart failure,

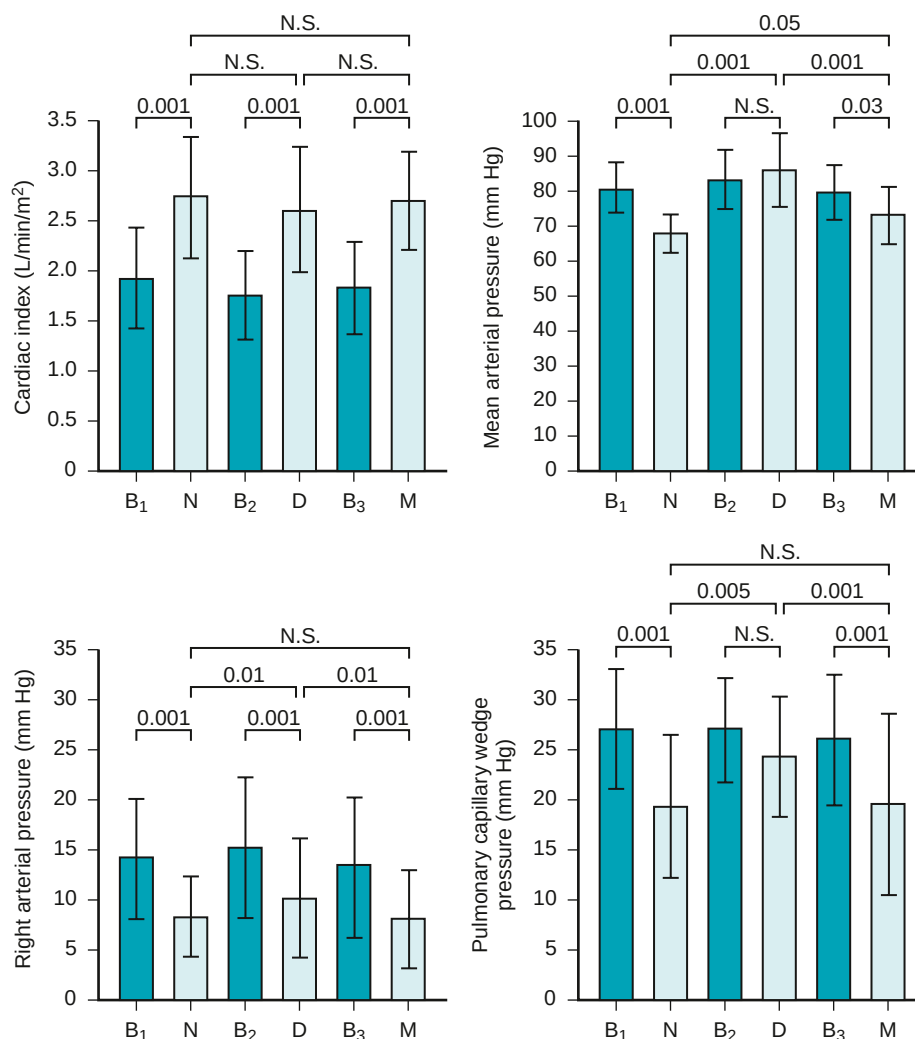


Figure 38-4. The comparative effects of nitroprusside (N), dobutamine (D), and milrinone (M) on cardiac index, mean arterial pressure, right atrial pressure, and pulmonary capillary wedge pressure in patients with severe heart failure.⁷⁹ The agents were administered in doses that caused comparable increases in cardiac index. Under these conditions, nitroprusside and milrinone significantly reduced mean arterial pressure, but dobutamine had no effect. All three agents reduced right atrial pressure, although the effect of dobutamine was less pronounced. Nitroprusside and milrinone significantly reduced pulmonary capillary wedge pressure, and this effect was significantly more pronounced than the effect of dobutamine. B, baseline hemodynamics (Adapted from Monrad ES, Baim DS, Smith HS, Lanoue AS: Milrinone, dobutamine, and nitroprusside: comparative effects on hemodynamics and myocardial energetics in patients with severe congestive heart failure. *Circulation* 1986;73:III-168.)

suggesting it may also be useful in this context as a bridge to aortic valve replacement.⁵⁵

Nitroprusside is also used in patients with chronic heart failure due to dilated cardiomyopathy, both to manage acute decompensation and to determine whether pulmonary hypertension is acutely reversible during the evaluation for cardiac transplantation.^{56,57} Following optimization of hemodynamics with intravenous nitroprusside and diuretic therapy, patients should be titrated on to oral vasodilator/diuretic therapy before discharge. Finally, nitroprusside is often the parenteral agent of choice for treating hypertensive emergencies as it can be rapidly titrated to blood pressure goals.⁵⁸

The infusion of nitroprusside should be guided by close hemodynamic monitoring, ideally with a pulmonary artery catheter and radial or femoral arterial line. Nitroprusside may be started at a rate of 10 to 20 $\mu\text{g}/\text{min}$ (or 0.1 to 0.2 $\mu\text{g}/\text{kg}/\text{min}$) and increased by 20 $\mu\text{g}/\text{min}$ every 5 to 15 minutes until the

hemodynamic goal is achieved (e.g., a systemic vascular resistance of 1000 to 1200 dynes-sec-cm⁻⁵ and a pulmonary capillary wedge pressure of less than or equal to 16 to 18 mm Hg) while maintaining an adequate systolic blood pressure (generally, >80 mm Hg). Doses of 300 $\mu\text{g}/\text{min}$ (5 $\mu\text{g}/\text{kg}/\text{min}$) or higher are seldom required and increase the risk of toxicity.

Nitroprusside is a potent vasodilator and its use may be limited by hypotension. In patients with underlying coronary artery disease, drug-induced hypotension accompanied by reflex tachycardia may worsen myocardial ischemia. In patients with acute decompensated heart failure, hemodynamic deterioration may occur following the withdrawal of nitroprusside, apparently due to a transient “rebound” increase in systemic vascular tone.⁵⁹ Other adverse effects of nitroprusside are due to the accumulation of its metabolites: cyanide and thiocyanate.⁶⁰ The build-up of cyanide results in lactic acidosis and methemoglobinemia, and may manifest itself as nausea, restlessness, and dysphoria.

Cyanide toxicity is most likely to occur in patients with liver dysfunction or following prolonged infusions, but may occur even in patients with normal hepatic function who have received the drug for only a few hours. If cyanide toxicity is suspected, serum levels should be drawn and the infusion stopped. In severe cases, treatment with sodium nitrate, sodium thiosulfate, or vitamin B₁₂ may be necessary. Cyanide is converted in the liver to thiocyanate, which is cleared by the kidney. The half-life of elimination of thiocyanate is 3 to 7 days. Thiocyanate toxicity generally occurs gradually and is manifested by nausea, confusion, weakness, tremor, hyperreflexia and, rarely, coma. Thiocyanate toxicity is more likely to occur in patients with renal dysfunction and with prolonged infusions or high rates of infusion. If mild, it can be managed by cessation of the drug; in severe cases, hemodialysis may be necessary.

Nitroglycerin

When administered parenterally, nitroglycerin has an immediate onset of action and a plasma half-life of 1 to 4 minutes. It is cleared by vascular endothelium, hydrolyzed in the blood, and metabolized in the liver. At lower infusion rates, its main cardiovascular effect is venodilation, with a resultant fall in ventricular volumes and filling pressures. At higher infusion rates, nitroglycerin also causes arterial dilation, resulting in decreases in both pulmonary and systemic vascular resistance⁵¹ (see Table 38-4).

Nitroglycerin plays several important roles in the cardiac intensive care unit.⁵² In the setting of cardiogenic pulmonary edema, especially when due to myocardial ischemia or infarction, nitroglycerin provides immediate symptomatic relief and improves both hemodynamics and oxygen saturation.⁶¹ By causing direct coronary vasodilation, nitroglycerin also has the theoretical advantage of improving myocardial perfusion and limiting infarct size.⁶² Intravenous nitroglycerin is often useful in the management of patients with new onset heart failure or acute decompensation of chronic heart failure, particularly in patients who are refractory to diuretic therapy and continue to manifest elevated right- and left-sided filling pressures, in patients with disproportionate right-sided failure, and in patients in whom nitroprusside is not tolerated.

Intravenous nitroglycerin is usually started at a low infusion rate of 20 to 30 µg/min, and increased by 10 to 20 µg/min every 5 to 10 minutes until the desired response is observed or a dose of 400 µg/min is reached. In patients with acute decompensated heart failure, upward titration should be guided by filling pressures and systemic vascular resistance or, if invasive monitoring is not available, by signs and symptoms of pulmonary and/or systemic venous congestion. While awaiting intravenous access, nitroglycerin can be administered by the sublingual, buccal, or transdermal route.

Use of nitroglycerin may be limited by hypotension, which may require discontinuation of the drug and/or supportive care with intravenous fluids and leg elevation. Other common side effects related to vasodilation include headache, flushing and diaphoresis. Some patients with heart failure will not respond to the acute administration of nitroglycerin.⁶³ This resistance is usually seen in patients with significant right-sided failure and peripheral edema, and often resolves following diuresis.⁶⁴ In addition, patients may develop pharmacologic tolerance to nitroglycerin. Strategies to prevent the development of such tolerance include avoidance of excessive dosing, limiting fluid retention, and the use of intermittent dosing.^{65,66}

Nesiritide

Nesiritide (recombinant human B-type natriuretic peptide) is identical to and mimics the actions of the endogenous BNP molecule. Clinical studies with intravenous infusion of nesiritide in patients with acute decompensated heart failure have shown that it exerts potent, dose-related vasodilator effects that are rapid in onset and sustained for the duration of drug infusion.⁶⁷ Balanced arterial and venous vasodilation is reflected by decreases in systemic vascular resistance, systemic arterial pressure, pulmonary capillary wedge pressure, and right atrial pressure. Vasodilation in the absence of symptomatic hypotension occurs without a change in heart rate and is associated with increases in stroke volume and cardiac output.

Administration of nesiritide in the short-term treatment of decompensated heart failure resulted in dose-dependent reductions in pulmonary capillary wedge pressure and improved clinical status compared with placebo.⁶⁸ When compared with standard vasoactive therapy such as dobutamine, nesiritide produced a similar improvement in clinical status and dyspnea. In another randomized, controlled trial, nesiritide reduced pulmonary capillary wedge pressure significantly more than nitroglycerin, and resulted in a similar improvement in dyspnea and clinical status.⁶⁹

When compared with dobutamine, nesiritide is less likely to cause ventricular arrhythmias and may be associated with clinical benefit, including reduced 6-month mortality and a trend toward lower heart failure readmission rates.^{70,71} However, there has been concern about the possible adverse effects of nesiritide on survival and renal function. Pooled meta-analyses found a trend to increased 30-day mortality and a greater degree of worsening renal function among patients treated with nesiritide.^{72,73}

In general, nesiritide is given as an initial intravenous bolus of 2 µg/kg, followed by a continuous infusion of 0.01 µg/kg/min. For patients with systolic blood pressures between 90 and 100 mm Hg, it is more prudent to initiate nesiritide at a dose of 0.005 µg/kg/min without a bolus. In hypertensive patients or those with marked congestion, the dose may be increased (usually by 0.005 µg/kg/min, preceded by a bolus of 1 µg/kg) if there is no therapeutic response, after 3 to 24 hours, up to a maximum of 0.03 µg/kg/min. The main adverse effect is dose-related hypotension. If it occurs, the infusion should be discontinued and restarted when the blood pressure has stabilized, at a 30% to 50% lower dose without a repeat bolus.

Given the concerns about safety, nesiritide is reserved for patients with severe acute decompensated heart failure who remain dyspneic despite diuretics, and who are not hypotensive or in cardiogenic shock.

Hydralazine

Hydralazine is a potent direct-acting arteriolar smooth muscle dilator that causes both pulmonary and systemic vasodilation. Although nitroprusside and nitroglycerin are generally preferred as parenteral vasodilators in the acute management of heart failure, there are specific situations in which hydralazine given intravenously may be a useful or necessary alternative. In particular, hydralazine may be useful in patients who have become toxic with nitroprusside or continue to have an elevated systemic vascular resistance despite the use of a maximally tolerated dose of nitroprusside or nitroglycerin. In addition, hydralazine may be safely administered to pregnant women with heart failure⁷⁴ or severe hypertension.^{75,76}

When used parenterally, hydralazine should be started at a low dose (5 mg given as an intravenous bolus every 4 to 6 hours), and increased gradually up to 25 to 30 mg, as tolerated. The onset of action is rapid, and the magnitude of the hemodynamic effects may be unpredictable. Patients should therefore be monitored with an intra-arterial line. Nausea may be a limiting side effect in the acute setting.

Enalaprilat

Enalapril, a commonly used oral angiotensin-converting enzyme inhibitor, is cleaved by plasma and tissue esterases to form enalaprilat, the active form of the drug. When given parenterally, enalaprilat acts as a balanced vasodilator resulting in decreased right and left heart filling pressures.⁷⁷ Enalaprilat is given as an intravenous bolus (0.625 to 1.25 mg every 6 hours). Although the onset of action is rapid (minutes), the duration of effect is prolonged (several hours). The major adverse effect is hypotension, which is more commonly seen in patients who are volume-depleted.

Enalaprilat may be of value in the treatment of acute decompensated heart failure or hypertensive urgencies.⁷⁸ However, because of the somewhat unpredictable magnitude of the response and its prolonged duration of action, enalaprilat is not a first-line agent for the treatment of patients with myocardial infarction or new onset heart failure. Enalaprilat is contraindicated in pregnancy.

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Diuretics and Newer Therapies for Sodium and Edema Management in Acute Decompensated Heart Failure

Robert J. Cody

CHAPTER 39

Decompensated Heart Failure and Edema
Pharmacokinetics of Diuretic Therapy
Practical Considerations
Supplemental Therapies for Sodium and Edema Management

Refocusing Therapy: Acute Decompensated Heart Failure Syndromes
Conclusion

FREQUENTLY, ACUTE cardiac decompensation is the clinical expression of left ventricular dysfunction, occurring as the result of diverse etiologies. Even at advanced stages, many patients initially thought to require transplantation due to acute decompensation, can continue to be managed with medical therapy. Many factors contribute to progression of heart failure, from mild forms to the advanced or refractory condition. However, the precise characteristics which govern the rate of progression will vary from patient to patient. As a result, the onset of decompensation or refractory presentation is difficult to predict, and may be abrupt in onset. In this regard, evidence of deterioration must be monitored carefully. For patients with chronic heart failure, fluid retention is typically considered the primary cause of abrupt decompensation, and surveys of hospital admissions support this observation. However, it is important to remember that fluid retention is just one of many factors that can result in abrupt decompensation (Table 39-1). The hallmark of acute cardiac decompensation is pulmonary edema, which results from excessive sodium retention, acute left ventricular dysfunction, or mechanical disorders of the left ventricle. Sodium retention results from the inability of the body to excrete sodium at a rate commensurate with dietary sodium intake. In fact, the characteristics which are identified as the hallmark of acute cardiac

decompensation are for the most part findings of excess sodium retention: pulmonary congestion, peripheral edema, increased jugular venous pressure, an S3 gallop, and hepatomegaly/ascites. In addition to urgent care measures, the most common therapy of acute cardiac decompensation is the use of diuretics. In recent years, newer approaches to sodium and fluid management have been developed, which may improve clinical outcomes and reduce hospital morbidity during the time of acute decompensation. In this chapter, emphasis will be placed upon acute therapy with diuretics, and the transition to a more stable chronic regimen. Newer classes of therapy will also be highlighted.

Decompensated Heart Failure and Edema

Clinical Conditions

Acute pulmonary edema is often the result of the many presentations of coronary artery disease and its complications. A patient may have a massive myocardial infarction, and subsequently develop papillary muscle dysfunction or a ventricular septal defect, which could each contribute to worsening left ventricular dysfunction and pulmonary edema. Also, a patient with previous left ventricular dysfunction may have worsening left ventricular function with myocardial ischemia or infarction with resultant acute pulmonary edema. Although coronary artery disease is probably the most common etiology of acute cardiac decompensation with resultant pulmonary edema, other etiologies include aortic stenosis and diastolic dysfunction in hypertensive crisis.

Mechanisms

Cardiac decompensation is characterized by decreased left ventricular systolic function, and in most cases, abnormal diastolic function. The resultant decrease of cardiac output and increased ventricular end-diastolic pressure set the stage for sodium retention (Fig. 39-1). Decreased cardiac output and increased

Table 39-1. Conditions That May Be Characterized as Acute Decompensated Heart Failure

Pulmonary edema
Progressive or persistent severe fluid retention
Fatigue or weakness with minimal exertion
Frequent nocturnal decompensation/dyspnea
LV dysfunction due to new or recurrent angina
Progressive renal failure of varying origins
Uncontrolled hypertension

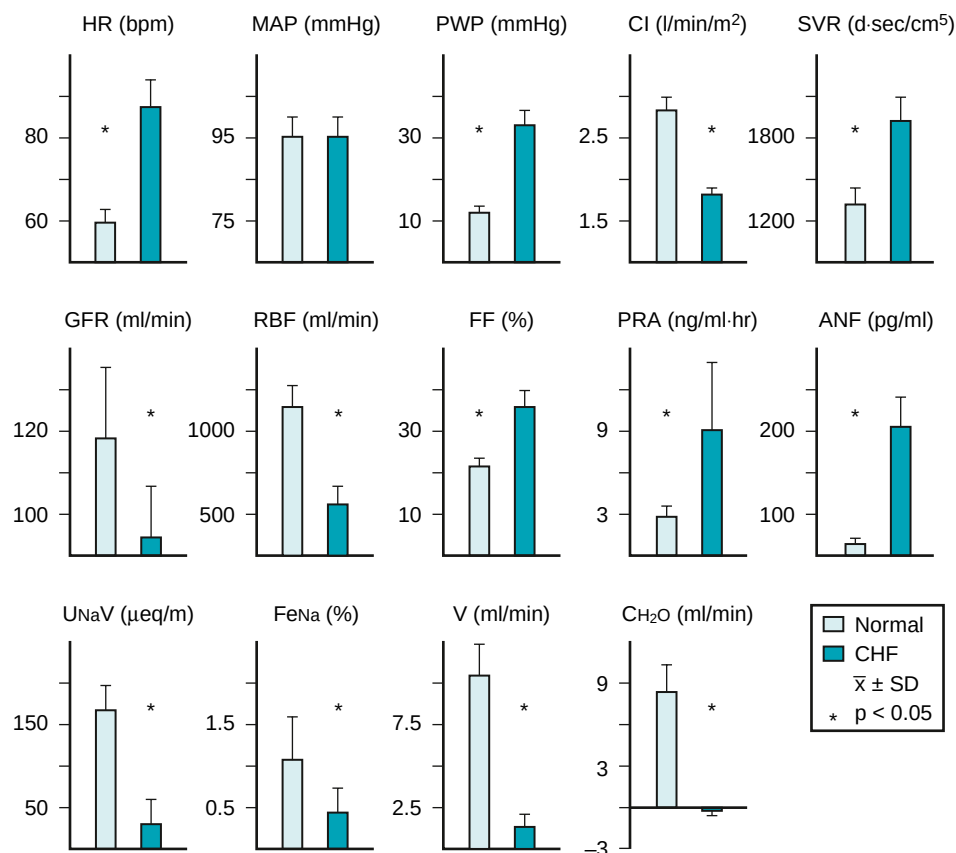


Figure 39-1. Comparison of systemic hemodynamics, renal hemodynamics, and renal excretory function and neurohormonal levels in normal individuals and in patients with moderate to severe heart failure. ANF, atrial natriuretic factor; CH₂O, clearance of free water; CHF, congestive heart failure; CI, cardiac index; Fe_{Na}, fractional excretion of sodium; FF, filtration fraction; GFR, glomerular filtration rate; HR, heart rate; MAP, mean arterial pressure; PRA, plasma renin activity; PWP, pulmonary wedge pressure; RBF, renal blood flow; SVR, systemic vascular resistance; UNaV, urinary sodium volume; V, urinary volume. (Data from Cody RJ, Pickworth KK: *Approaches to diuretic therapy and electrolyte imbalance in congestive heart failure*. In Deedwania PC [ed]: *Update in Congestive Heart Failure*, vol 12. Philadelphia, Saunders, 1994, p 37.)

systemic resistance produce decreased renal blood flow, and magnitude of renal blood flow reduction is correlated with decreased cardiac output,^{1,2} and diminished renal blood flow is a stimulus for activation of neurohormonal vasoconstriction pathways, particularly the renin system,^{3,4} which produces vasoconstriction and aldosterone secretion. Total body water, extracellular fluid, and plasma volume are increased compared with controls.⁵ Even within the heart failure population, there may be a spectrum of blood volume expansion (Fig. 39-2). When this is moderate to severe, impaired renal function and increased cardiac filling pressures occur. These hemodynamic responses become the basis for sodium retention.

The reduction of the glomerular filtration rate in heart failure is highly correlated with hemodynamic parameters, where the greatest reduction of cardiac output and renal blood flow are associated with the greatest reduction of the glomerular filtration rate.^{1,6} Renal blood flow and function tend to decrease with age in normal subjects, and an age effect can be superimposed on the overall reduction in renal blood flow and function due to the heart failure process.⁶ The resultant diminished delivery of sodium to the distal nephron at the level of the macula densa becomes a potent stimulus for renin release.⁷ Aldosterone further increases sodium retention at the distal nephron at the expense of potassium excretion. Although current therapy for

heart failure may improve cardiac output and renal blood flow, no current oral therapy has uniformly improved the glomerular filtration rate.

Neurohormonal factors that promote retention of sodium and water include aldosterone, vasopressin, angiotensin II, norepinephrine, and the vasoconstrictor prostaglandins; in contrast, prostacyclin, dopamine, and atrial natriuretic factor favor sodium excretion.^{3,4} The effect of vasopressin is primarily the promotion of free water retention, rather than sodium retention, and this typically contributes to hyponatremia.

Pharmacokinetics of Diuretic Therapy

Response to Diuretic Administration for Acute Cardiac Decompensation

The sites of diuretic actions and their role in the edema of cardiac decompensation have been reviewed.^{10,11} In the last decade, there have not been substantial breakthroughs in new diuretic development or mechanisms. The hemodynamic response to diuretic therapy has been characterized primarily in the setting of pulmonary edema. The acute hemodynamic response revealed a vasodilator effect¹²⁻¹⁴ and reduction of cardiac filling pressures.¹²⁻¹⁵ During acute decompensated heart failure, changes in cardiac output varied from increased or no change to

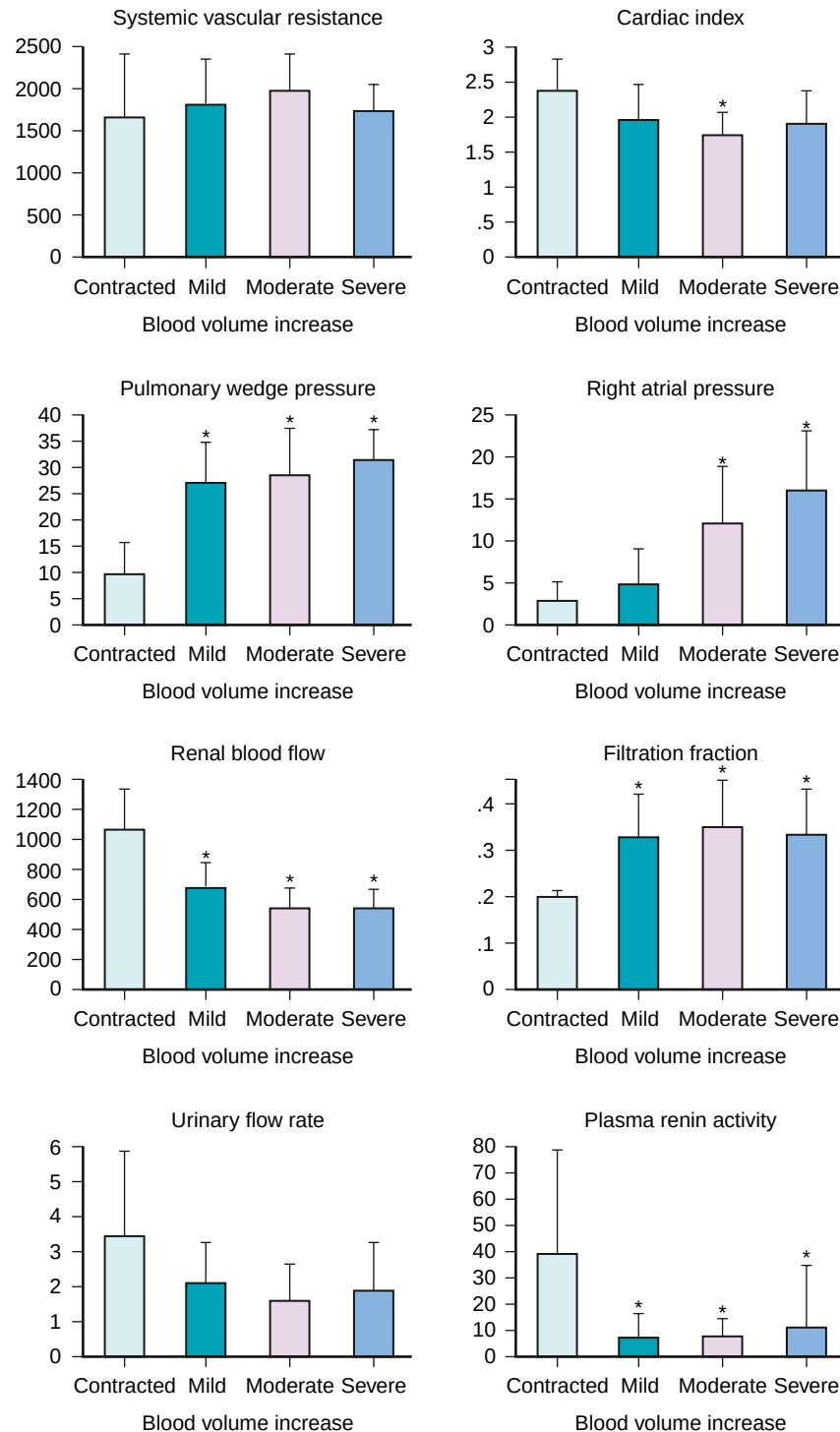


Figure 39-2. Blood volume, measured by ^{125}I albumin, is given on the x axis as a percent of normal blood volume. Four groups of heart failure patients receiving digoxin and diuretics but no angiotensin-converting enzyme inhibitors are identified: patients with contracted blood volume ($n = 4$; $-12 \pm 6\%$ < normal); patients with a mild increase in blood volume ($n = 8$; $14 \pm 3\%$ > normal); patients with a moderate increase in blood volume ($n = 7$; $25 \pm 3\%$ > normal); and patients with a severe increase in blood volume ($n = 8$; $40 \pm 10\%$ > normal). Systemic vascular resistance does not differ among the groups, but cardiac index decreases with blood volume expansion. Pulmonary capillary wedge and right arterial pressures increase. The expansion of blood volume is associated with progressive reduction of renal blood flow and compensatory increase of renal filtration fraction. Urine flow rate is also decreased in patients with increased blood volume, but is not significantly reduced compared with patients with contracted blood volume. With progressive increase of blood volume, plasma renin activity (ng/mL/hr) is suppressed. Despite diuretic therapy, there may be a range of blood volume expansion, which influences cardiac and renal function. * $P < .05$ by analysis of variance.

significant reduction, and changes in hemodynamics could proceed, or lag, production of diuresis. Such evaluations were conducted in diverse patient populations and must be interpreted accordingly. It has been stated that the vasodilator effect could precede the occurrence of diuresis, but the database for this effect is limited. Studies have reported either vasoconstriction,¹⁶ or initial vasodilation followed by vasoconstriction¹⁷ with acute or short-term follow-up. A review of the cited literature therefore reveals a fully divergent range of hemodynamic response to diuretics, although the majority of acute studies demonstrate a reduction of cardiac filling pressures.¹²⁻¹⁵ Loop diuretics have been shown to decrease renal vasculature resistance and to increase total and cortical renal blood flow.^{13,18,19} However, this may be related to severity of heart failure.²⁰ It is difficult to isolate a single neurohormonal factor as being primarily responsible for the overall hemodynamic and regional hemodynamic response to diuretics. Acute diuretic therapy may increase renin and aldosterone.^{16,17,20,21} Sympathetic nervous system activity also increases in response to diuretics.^{20,21} The impact of neurohormonal activation is an attenuation of the otherwise favorable effects of diuretics.

Loop Diuretics

As this chapter focuses on acute cardiac decompensation, the response to parenteral diuretic therapy will be emphasized (Table 39-2), without an extensive review of pharmacology. The term loop diuretic has evolved to encompass pharmacologic compounds which exert their primary action on the thick ascending loop of Henle. To reach the intraluminal site of action, these organic acids must first be secreted into the proximal tubule via the organic acid pathway. Once in the lumen, active reabsorption of chloride is inhibited in both the medullary and cortical portions of the loop of Henle. Decreased sodium reabsorption also occurs since the chloride ion is cotransported with sodium and potassium.

The three loop diuretics traditionally used in the United States to treat the edema of heart failure are furosemide, bumetanide, and torsemide. They are of equal efficacy but vary in pharmacokinetic properties.^{11,22} Ethacrynic acid remains available, but has a progressively diminishing role for edema management.²³⁻²⁵ Despite equal efficacy among loop diuretics, clinicians will often substitute one for the other with the hope of improved efficacy. Torsemide has a greater duration of action than its counterparts, but in general, the strategy of changing from one loop diuretic to another is typically not effective.

After oral administration, furosemide has 40% bioavailability, bumetanide has 80%, and torsemide has greater than 80% bioavailability. A diminished diuresis and a prolonged renal elimination of the drug may be expected in heart failure when renal dysfunction is evident. Torsemide has two active metabolites, which probably accounts for its longer elimination half-life of 3 hours. Residual loop diuretic concentration is eliminated by nonrenal mechanisms, including hepatic degradation and excretion. Because of the differences in bioavailability and potency, equivalent doses of bumetanide, furosemide, and torsemide are 1 mg, 40 mg, and 20 mg, respectively. All three agents are extensively bound to plasma proteins and are rapidly secreted by the organic acid pathway of the proximal tubule. In chronic renal failure, competition for this pathway by exogenous and accumulated endogenous organic acids causes lower peak concentration of the drug at its site of action. Therefore, a diminished diuresis and a prolonged renal elimination of the drug may be expected in heart failure when renal dysfunction is evident. The diuretic effect is apparent within 30 minutes after oral administration and peaks in 1 to 2 hours.²⁶⁻³⁰ Bumetanide has a somewhat shorter duration of action than that of furosemide or torsemide. Torsemide, like other loop diuretics, must be secreted into the urine by the organic acid secretory system in the proximal tubule to be effective.²³ It produces a maximum sodium excretion rate at approximately the same time with either intravenous or oral administration. Although the pharmacokinetics of torsemide are linear, increases in doses above 50 mg do not appear to increase the maximum sodium excretion rate but do increase the duration of the pharmacodynamic effect. One study has defined a ceiling dose of 100 mg of torsemide in patients with renal insufficiency and has recommended that repeated administration of torsemide is more effective than increasing the dose at this point.²³ It has been shown in another study that 20 mg of intravenous torsemide is approximately as effective as 40 mg of intravenous furosemide.²⁴ However, additional well-controlled trials of torsemide are necessary to determine whether it provides clinical benefit beyond current loop diuretics.

Thiazides and Potassium-Sparing Diuretics

Thiazide diuretics are derivatives of the benzothiadiazine structure.^{11,22} Like loop diuretics, they are organic acids and are highly protein-bound. Since they cannot be filtered, they gain access to the tubular lumen via the organic acid secretory pathway of the proximal tubule. Chlorothiazide is the only thiazide available in a soluble form that permits intravenous administration. This

Table 39-2. Pharmacokinetics of Intravenous Diuretics: Are there appreciable differences?

Drug	Route	Onset	Peak	Duration	Dosage*
Loop Diuretics					
Ethacrynic acid	IV	5 min	15-30 min	2 hr	50-100 mg
Furosemide	IV	5 min	30 min	2 hr	20-120 mg
Bumetanide	IV	5 min	30-45 min	2 hr	0.5-1 mg
Torsemide	IV	5 min	15-30 min	4-6 hr	20-100 mg.
Thiazide					
Chlorothiazide	IV	15 min	30 min	2 hr	250-500 mg

*Clinically accepted dosages and intervals in heart failure which are not strictly determined by pharmacokinetics.

formulation has recently been discontinued and limited stores remain. Its appreciable benefits, combined with an intravenous loop diuretic, are now of historical interest. Oral hydrochlorothiazide or metolazone are effective in most cases, but delayed gastric and small bowel absorption are common in the presence of severe edema. Despite this limitation, the combination of loop and thiazide diuresis appreciably augments diuresis. Experimental animal data demonstrate reactive hypertrophy of the distal nephron during long-term sodium depletion.³¹ With distal nephron tubular hypertrophy, the blockade of sodium reabsorption produced by a loop diuretic at the thick ascending limb is often attenuated. This adverse structural adaptation is overcome by the addition of a thiazide type of diuretic, which blocks sodium reabsorption at the distal nephron.

Although potassium-sparing diuretics uniformly act at the distal nephron and collecting duct, their effect is achieved by two different mechanisms.^{11,22} Active sodium reabsorption in the distal tubule and the collecting duct occurs in exchange for potassium and hydrogen. One mechanism is mediated by aldosterone and may be antagonized by spironolactone, which is a competitive receptor antagonist. The effects of triamterene and amiloride are independent of mineralocorticoids, and they act by direct inhibition of sodium transport. Differing from spironolactone, these two drugs must first reach their site of action by means of glomerular filtration and the organic base secretory pathway of the proximal tubule. Overall, these agents decrease sodium reabsorption, potassium excretion, and theoretically potentiate hyperkalemia, although the latter is uncommon in heart failure. Pharmacokinetic properties of the potassium-sparing diuretics help explain their differences in onset and duration of action. Onset of diuretic action occurs rapidly, 2 to 4 hours with amiloride and triamterene. This effect may persist for 24 hours despite early peak plasma concentrations and an elimination half-life of 6 to 9 hours. Following a single oral dose of spironolactone, peak serum concentrations of the parent drug are seen in 1 to 2 hours, whereas the active metabolites peak in 2 to 4 hours.

Although spironolactone is traditionally considered a potassium diuretic, its greatest benefit is as an antialdosterone agent. The RALES trial demonstrated significant clinical and survival benefit, independent of a diuretic effect. Survival included a significant reduction of sudden cardiac death compared with a placebo.

Practical Considerations

The Cycle of Sodium and Water Management in Heart Failure

When a patient can no longer be managed as an outpatient—for persistent severe edema, weakness, fatigue, or dyspnea, or when acute decompensation occurs in an otherwise stable heart failure patient—hospitalization is warranted. A decision to pursue parenteral therapy should be initiated from the moment of admission, while diagnostic studies are pending (Table 39-3). This should include intravenous diuretics and electrolyte replacement. This includes intravenous inotropic support such as dobutamine.⁸ When afterload reduction is desired, intravenous nitroprusside can be used. An alternate approach to vasodilation is the use of intravenous milrinone, which has both inotropic and direct vasodilator properties. Intravenous nitroglycerin is frequently used to treat acute decompensation of heart failure, but it is important to remember that most patients demonstrate hemodynamic tachyphylaxis within the first 24 hours of administration, so that hemodynamics return toward baseline and are not significantly different than a placebo. In view of the diverse causes of acute cardiac decompensation, the initial therapeutic intervention should be accompanied by appropriate diagnostic studies to identify the etiology of cardiac decompensation to plan more tailored therapeutic interventions.

Optimizing Intravenous Diuretic Response

Intravenous diuretic therapy may be used acutely in several clinical situations. In pulmonary edema, the obvious benefit of acute intravenous diuretic therapy is the rapid clearance of pulmonary congestion, likely mediated by natriuresis and diuresis, a reduction of intravascular volume, and vasodilation. As subacute decompensation is a prelude to pulmonary edema, the goals of intravenous diuretic therapy are similar to the treatment of pulmonary edema. The primary goal of intravenous diuretic therapy is the elimination of edema; concerns regarding adverse activation of neurohormonal activity and electrolyte depletion are of lesser importance, although potassium and magnesium intake should be supplemented. For acute reversal of sodium retention and fluid overload, therapy with a loop diuretic is indicated. It should be given intravenously to a ceiling dose that is twice the normal dose (e.g., furosemide 80 mg; bumetanide

Table 39-3. Fluid Management to Minimize Hospitalization Frequency and Duration

Outpatient Management	Inpatient Management	
	At Admission	At Discharge
- Identify target diuretic dosage - Daily weights 2000 mg sodium intake limit 2-3 liter fluid Limit - Phone check for patient status - BNP measurement* - Patient and family education regarding fluid retention	- Identify contributing etiologies for decompensation - Intensify diuretic therapy: - intravenous route - combination of diuretics - Fluid restriction - Inotropic agents? - AVP antagonist (hyponatremia) - Additional supporting therapy?	- Treat/correct/mitigate factors producing edema - Reset oral diuretic regimen - Resume/reset ACE inhibitor dosage - Add thiazide diuretic if necessary - Add spironolactone for survival benefit and electrolyte effects - Patient and family education regarding fluid retention

*At the time of this writing, BNP measurement is not recommended for routine follow-up of all patients. However, for problematic management issues, for long distance telemanagement, and for patients with significant chronic lung disease, the status of BNP plasma levels provides very useful information for trends of fluid retention and pulmonary congestion.

2 mg; torsemide 40 mg) and increased as necessary, combined with other agents. A thiazide type of diuretic in combination with a loop diuretic is often very effective.³²⁻³⁵ However, an oral thiazide type of diuretic, particularly metolazone, may require several days to achieve its maximal favorable response because of delayed absorption. The ability to use intravenous chlorothiazide (Diuril) is often overlooked. Unlike hydrochlorothiazide, chlorothiazide can be given intravenously in a dose of 250 to 500 mg, which is equivalent to oral hydrochlorothiazide dosage of 25 to 50 mg; when combined with a loop diuretic, it will produce greater diuresis than the loop diuretic alone. This is further discussed in the section dealing with resistance to diuretics.

Diuretic-Induced Electrolyte Imbalance

Electrolyte abnormalities in congestive heart failure are due to both the underlying pathophysiology and the concurrent administration of diuretic therapy.²² The pathologic factors predisposing to electrolyte abnormalities include abnormal neurohormonal activation and marked reduction of renal blood flow and function. Angiotensin II will impede the excretion of a given sodium load by direct effects on the tubular cells of the nephron. The enhanced stimulation of aldosterone secretion because of angiotensin II results in potassium excretion and sodium retention at the distal nephron. This not only contributes to sodium retention, but also results in total body potassium depletion and hypokalemia. Magnesium excretion is coupled with potassium excretion in the exchange for sodium. Hyponatremia is a hallmark of heart failure. Although well-correlated with activation of the renin system (and a good surrogate of this activity), its occurrence is the result of enhanced arginine vasopressin activity at the D2 vasopressin receptor site of the distal nephron tubule. Activation of the D2 receptor reduces free water clearance. This solute-free retention of water, combined with excessive dietary intake of sodium and water, results in hyponatremia; this is a common chronic occurrence in heart failure.^{44,45} In addition to the imbalance produced by abnormal neurohormonal activation, electrolyte imbalance is sustained by the chronic renal insufficiency that occurs in the majority of heart failure patients. Furthermore, diuretics produce hypokalemia, hyponatremia, hypocalcemia, hypomagnesemia, hyperuricemia, and metabolic alkalosis.^{46,47} Hypokalemia is the most common electrolyte disturbance, mediated by direct tubular mechanisms and hypersecretion of aldosterone. Hypokalemia and hypomagnesemia may be associated with myalgias, leg cramps, and an increase in ventricular arrhythmias. Most patients require the concomitant use of potassium supplements to correct hypokalemia; converting enzyme inhibitors may also reduce potassium loss. Most commonly, diuretic-induced hypokalemia is associated with a metabolic alkalosis and a coexisting chloride deficit. Administration of potassium by the intravenous route is recommended to correct moderate to severe potassium deficits, with or without the occurrence of cardiac arrhythmias. This route is also useful when oral replacement is not feasible or not tolerated because of a decrease in gastrointestinal motility. Oral, slow-release potassium chloride preparations are employed in the chronic management of diuretic-induced hypokalemia. Currently there is no dosage form that is superior to another with respect to the ulcerative effect on the gastrointestinal mucosa. The dosage of KCl is adjusted on an individual basis and is dependent on the use of other medications, such as angiotensin-converting enzyme inhibitors or concomitant diuretics. Generally, patients require

between 40 to 120 mEq/day to maintain potassium homeostasis, but requirements may be increased in the setting of acute diuretic administration.

Acute diuretic therapy also leads to hypomagnesemia.⁴⁸ Magnesium, primarily an intracellular ion, plays a pivotal role in mitochondrial functions, oxidation-phosphorylation reaction, and neuromuscular transmission.⁴⁹ Potassium and magnesium have an interrelationship, whereas magnesium is a cofactor in the appropriate function of the sodium-potassium ATPase pump. Therefore, hypokalemia may persist until the magnesium deficiency is corrected. Although normal serum magnesium concentrations range from 1.6 to 2.0 mEq/L, only 1% of magnesium is found in the extracellular compartment. The potential problem of magnesium deficiency in the heart failure population is the occurrence of lethal cardiac arrhythmias. Intravenous supplementation is essential in this situation. The administration of 2 to 5 g (equal to 16 to 40 mEq) of MgSO₄ by slow IV infusion, at 1 g/hr, to be repeated in 12 hours if needed, will correct magnesium at a satisfactory rate.

Diuretic-Resistant Edema

Patients should be considered to have *diuretic resistance* when they demonstrate progressive edema despite escalating oral or intravenous diuretic therapy.¹¹ Diuretic resistance should be contrasted to *diuretic adaptation*, which involves the activation of counterbalancing endogenous structural or functional mechanisms which tend to limit the clinical effects of diuretics.

The factors which contribute to diuretic resistance have been summarized.^{35,36} Renal insufficiency can reduce tubular secretion of the diuretic and the filtered load of sodium. Therefore, patients with decreased renal function due to heart failure¹ or superimposed age,^{1,6} frequently have reduced responses to diuretics. In addition, studies have demonstrated that indomethacin and other nonsteroidal anti-inflammatory agents reduce the maximal response to furosemide.³⁷ Mesenteric congestion may limit the absorption and bioavailability of orally administered medications.

Escalating dosage of intravenous loop diuretics is the most common approach, and the dosage should be rapidly doubled until the desired effect is produced. An ultra-high dose of loop diuretic may be effective^{38,39}; however, the overall response to ultra-high doses is often unimpressive. Also, continuous intravenous infusion of furosemide after a loading dose has been shown to be as effective at least as intermittent bolus therapy in producing diuresis and natriuresis.

An additional approach is based upon the concept that a continuous infusion of a loop diuretic may be more effective than intermittent bolus administration in terms of net sodium excretion.^{40,41} Careful metabolic studies have demonstrated a greater net sodium excretion using this approach, compared with intermittent bolus administration, despite comparable amounts of bumetanide appearing in the urine.⁴¹ In chronic renal insufficiency, continuous intravenous bumetanide has been shown to produce a greater natriuresis than equivalent bolus intravenous doses. Continuous bumetanide produces lower peak levels and therefore may decrease toxicity of the diuretic in patients with impaired renal function.

Alternatively, and perhaps more physiologic, is the combination of a thiazide and a loop type of diuretic, in view of the structural hypertrophy of the distal nephron described earlier. Although precise dose limits are difficult to define when a patient

achieves a requirement, for instance, of 240 mg of furosemide daily, addition of an intravenous (chlorothiazide) or oral thiazide type of diuretic will be more effective than further increases of the loop diuretic. The combination of loop/thiazide diuretic will be more effective than ultra-high doses of a loop diuretic alone.

In severe acute decompensation, when response to parenteral diuretics is completely attenuated, or in the patient who requires rapid fluid removal, acute ultrafiltration and hemodialysis can be used.^{42,43}

When Diuretics Fail

In acutely decompensated heart failure with edema, the failure of diuretics to adequately reduce edema and improve symptoms is a palpable risk. Several clinical features characterize the patient with diuretic failure. These include severe hypotension, renal impairment and hyponatremia, coexistent disorders such as diabetes, and hypertensive nephrosclerosis which further impair the effective effects of diuretics. This profile is accelerated in the elderly, where reduction of glomerular filtration is a common recurrence factor of the aging process, even in the absence of heart failure. In such circumstances mechanical intervention is necessary.

Ultrafiltration provides the most common and accessible form of sodium and water clearance in the setting of diuretic failure. It requires high flow vascular access and adequate systemic blood pressure to be effective. It can often be accomplished without adverse effects on baseline hemodynamics and renal function. Newer approaches to bedside fluid removal exist, but are sufficiently recent that standardized recommendations cannot be given. In the setting of electrolyte imbalance and insufficient clearance of metabolic catabolic products, hemodialysis is necessary.

To avoid the risk of diuretic failure, associated nephrotoxic agents should be identified and avoided. These include nephrotoxic antibiotics and anti-inflammatory agents with known adverse renal effects. The most notorious among the latter is indomethacin. Agents that also produce interstitial nephritis should be identified and avoided. Paradoxically, long-term administration of loop diuretics in excessive doses may produce interstitial nephritis, and the discontinuance of such therapy may result in spontaneous recovery of diuresis.

Supplemental Therapies for Sodium and Edema Management

Aldosterone Antagonists

There are numerous studies that now confirm the specific benefit of blocking aldosterone through use of spironolactone or eplerenone.⁵⁰ Most trials have examined the chronic effect of aldosterone antagonists, but have also demonstrated that these compounds can be administered safely in the acute care situation. Specific attention should be given to serum potassium in the setting of ACE inhibitor or angiotensin receptor blocker therapy to avoid hyperkalemia. However, most patients receiving large doses of loop diuretics are more at risk for hyperkalemia as indicated previously. Therefore, aldosterone antagonists may aid the correction of hypokalemia.

Vasopressin Antagonists

In contrast to natriuretic peptides, compounds that block arginine vasopressin are associated with a water diuresis (aquaresis) by reversing the retention of solute-free water that is produced

by high circulating levels of vasopressin in heart failure.⁵¹ Early attempts to commercialize effective antagonists of vasopressin over the last 2 decades met with a variety of obstacles. Currently, three vasopressin antagonists have been developed for oral or intravenous administration and are at various stages of development. This class is now being referred to as *vaptans*, and they may block both the D₁ receptor, which regulates vasoconstriction, and the D₂ receptor, which blocks free water clearance by the kidney. Alternatively, vasopressin antagonists may specifically block the D₂ receptor.⁵¹ Administration of these agents has been associated with substantial weight reduction, aquaresis, and correction of serum sodium levels.

The use of this class of agents may bring particular benefit to the management of acute decompensation and edema of heart failure, where extensive edema and clinical compromise cannot be effectively managed by diuretics because of the presence of profound hyponatremia, and one is left with the rather unsatisfactory option of slowly waiting for sodium correction by means of stringent fluid restriction.

Natriuretic Peptides

Since the initial discovery and clinical assessment of natriuretic peptides more than 20 years ago, the anticipation has been that pharmaceutical agents derived from these peptides would provide a physiologic approach to sodium and water management in edema-forming states. In small controlled studies of heart failure, one may demonstrate a small but statistically significant increase of sodium excretion in response to natriuretic peptides.^{52,53} However, these agent do not mount a clinically significant diuresis in heart failure. From the time of initial characterization until the present, heart failure patients should have a blunted response of sodium and water excretion compared with normal subjects when exposed to either oral or intravenous administration of natriuretic peptides. In contrast, the direct vasodilator properties of the natriuretic peptides are retained in heart failure; of the natriuretic peptides, the intravenous formulation of brain natriuretic peptide produces a vasodilator effect that is statistically greater than nitroglycerin, in comparative trials. Based on smaller studies, a small but significant increase of sodium excretion can be detected compared with the placebo. However, the magnitude of the response is meager compared with the response to a dose of loop diuretic, and certainly less than the augmentation that one identifies when a thiazide type diuretic is added to a loop diuretic.

Adenosine Antagonists

It is well recognized that the greatest sodium and water absorption occurs in the proximal nephron. Since loop diuretics work primarily in the thick ascending limb of the loop of Henle, their effectiveness is compromised by the limited amount of sodium that reaches their primary site of action. Blocking the proximal nephron site of sodium reabsorption by antagonizing the adenosine receptor is a well-recognized concept. Newer approaches to the design and delivery of adenosine antagonists have yielded potential adenosine antagonists for intravenous and, potentially, oral administration. Clinical trials of these agents are in progress.¹¹

Positive Inotropic Agents: Augmented Diuresis?

A recurring question is whether dobutamine and milrinone can augment diuresis in the edematous patient with decompensated heart failure. A rationale for this concept can be developed based

on the pathophysiology of decompensated heart failure. Many patients with advanced heart failure have impaired renal function due to hypoperfusion. In that setting, reduction of glomerular filtration produces proximal sodium and water retention, and limits tubular transport of sodium to the loop of Henle, where loop diuretics are effective. It is thus rational to postulate that increasing cardiac output and cardiac decompression produces improved regional perfusion and responsiveness to diuretic therapy. However, adequately controlled studies have not demonstrated improved diuresis attributable to inotropic therapy.

Refocusing Therapy: Acute Decompensated Heart Failure Syndromes

In view of the morbidity and mortality associated with recurring acute heart failure, and its associated heavy economic burden, there is a refocusing of effort toward improving the therapy of patients having acute decompensated heart failure syndromes (ADHFS).^{54,55} This is not a new disease or new constellation of diseases. ADHFS represent the features of heart failure, either acute, or decompensated chronic heart failure, that usually necessitate hospitalization. Because this is a heterogeneous group of patients, it is necessary to remember that there is no single therapy that can be prescribed for all patients. However, diuretics, and newer agents that augment free water clearance (aquaretics) and sodium excretion (natriuretics) will be at the forefront of this therapy, together with traditional diuretics, since excessive fluid retention typically is a major contributing factor to the acutely decompensated state of heart failure.⁵⁶

Conclusion

Diuretics remain the most poorly characterized class of heart failure therapy. These agents are diverse, maximal doses are often exceeded, and guidelines for optimal combinations do not exist. The use of diuretics in acute cardiac decompensation remains a combination of science and art form. The desired end point, in the absence of more objective changes, remains the relief of the symptoms related to edema: dyspnea and congestion. However, a careful use of diuretics in appropriate combination with other more specific therapies of acute cardiac decompensation will produce clinical improvement without adverse consequences.

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Antiarrhythmic Electrophysiology and Pharmacotherapy

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CHAPTER 40

Physiology
His-Purkinje Action Potential
SA Node and AV Node Action Potential
Classification

Sicilian Gambit
Antiarrhythmics of Clinical Relevance in the CCU
Conclusion

CARDIAC ARRHYTHMIAS continue to be a significant cause of morbidity and mortality in the developed world and add to the complexity of management of critically ill patients. Over the past 2 decades treatment strategies have expanded to include other approaches such as catheter ablation and implantable cardiac defibrillators. Although these strategies have demonstrated significant superiority over antiarrhythmics, they have not eliminated the problem of cardiac arrhythmias. Furthermore, these approaches can be difficult to apply to patients in the acute setting. Antiarrhythmic agents continue to be a vital adjunct to these therapeutic approaches.

Despite the important role that antiarrhythmics play to combat cardiac arrhythmias, it has been difficult to overcome the stigma associated with these drugs. This stigma has stemmed from earlier published trials such as the CAST and CAST II trials evaluating class IC antiarrhythmics and the SWORD trial evaluating sotalol in patients with coronary artery disease and left ventricular dysfunction. These trials demonstrated increased mortality, significant side effects, and marginal efficacy.^{1,2,3} The Achilles heel of these agents is their propensity for proarrhythmia that results in more dangerous arrhythmias than the ones they were initially intended to treat. This led to a re-evaluation of the wisdom of using relatively simple agents that took aim at single molecular targets, such as sodium or potassium channels. Subsequently, researchers pursued the development of newer antiarrhythmic agents that target multiple molecules or complex arrhythmogenic pathways, such as amiodarone or d,l-sotalol. There was a renewed interest and emphasis on the use of β -blockers, which do not specifically target ion channels. In addition there has been significant interest in understanding the genetic basis of susceptibility to serious arrhythmias in individuals with genetic syndromes such as long QT and Brugada syndromes.

Despite their potentially serious side effects, antiarrhythmics continue to be a valuable tool when used appropriately and in a targeted manner. The aim of this chapter is to provide a clear and concise overview of the physiologic basis and applicable pharmacology that makes these drugs useful, and to discuss the ones most clinically relevant to the management of the acutely ill patient.

Physiology

Normal cardiac electrical activity is determined by the shape of the cardiac action potential. Antiarrhythmic agents exert both desirable therapeutic effects and undesirable side effects by their capacity to alter the shape of the action potential. These actions are mediated by their ability to affect the ion channels that control it. Therefore, a review of the basic physiology of the cardiac action potential is imperative to understanding the mechanism of action of these drugs.

Over the past 2 decades our knowledge and understanding of cardiac cellular electrophysiology has increased as a result of cutting edge techniques, such as the cloning and sequencing of proteins and ion channels. A detailed description of the many ion channels discovered to date, and their respective roles, is beyond the scope of this chapter. A more fundamental approach to the basic principles that produce the action potential is described.

A simplified model of the His-Purkinje action potential (fast response tissue) is discussed first followed by descriptions of the action potential of the sinoatrial (SA) and atrioventricular (AV) nodes (slow response tissue).

His-Purkinje Action Potential

The His-Purkinje action potential can be conceptually divided into periods of depolarization, repolarization, and resting states. However, the action potential is traditionally divided into five different phases (phases 0-4) to describe the activity of various ion channels that bring about any of these three states (Fig. 40-1, A and B). Phase 4 corresponds to the resting state when the cell is not being stimulated and is ready for subsequent depolarization. Phase 0 corresponds to depolarization of the myocardial cell. It initiates a cascade of events involving the influx and efflux of multiple ions, leading to phases 1-3, manifesting in repolarization and refractoriness.

Phase 4

The normal resting membrane potential in the ventricular myocardium is between -85 to -95 mV. This membrane potential is determined by the balance of inward sodium (Na^+) and calcium

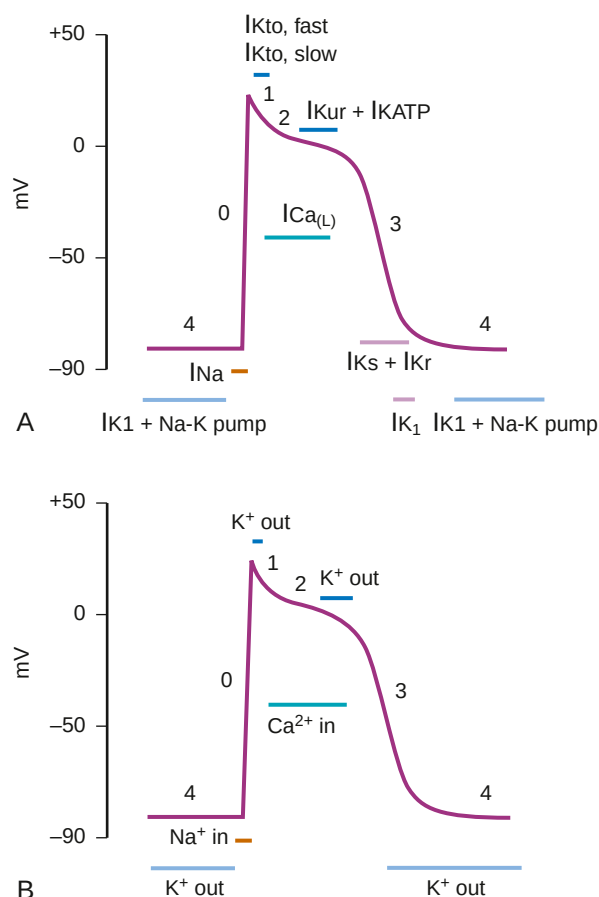


Figure 40-1. **A**, Ion channels responsible for the His-Purkinje action potential. This diagram shows the action of the various ion channels responsible for the His-Purkinje action potential over the time it takes for a complete cycle of depolarization and repolarization. **B**, Ion flux responsible for the His-Purkinje action potential. This diagram shows the influx and efflux of various ions in the His-Purkinje action potential over a single complete cycle of depolarization and repolarization; this corresponds to the action of their respective ion channels seen in **A**.

(Ca^{2+}) currents and outward potassium (K^+) current. The equilibrium potential for a given ion is determined by the concentrations of that ion inside and outside the cell. K^+ is the principal cation intracellularly, whereas phosphate and conjugate bases of organic acids are the dominant anions. Extracellularly, Na^+ and chloride (Cl^-) are the principal cation and anion, respectively. Therefore, when K^+ channels open, K^+ ions flow outside the cell along their concentration gradient, leaving the cell with a more negative membrane potential.

The resting membrane potential is generated by the inward rectifier current (I_{K1}), the predominantly open channel during this phase. The maintenance of this electrical gradient is because of various ion pumps and exchange mechanisms, such as the Na^+ - K^+ ion exchange pump and the Na^+ - Ca^{2+} exchanger current.

This phase of the action potential is associated with cardiac diastole.

Phase 0 (Depolarization)

Rapid depolarization occurs when the resting cell is brought to threshold causing activation (opening) of fast Na^+ channels. This results in rapid influx of Na^+ ions caused by increased cell

membrane permeability to Na^+ . The slope of phase 0 represents the maximum rate of cell depolarization (V_{max}) and governs the conduction velocity of a cardiac impulse through cardiac cells. This can be altered by drugs such as the class I antiarrhythmics, which retard conduction velocity, and V_{max} .

Voltage-gated Na^+ channels can exist in either the resting, open (phase 0), or inactive state. The response of these Na^+ channels is dependent on the membrane potential at the time of stimulation. If the membrane potential is at baseline (-95 mV), then all resting Na^+ channels open simultaneously, resulting in a dramatic influx of Na^+ ions. If, however, the membrane potential is above baseline (less negative), then some Na^+ channels may be in the inactive state and unable to open, resulting in a smaller response with less influx of Na^+ ions (lower V_{max}). This has clinical relevance as class I antiarrhythmics prefer binding to inactive Na^+ channels. Furthermore, this reduced cellular excitability may render cardiac cells prone to variable refractoriness, delayed conduction, and various arrhythmias.

Phase 1 (Early-Rapid Repolarization)

This phase represents the initial stages of cellular repolarization and is caused predominantly by closure of the fast acting Na^+ channels. However, the net downward deflection of the action potential is also attributable to transient outward flux of K^+ ions as a result of two K^+ channels ($I_{to, fast}$ and $I_{to, slow}$) opening and then closing.

Phase 2 (Plateau)

Although this phase may appear to be a particularly stagnant part of the action potential, it is in fact one of the most complex and dynamic portions. Multiple ions make small contributions resulting in a relatively constant, positive value of the membrane potential. The predominant forces are outwardly directed K^+ ions and inwardly directed Ca^{2+} ions, which maintain an equal balance. The outward flux of K^+ through the delayed rectifier K^+ channel (I_{Kur}) and through the ADP activated K^+ channel (I_{KATP}), is balanced against rapid inflow of Ca^{2+} through L-type Ca^{2+} channels ($I_{Ca, L}$).

The plateau phase is unique to the cardiac cell and represents an interruption to rapid repolarization, extending the duration of the action potential and therefore the refractoriness of the cardiac cell. The benefit of this is to allow for a single contraction of myocardium to occur before the generation of a subsequent action potential, thus the heart can never be "tetanized," which would be incompatible with cardiac function.⁴

Phase 3 (Repolarization)

L-Type Ca^{2+} channels are now closed while slow delayed rectifier K^+ (I_{Ks}) channels are open and trigger opening of other channels, such as the rapid delayed rectifier K^+ channel (I_{Kr}). This results in a net outward flux of positive cations, thereby facilitating cellular repolarization. The I_{K1} channel is activated late in phase 3 and continues on to contribute to the resting membrane potential of phase 4.

SA Node and AV Node Action Potential

SA and AV nodal action potentials are very similar with only minor differences between them in phase 0. They are significantly different from fast response tissue's action potentials

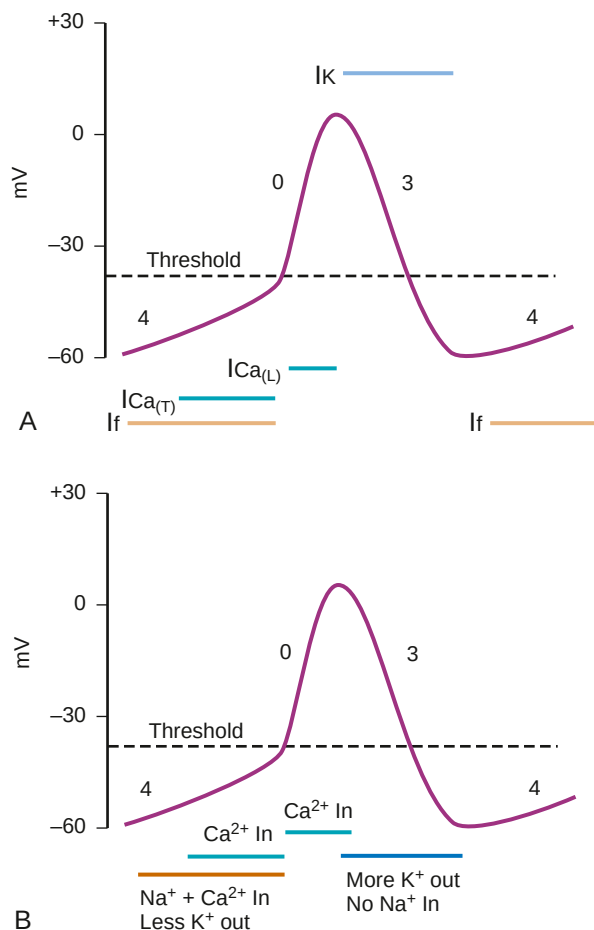


Figure 40-2. **A**, Ion channels responsible for the sinoatrial/atrioventricular (SA/AV) node action potential. This diagram shows the action of the various ion channels responsible for the SA/AV node action potential (slow response tissues) over the time it takes for a complete cycle of depolarization and repolarization. **B**, Ion flux responsible for the SA/AV node action potential. This diagram shows the influx and efflux of various ions responsible for the SA/AV node action potential (slow response tissues) over a single complete cycle of depolarization and repolarization; this corresponds to the action of their respective ion channels seen in **A**.

previously described. These slow response tissue action potentials are divided into three phases instead of five (Fig. 40-2, A and B). Phase 4 is the spontaneous depolarization (pacemaker potential) phase that triggers the action potential once the membrane potential reaches threshold (between -40 and -30 mV). Phase 0 is the depolarization phase of the action potential. This is followed by phase 3 repolarization. Once the cell is completely repolarized at about -60 mV, the cycle is spontaneously repeated.

Phase 4—Spontaneous Depolarization (Pacemaker Potential)

The unique firing of pacemaker cells is attributable to their capacity to slowly and spontaneously depolarize. The resting potential of a pacemaker cell (-60 mV to -70 mV) is caused by ongoing efflux of potassium ions. Potassium permeability decreases with time, contributing to the slow depolarization. Additionally a slow inward flow of sodium, called the “funny

current” (I_f) and an inward flow of calcium through T-type calcium channels (ICa_T) all make the cell more positive. When the threshold potential (-40 mV to -50 mV) is reached, the cells enter the depolarization phase.

Phase 0—Depolarization

The predominant ion activity during this phase is dependent on the influx of calcium through L-type calcium channels as opposed to sodium influx in fast response tissues. In fact I_{Na} channels are largely absent from these cells.

The upstroke (V_{max}) and therefore the conduction velocity in a pacemaker cell is significantly slower than in the fast response tissue cells, with the AV node action potential demonstrating a faster V_{max} than that of the SA node.⁵

Phase 3—Repolarization

Calcium channels are rapidly inactivated with simultaneous decrease in sodium permeability. This is combined with increased potassium permeability with resultant efflux of potassium, slowly repolarizing the cell once more to its resting potential.

Autonomic Innervation

Both sympathetic and parasympathetic nerve fibers are abundantly found in both the SA and AV nodes; however, parasympathetic nerve fibers are only minimally located in fast response tissue. Therefore, parasympathetic tone fluctuations are notable in the SA and AV nodes with minimal or no effect on fast response tissue.

Increased sympathetic tone results in enhanced automaticity, increased conduction velocity (V_{max}), and decreased refractoriness. These effects combine to produce an increased number of action potentials that are propagated faster. Increased parasympathetic (vagal) tone has the opposite effect, with diminished automaticity and conduction velocity but increased refractoriness. These observations have an important impact on clinical arrhythmias and their management.

It is helpful to keep in mind the various roles of ion channels on the different stages of the action potential, in both fast and slow response cells, to achieve an understanding of the potential key effects of antiarrhythmic agents. In addition, the Vaughan-Williams classification of antiarrhythmic drugs is based upon which ion channels they affect.

Classification

Vaughan-Williams

This is currently the most widely used classification of antiarrhythmic drugs (Table 40-1). This classification was initially introduced by Vaughan Williams^{6,7} and was based on the electrophysiologic effects of antiarrhythmics. It was later modified by Harrison⁸ with the recognition that drugs in the same class have different potencies and that the same drug may exert multiple class effects.

Amiodarone has effects across all classes, blocking Na^{+} channels in depolarized tissues, but is also capable of affecting Ca^{2+} and K^{+} channels and adrenergic receptors. This makes it an extremely versatile drug capable of affecting a wide variety of arrhythmias. Sotalol has a significant β -blocker effect in addition to its class III action. Ibutilide can also enhance the slow delayed sodium current. Although moricizine has diverse effects

Table 40–1. Vaughan-Williams Classification of Antiarrhythmics and Their Mechanism of Action

Class	Mechanism	Drugs
I	Na ⁺ channel blockers	
A	Slows conduction velocity (V _{max}) and prolongs action potential. Results in decreased conductivity and increased refractoriness.	Quinidine, procainamide, disopyramide
B	Minimal effect on conduction velocity (V _{max}) and shortens action potential duration. Results in decreased refractoriness.	Lidocaine, mexiletine
C	Significant slowing of conduction velocity (V _{max}), minimal effect on action potential duration. Results in decreased conductivity and no change in refractoriness.	Flecainide, propafenone, moricizine
II	β-blockers Decrease sympathetic tone affecting SA and AV nodes	Atenolol, esmolol, propranolol
III	K ⁺ channel blockers No effect on conduction velocity with significant increase in action potential duration. Results in no change in conductivity but marked increase in refractoriness.	Amiodarone, sotalolol, dofetilide, ibutilide, azimilide
IV	Ca ²⁺ channel blockers Affect SA and AV node by direct cell membrane effects	Verapamil, diltiazem (non-dihydropyridine)
V	Other mechanisms Affect SA and AV nodes by increasing vagal tone	Digoxin, adenosine

across different classes, this drug is not currently used because it has been demonstrated to increase mortality.

Class I Antiarrhythmics and Use Dependence

Class I drugs are all Na⁺ channel blockers with varying potency and are classified based on their effect on the action potential upstroke or V_{max} and therefore their ability to alter conduction velocity. They can prolong it, shorten it, or have no net effect (Fig. 40-3). Their different potency is due to variable rates of binding and dissociation from the channel receptor.⁹ Class IC are the most potent Na⁺ channel blockers because they have the slowest binding and dissociation from the receptor; class IA are the least potent (fastest binding and dissociation); and class IB are moderately potent. Faster heart rates allow less time for drug-receptor dissociation, resulting in an increased total number of blocked receptors and more effective antiarrhythmic action. This is known as “use dependence” and is most noted with class IC agents.¹⁰ These effects can result in prolonged conduction velocity and manifest by widening of the QRS complex on the surface electrocardiogram (ECG), especially during tachycardia.

Class III Antiarrhythmics and Reverse Use Dependence

Class III antiarrhythmic agents extend the plateau phase of the action potential by blocking K⁺ channels. They effectively prolong repolarization and the action potential duration with a resultant increase in refractoriness without a change in conductivity (Fig. 40-4). This manifests as prolongation of the Q–T interval on the surface ECG. These effects are most pronounced during slow heart rates. This is known as “reverse use dependence” and thus, longer Q–T intervals are noted at slower heart rates.¹¹ This provides the potential for dangerous arrhythmias such as torsades de pointes.¹² This is known as proarrhythmia and is one of the most serious, life-threatening side effects associated with antiarrhythmic drug use. Amiodarone, however, appears to be the exception, with proarrhythmia being reported only uncommonly.¹³

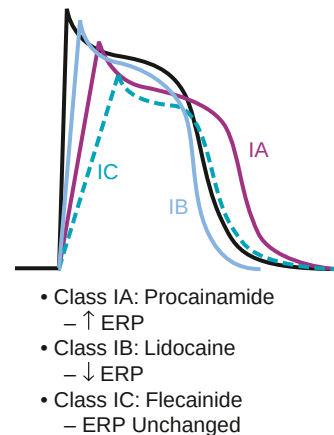


Figure 40-3. Effect of class I antiarrhythmics on the His-Purkinje action potential. All class I antiarrhythmics retard the slope of phase 0 of the action potential resulting in a decrease of V_{max} and a decrease in the conduction velocity of the cardiac cell. Class IC agents slow the upstroke of the action potential (V_{max}) the most, resulting in prolongation of the action potential. This prolongation causes a marked decrease in conductivity, but has little overall effect on the effective refractory period. Class IC agents do not alter refractoriness significantly. Class IA agents slow the upstroke (V_{max}) moderately, prolonging the action potential, decreasing conduction velocity, and increasing refractoriness. Class IB agents have a very small effect on the V_{max}, shortening the action potential, which results in an overall decrease in refractoriness.

Class II Antiarrhythmics

These drugs act by competitive inhibition of the β-adrenergic receptor, and largely affect the SA and AV node. Yet they also have mild Na⁺ channel inhibitory effects. There is a preponderance of data demonstrating the antiarrhythmic properties of β-blockers. β-blockers have played an increasingly important role in increasing survival in patients with coronary heart

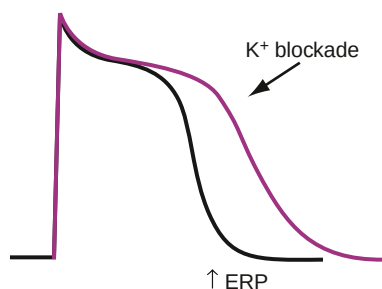


Figure 40-4. Lengthening of effective refractory period on class III antiarrhythmics. All class III agents cause a blockade of K^+ channels. As a result, the rate of outward flux of K^+ is slowed down during phases 2 and 3, which causes a prolongation of the time it takes a cardiac cell to return to the resting membrane potential. This prolongs the effective refractory period of the cardiac cell, resulting in an increased time before it is ready for the subsequent depolarization.

disease and congestive heart failure, along with adjunctive therapy to implantable cardiac defibrillators (ICDs) by decreasing the incidence of sudden cardiac death (SCD). Although not all of the beneficial effects of β -blockers are understood it is likely that they essentially work by reversing or preventing the proarrhythmic actions of sympathetic activity.¹⁴ These include increased automaticity because of enhanced phase 4 depolarization in the SA and AV nodes, increased membrane excitability in phase 2 and 3 of the His-Purkinje action potential, increased V_{max} , and increased delayed afterpotentials, which can lead to increased triggered activity type arrhythmias. They are therefore most effective in tissue under intense adrenergic stimulation (e.g., in ischemia) and it is not surprising that their effects are most obvious in patients having acute myocardial infarction and decompensated heart failure.

Class IV

The non-dihydropyridine calcium channel blockers (verapamil and diltiazem) are the only ones that exhibit significant electrophysiologic and antiarrhythmic properties. These are mediated through their ability to block the slow calcium channel. Their antiarrhythmic properties are exerted through two main effects. Their most prominent activity is to block the slow calcium channel in the action potential of the SA and AV node, effectively slowing phase 4 spontaneous depolarization. This results in a variable slowing of the heart rate (similar to β -blocker-induced adrenergic blockade)¹⁵ and slowing conduction through the AV node, manifested by bradycardia and prolongation of the P-R interval on the surface ECG.

The other action is their ability to shorten the plateau phase of the action potential of ventricular myocytes, therefore inhibiting early afterdepolarizations (EADs).¹⁶ EADs are due to fluxes in calcium and appear to occur mostly under conditions that prolong the action potential (e.g., hypoxia, drug induced), giving rise to torsades de pointes. Therefore, calcium channel blockers may play an active role in the prevention of these types of arrhythmias.

Atypical Agents (Class V)

Although there is no designated class V in the Vaughan-Williams classification of antiarrhythmics, it is unofficially used to place atypical agents whose antiarrhythmic properties do not belong

to any of the other ion-based antiarrhythmics. These include drugs such as digoxin and adenosine and will be discussed individually later in the chapter because of their potential utility in the critical care setting

Sicilian Gambit

Although the merits of the Vaughan-Williams classification are its simplicity and wide recognition, providing a useful mode for communication regarding the use of antiarrhythmics, it does not take into account several complexities. These include drugs' ability to exert effects that cross into different classes, having variable potencies within the same class, and causing other effects such as changes in metabolism, autonomic stimulation, or hemodynamics. The Sicilian gambit¹⁷ (Table 40-2) was introduced as a method of rationalizing the approach to the use of antiarrhythmics. Although not widely known and far more complex in its original format, it is included here for its emphasis on approaching antiarrhythmic drug choice based on the mechanism of each individual arrhythmia and the perceived "vulnerable parameter" that can be affected to terminate it.

Pharmacology

Pharmacologic concerns of drug therapy can be divided into two main disciplines. The first is pharmacokinetics, which describes the process of drug delivery to its target site. It encompasses the processes of drug absorption, distribution, metabolism, and elimination. This can be summarized in the relationship between drug dose and plasma concentration over time. This should not be confused with pharmacodynamics, which describes target-specific drug interaction, and the resultant downstream whole body effects. This can be thought of as the relationship between drug concentration and magnitude of drug effect.

Obviously, both of these processes can then be impacted by various factors such as drug absorption, bioavailability, volume of distribution, drug clearance, elimination, and half-life. Due to the complexity of drug transport and activity, genetic variability, and the heterogeneous and often abnormal metabolic milieu of the critically ill patient, significant interpatient variability can be expected in their response to the same drugs.

Drug Absorption

This is the process by which orally administered drugs are taken up from the gastrointestinal tract and enter into the systemic circulation. Bioavailability describes the percentage of drug that reaches the circulation unchanged, as compared with intravenous drug administration, which represents 100% bioavailability.

In general, bioavailability can be altered by two main factors. The first considers the successful gut uptake of the drug, which can be affected by various factors such as drug dissolution rates, different formulations, gastric pH levels, and bacterial flora. The second main factor is presystemic (first pass) clearance through the liver, where drugs may undergo metabolism, alteration, or excretion by hepatocytes into the bile, thereby affecting bioavailability.

With rare exceptions, most drugs administered in the critical care setting are administered in the intravenous form and therefore many of the issues surrounding drug absorption do not apply in this circumstance.

Table 40–2. Sicilian Gambit (Modified)*

Mechanism	Arrhythmia	Vulnerable Parameter (Effect)	Drugs (Effect)
Automaticity			
Enhanced automaticity	Inappropriate sinus tachycardia Some idiopathic ventricular tachycardias	Decrease phase 4 depolarization	β -blockers Na^+ channel blockers
Abnormal automaticity	Atrial tachycardia	Maximum diastolic potential (hyperpolarization)	Muscarinic receptor agonists
	Accelerated idioventricular rhythms	Phase 4 depolarization (decrease)	Ca^{2+} or Na^+ channel blockers
Triggered Activity			
Early afterdepolarization (EAD)	Torsades de pointes	Shorten action potential duration Suppress EAD	β -blockers Ca^{2+} channel blocker; Mg^{2+} ; β -blockers
Delayed afterdepolarization (DAD)	Digitalis-induced arrhythmias	Calcium overload (unload) DAD suppression	Ca^{2+} channel blockers Na^+ channel blockers
	Right ventricular outflow tract ventricular tachycardia	Calcium overload (unload) DAD suppression	β -blockers Ca^{2+} channel blockers
Na^+ Channel-Dependent Re-entry			
Long excitable gap	Typical atrial flutter	Depress conduction and excitability	Class IA, IC Na^+ channel blockers
	AV reciprocating tachycardia	Depress conduction and excitability	Class IA, IC Na^+ channel blockers
	Monomorphic VT	Depress conduction and excitability	Na^+ channel blockers
Short excitable gap	Atypical atrial flutter	Prolong refractory period	K^+ channel blockers
	Atrial fibrillation	Prolong refractory period	K^+ channel blockers
	AV reciprocating tachycardia	Prolong refractory period	Amiodarone, sotalol
	Polymorphic and uniform ventricular tachycardia	Prolong refractory period	Class IA Na^+ channel blockers
	Bundle branch reentry	Prolong refractory period	Class IA Na^+ channel blockers; amiodarone
Ca^{2+} Channel-Dependent Re-entry			
	Atrioventricular nodal reentrant tachycardia	Depress conduction and excitability	Ca^{2+} channel blockers
	AV reciprocating tachycardia	Depress conduction and excitability	Ca^{2+} channel blockers
	Verapamil-sensitive ventricular tachycardia	Depress conduction and excitability	Ca^{2+} channel blockers

*Classification of drug actions on arrhythmias based on their ability to modify a vulnerable parameter of the arrhythmia.

Adapted from the Task Force of the Working Group on Arrhythmias of the European Society of Cardiology: The Sicilian gambit: a new approach to the classification of arrhythmic drugs based on their actions on arrhythmogenic mechanisms. *Circulation* 1991;84(4):1831-1851.

Distribution

A drug is distributed to the best perfused tissues first, termed the central compartment, such as the heart, lungs, and brain. Subsequently, it reaches less perfused tissues such as the skin and muscle—the peripheral compartment. Some drugs such as amiodarone have very slow distribution to tissues such as adipose, termed the deep compartment, which prevent it from reaching a steady state until these tissues are saturated.

The volume of distribution (Vd) of a particular drug refers to a theoretical space or volume into which the drug is distributed and can be used to describe the relationship between drug dose and plasma concentration. This can in turn be affected by changes in the actual plasma volume reflected by tissue

perfusion, as can be noted in cases of congestive heart failure or shock. Alternatively, tissue affinity, fraction of drug bound to proteins (only the free portion of a drug produces the desired effect) and degree of lipid or water solubility can all play a role in altering the volume of distribution.

A classic example is lidocaine administration in heart failure patients. The Vd may be reduced by 40%¹⁸ because of decreased perfusion and therefore unless lidocaine bolus doses are reduced in these patients, lidocaine toxicity can result.

Most antiarrhythmics are bound to α_1 -glycoprotein. This protein's concentration increases with acute and critical illness (such as shock, trauma, or severe bacterial infection). The result may be decreased effectiveness of the antiarrhythmic agent

despite an unchanged plasma concentration, as the fraction of unbound (free) active drug is smaller.

Metabolism and Elimination

Most antiarrhythmics are metabolized hepatically by the cytochrome P450 system, and many undergo extensive first pass metabolism. This accounts for the large ratio of oral to intravenous doses of such medicines as verapamil, metoprolol, or propafenone. Others such as lidocaine are so completely eliminated by the first pass effect that oral dosage is useless.¹⁹

Metabolism of the parent drug produces metabolites that may or may not be active. Furthermore, these metabolites may have similar or different effects than the parent drug. Classic examples include amiodarone metabolism to desethylamiodarone, which accounts for a persistent drug effect beyond the drug's half-life. Procainamide, however, a class Ia agent, is metabolized to *N*-acetylprocainamide (NAPA), which has a predominant class III effect.

A drug's half-life describes the time required to reduce a plasma drug concentration by 50%. This may be secondary to either drug metabolism and elimination or redistribution. It typically requires five half-lives to eliminate a drug from the plasma completely and five half-lives to achieve a steady state. Since only three doses are required to achieve greater than 90% steady state plasma concentrations, drug loading doses should only be used when such an interval is clinically unacceptable such as in life-threatening arrhythmias in critically ill patients. In such situations, a loading dose may be given to achieve desirable plasma concentration levels much faster.²⁰

Antiarrhythmics of Clinical Relevance in the CCU

Although detailed accounts of every antiarrhythmic are available elsewhere, the focus of this review is to discuss the antiarrhythmics that have the most clinical relevance to the management of the critically ill patient in the acute care setting. Older medications no longer in current use and those that cannot be administered intravenously or are contraindicated in critical illness are not discussed (Table 40-3).

Class IA

Of the drugs in this class, procainamide is the only agent with a potential role in the modern critical care setting.

Procainamide

Procainamide is a Na⁺ channel blocker that results in reduced V_{max} associated with decreased conduction velocity and prolongation of the His-Purkinje action potential, and therefore the effective refractory period.²¹ Its effect on prolongation of the action potential is mediated through its active metabolite *N*-acetylprocainamide (NAPA), which is a class III antiarrhythmic agent. In addition it can suppress automaticity in slow response tissues (SA and AV nodes)²² and triggered activity in normal Purkinje fibers.²³

Clinical Effects

The surface ECG may reflect prolongation of the P-R interval and QRS intervals without significant effect on the RR interval.²⁴ Widening of the QRS is increased at faster heart

rates or high plasma concentrations.²⁵ Widening of the QRS to greater than 25% has been recommended as a useful end point of procainamide's myocardial effect.²⁶ In addition, prolongation of the Q-T interval can be seen and may herald proarrhythmia.

Indications

Intravenous procainamide continues to be the drug of choice for the acute treatment of atrial fibrillation in Wolf-Parkinson-White syndrome. However, ibutilide, as an alternative, has also been shown to be effective for this.²⁷ Procainamide's effect is achieved through suppression of both antegrade and retrograde conduction across accessory pathways, which reflects its ability to increase refractoriness and decrease conduction velocity in cardiac tissue.

Procainamide has been recommended above amiodarone and lidocaine (level of evidence IIA) for acute resuscitation of hemodynamically stable wide complex tachycardia in patients with normal cardiac function.²⁸⁻²⁹ Amiodarone, however, has been advocated as an alternative. This is because of the fact that both agents are effective in the treatment of ventricular and supraventricular tachycardias.

A versatile drug, procainamide can be administered in both an oral and intravenous form. Prolonged oral use of procainamide, however, is not advocated because it is more poorly tolerated than other currently available alternatives and is contraindicated in renal failure. Furthermore, the EVSEM trial demonstrated procainamide and other class I agents to be less effective in the treatment of ventricular tachyarrhythmias than sotalol and amiodarone.³⁰

Dosage and Administration

In the acute setting, it is administered with a loading dose of 15 to 18 mg/kg over 20 to 30 minutes, but this dose should be reduced to 12 mg/kg in significant renal or cardiac impairment. Blood pressure and continuous ECG monitoring is mandatory to detect acute hypotension, QRS, and Q-Tc prolongation. Alternatively, it can be administered intravenously at a dose of 100 to 200 mg over 5 minutes to a maximum dose of 1000 mg. ACLS guidelines suggest infusing 20 mg/min until arrhythmia is controlled, hypotension occurs, QRS complex widens by 50% of its original width, or a total of 17 mg/kg is given. Maintenance intravenous infusion is administered at a dose of 1 to 4 mg/min.

Pharmacokinetics

Procainamide is acetylated in the liver by *N*-acetyltransferase to *N*-acetylprocainamide (NAPA), an electrophysiologically active product with antiarrhythmic class III properties. This product has a plasma half-life of 4 to 15 hours and is renally cleared. Rate of acetylation varies individually and variation in renal clearance makes monitoring of both procainamide and NAPA levels mandatory (sum of <80 μM) to prevent proarrhythmia, especially torsades de pointes.

Side Effects

Procainamide is associated with a host of side effects that include blood dyscrasia with potentially life-threatening pancytopenia and agranulocytosis, which may be mediated by either allergic, hypersensitive, or immunologic mechanisms. This can occur days to weeks after drug initiation, and necessitates immediate

Table 40–3. Commonly Used Antiarrhythmic Agents in the ICU

Drug	Usual Dosage Ranges				Half-Life (hr)	Bioavailabil-ity (%)	Metabolism	Pregnan- cy Class
	Intravenous (mg)		Oral (mg)					
	Loading	Maintenance	Loading	Maintenance				
Procain- amide	12-18 mg/kg at 0.2-0.5 mg/kg/min	1-4 mg/min	500-1000	250-1000 q4-6h	3-5	70-85	Kidneys	C
Lidocaine	1-3 mg/kg at 20-50 mg/ min	1-4 mg/min	N/A	N/A	1-2	N/A	Liver	B
Propranolol	0.25-0.5 mg q 5 min to ≤ 0.20 mg/ kg			10-200 q6-8h	3-6	35-65	Liver	C
Amiodarone	15 mg/min for 10 min, 1 mg/min for 6 hr, 0.5 mg/min thereafter	0.5-1 mg/min	800-1600 qd for 7-14 days	200-600 qd	56 day	25	Liver	D
Ibutilide	1 mg over 10 min	N/A	N/A	N/A	6		Kidneys	C
Dofetilide	2 to 5 µg/kg infusion	N/A	N/A	0.125-0.5 q12h	7-13	90	Kidneys	C
Verapamil	5-10 mg over 1-2 min	0.005 mg/kg/ min		80-120 q6-8h	3-8	10-35	Liver	C
Adenosine	6-18 mg (rapidly)	N/A	N/A	N/A				C
Digoxin	0.5-1.0 mg	0.125-0.25 qd	0.5-1.0	0.125-0.25 qd	36-48	60-80	Kidneys	C

discontinuation of the drug. Cardiac side effects include left ventricular dysfunction, hypotension, and proarrhythmia with Q–T prolongation and torsades de pointes. Other nonspecific systemic side effects include gastrointestinal disturbances with nausea and vomiting, induced systemic lupus erythematosus syndrome, pyrexia, headache, and psychosis.

Class IB

Both lidocaine and mexiletine are included in this classification; however, mexiletine is only available in an oral form, which limits its use in the critical care setting. It may be helpful in suppressing automatic or re-entrant ventricular arrhythmias but this is only as an adjunct to other primary antiarrhythmics.

Lidocaine

Lidocaine is a Na⁺ channel blocker of intermediate potency and results in a decrease in V_{max} and therefore decreased conduction velocity. In contrast to class IA or IC antiarrhythmics, lidocaine causes a shortening of the action potential duration probably through an increase in I_{K1} activity.³¹ It also depresses automatic activity by decreasing the slope of phase 4 diastolic depolarization. These effects are limited to Purkinje fibers

and little or no effect is seen on atrial myocardium or on slow response tissues (SA and AV nodes).³² Interestingly, published data from prior trials demonstrated an increased incidence of asystole and bradycardia with lidocaine use³³; however, this has been debated.

Clinical Effects

Lidocaine is typically very well tolerated hemodynamically. Only rarely, with very high doses, is blood pressure and cardiac output depressed due to reduced contractility and ejection fraction. At therapeutic doses, there are no detectable changes on the ECG.³⁴

Indications

The role of lidocaine use and its potential benefits in acute myocardial infarction has been the source of heated debate as far back as the 1960s. Although earlier studies pointed to a decreased incidence of primary ventricular fibrillation and therefore reduced mortality, they were limited by lack of randomization and small sample sizes. Subsequent studies using prophylactic lidocaine in acute myocardial infarction demonstrated a decreased incidence of ventricular fibrillation but no significant decrease in all-cause mortality.³⁵⁻³⁶ Subsequent

meta-analyses also demonstrated a decreased incidence of ventricular fibrillation but not overall mortality.^{33,37-39} These findings were further compounded by an increasing body of evidence associating prophylactic antiarrhythmics with increased mortality, including the IMPACT study.⁴⁰ Mexiletine is often considered to be an “oral” form of lidocaine. As a result, prophylactic lidocaine use in acute myocardial infarction is no longer recommended.⁴¹

Currently, ACLS guidelines only recommend the use of lidocaine in the setting of shock-refractory ventricular fibrillation or pulseless ventricular tachycardia, and it is still not the preferred agent, coming in after amiodarone.²⁸ There is good evidence that other agents are more effective.⁴²

Lidocaine can be used in hemodynamically stable patients with recurrent polymorphic ventricular tachycardia and prolonged Q–Tc at baseline (torsades de pointes), since amiodarone and other Q–T prolonging agents should be avoided. However, evidence suggests that administration of magnesium, rapid rate ventricular pacing to 100 to 120 beats per minute, and isoproterenol infusion are more effective.⁴³

Lidocaine can be used as adjunctive therapy in patients having acute ischemic ventricular tachycardia or ventricular fibrillation, after reversing the acute ischemic cause, and if refractory to β -blocker and amiodarone therapy.

Dosage and Administration

A loading dose of 1.5 mg/kg is administered over 2 to 3 minutes, followed by a maintenance infusion rate of 1 to 4 mg/min. Since the bolus dose has a half-life of 15 minutes and the maintenance infusion requires 2 to 3 hours to achieve a steady state, repeated boluses may be required to achieve the desired effect.⁴⁴ A reduced dose is necessary in liver impairment or heart failure. Lidocaine can also be injected intramuscularly at a dose of 4 to 5 mg/kg, achieving therapeutic concentrations more reliably via the deltoid than the gluteal muscle.⁴⁴

Pharmacokinetics

Lidocaine undergoes extensive first pass metabolism and is therefore only administered in an intravenous form. It has a short half-life of 3 hours and is metabolized to metabolites with weak class I antiarrhythmic properties: glycinexylidide and monoethylglycinexylidide. It is highly bound to α_1 -acid glycoprotein, which may be increased in heart failure, making the free active drug less readily available. On the other hand, reduced clearance and volume of distribution in heart failure result in higher levels of the active drug, requiring a dosage reduction. Therapeutic plasma lidocaine levels range between 1.5 to 5.0 $\mu\text{g/mL}$ and should be monitored.

Side Effects

The most common side effects are related to central nervous system toxicity,⁴⁵ with various mental status changes that are usually mild and resolve with dose reduction. These are most frequently seen in the elderly, patients with heart failure, and those with liver impairment. Tremors are an early bedside sign of toxicity. High plasma levels have been shown to provoke generalized seizures.⁴⁶ Primary cardiovascular side effects include sinus slowing, asystole, hypotension, and shock. These occur with overdosing or with the overly rapid administration of lidocaine.

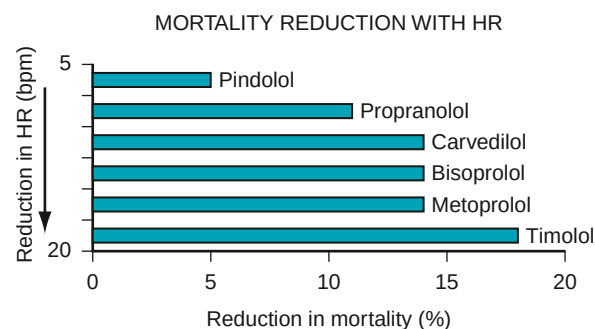


Figure 40-5. Relationship between the highest reductions in mortality in patients receiving β -blocker therapy with the greatest reductions in heart rate (HR). (Adapted from Kjekshus JK: Importance of heart rate in determining beta-blocker efficacy in acute and long-term acute myocardial infarction intervention trials. *Am J Cardiol* 1986;57:43F-49F.)

Class IC

This class of antiarrhythmics is not used in the modern day critical care setting. This is primarily due to the results of both of the CAST and CAST II trials.^{1,2} Both trials were ended prematurely after investigators noted a significant increase in arrhythmic deaths in patients treated with encainide, flecainide, and moricizine versus a placebo for suppression of premature ventricular contractions following myocardial infarction.

Class II

β -blockers have had a major impact on the treatment of cardiac arrhythmias. They are the only antiarrhythmics with a proven mortality benefit in the treatment of patients with acute myocardial infarction, coronary artery disease, and congestive heart failure. Although there are many different β -blockers, they are generally considered to possess a class effect with most of them providing equal benefit when titrated to equivalent therapeutic dosage. They may be generally classified into those with selective β_1 (cardiac) and those with β_2 (noncardiac) activity. Some have both. In addition, carvedilol also possesses α_1 -blocking activity and is seen as primarily beneficial in patients with congestive heart failure.

Some β -blockers such as pindolol also exert an intrinsic sympathomimetic action, which results in moderate activation of the β -receptor. This can ultimately result in an attenuated bradycardic effect or even a tachycardic response. This may have an adverse effect in patients with ischemic heart disease, and in fact the best mortality benefit has been demonstrated in β -blockers with the most bradycardic effects (Fig. 40-5).

The electrophysiologic effects of β -blockers are numerous but are thought to be predominantly due to blockade of the deleterious effects of adrenergic stimulation. These deleterious effects include abnormal automaticity due to enhanced phase 4 spontaneous depolarization, delayed after depolarizations (DADs) and triggered activity, and re-entrant excitation.⁴⁷ β -blockers have a profound effect on both the SA and AV nodes because of their dense adrenergic innervations, whereas they have a minimal to moderate effect on atrial, ventricular, and accessory pathway tissues unless these tissues are ischemic.

They also exert a membrane-stabilizing effect, which depresses excitability, delays conduction velocity, and prolongs refractoriness. In addition, β -blockers have been shown to

Table 40–4. Commonly Used β -blockers in the Critical Care Setting

Drug	β_1 Potency	β_1 Selectivity	IV Dosage	Half-Life	Elimination	Other Properties
Atenolol	1.0	++	5 mg every 10 min up to 10 mg	6–9 hr	Renal	None
Metoprolol	1.0	++	5 mg every 2–5 min up to 15 mg	3–4 hr	Hepatic	None
Esmolol	0.02	++	500 μ g/kg loading dose then 50–300 μ g/kg/min	9 min	Blood esterases	None
Propranolol	1.0	0	1 mg/min up to 5 mg	3–4 hr	Hepatic	Membrane stabilizing action
Labetalol	0.3	0	20 mg IV push then 40–80 mg every 10 min up to 300 mg, or infusion at 2 mg/min up to 300 mg	3–4 hr	Hepatic	α -Blocker

increase the ventricular fibrillation threshold, making ventricular tachycardia less likely to degenerate into ventricular fibrillation. This is probably the reason for the reduced incidence of sudden cardiac death noted in congestive heart failure trials using β -blockers.^{48,49,50}

Indications

β -blockers can be used for a wide variety of cardiac arrhythmias. These include supraventricular arrhythmias such as sinus tachycardia without an underlying reversible cause such as that seen in inappropriate sinus tachycardia or temporarily in hyperthyroidism until the primary disorder is addressed.⁵¹ They are also useful in slowing the ventricular response in arrhythmias such as atrial fibrillation, atrial flutter, or atrial tachycardia.⁵¹ They should not be used with the aim of converting these rhythms to sinus rhythm because they are ineffective, given their modest effects on nonischemic atrial and ventricular muscle tissue. Their activity is most effective on adrenergically innervated tissue, such as the SA and AV nodes.

Ventricular arrhythmias in the peri-infarct or post-coronary artery bypass surgery period, likely related to ischemic tissues, respond well to β -blocker therapy. They are also effective in suppression of adrenergically mediated or exercise induced ventricular arrhythmias such as right ventricular outflow tract tachycardias. β -blockers have also been shown to be effective in reducing sudden cardiac death in patients with long QT syndrome.

Dosage, Administration, and Pharmacokinetics

Multiple β -blockers are currently available for intravenous administration to critically ill patients. Listed here are the most commonly available of these drugs, appropriate doses, and routes of elimination (Table 40-4).

Side Effects

There is concern about exacerbating heart failure in patients with borderline compensation, as sympathetic drive may play an important role in maintaining cardiac output. Despite this concern, the evidence is that β -blockers are beneficial in heart failure patients and this effect of exacerbating heart failure was only observed in 6% of patients treated with carvedilol.⁵² Although increased dizziness and hypotension may occur, the absolute increase of these side effects was small and did not necessitate drug discontinuation in studies.⁵³ Significant bradyarrhythmias

have been noted in patients with SA node dysfunction or pre-existing AV node disease and may require back-up pacing if drug administration is necessary for the treatment of concomitant tachyarrhythmias.

Noncardiac adverse effects include exacerbation of bronchospastic disease, but this is typically observed with nonselective β -blockers. β_1 selective agents do not confer complete protection and should be used cautiously in these patients initially. The same applies to the use of β -blockers in patients with severe peripheral vascular disease because the drugs may exacerbate their symptoms; however, this is less noted with β_1 selective agents.⁵⁴

Retarded response to hypoglycemia due to blockade of epinephrine has been observed; however, data suggest that this is less serious with β_1 selective agents.⁵⁵ Although fatigue, depression, and sexual dysfunction are often-cited side effects, a systematic review of randomized trials found only small increases in these effects.⁵⁶

Class III

This class includes amiodarone, ibutilide, sotalol, dofetilide, azimilide, and bretylium. It is important to note that while classified as a class III agent, amiodarone has multiple actions across different classes. Since neither intravenous sotalol or azimilide have been approved by the Food and Drug Administration in the United States, they are unavailable for use in this country. In the presence of amiodarone and ibutilide availability, there is little use for dofetilide in the critical care setting. Bretylium is not currently used in modern medicine; therefore a discussion of the first two drugs only will be addressed in this chapter.

Amiodarone

Amiodarone is considered by some to be the most effective antiarrhythmic agent currently available. It is available in both intravenous form and oral tablets. Its wide range of effects across different antiarrhythmic classes makes it suitable for both acute therapy and long-term management of a host of arrhythmias with different mechanisms. These range from automatic to re-entrant supraventricular and ventricular arrhythmias. It has a very low incidence of proarrhythmia,^{57–5} making it ideal for administration in acute critical illness or for outpatient initiation. Its Achilles heel is its wide range of side effects that become more common with long-term therapy.

Initially developed in Belgium as an anti-anginal agent in 1962, it was later approved by the FDA for the treatment of ventricular arrhythmias in 1985. It is classified as a class III antiarrhythmic agent because of its effect of prolonging the action potential duration and increasing the refractory period of atrial and ventricular tissue.⁶⁰ It has this effect by virtue of its ability to block I_{Kr} , but also I_{Ks} with chronic use. In addition, it inhibits Na^+ and Ca^{2+} currents, which are class I and IV properties, respectively.⁶⁰ Its class I properties can result in widening of the QRS complex. It also has weak class II (β -blocker) activity and α_1 -blocking action with resultant bradycardia and vasodilation, which may mediate its anti-ischemic effects. Finally, it decreases peripheral conversion of T_4 to T_3 and impairs T_3 binding to myocytes, resulting in hypothyroid metabolism in cardiac cells.⁶¹

The degree of amiodarone's various properties and antiarrhythmic effects varies depending on whether it is given in an intravenous or oral preparation. Compared with the intravenous form, the oral preparation of amiodarone results in a more significant increase in action potential duration of atrial and ventricular tissues, slowing of phase 4 depolarization and automaticity, ventricular refractoriness, prolongation of the Q-Tc interval, and blockade of T_4 to T_3 conversion.⁶²

Clinical Effects

As a result of the various effects of amiodarone, the ECG may reflect slowing of the sinus rate, prolongation of the P-R interval and earlier Wenckebach block due to increased AV node refractoriness. In addition, widening of the QRS may also be noted. Q-Tc prolongation is also observed but is generally well tolerated and rarely causes proarrhythmia.

Due to its ability to prolong the action potential and increase refractoriness, it affects a re-entrant circuit of arrhythmia by prolonging the wave length and decreasing the excitable gap. This results in the leading edge of the re-entrant circuit colliding with the wake of the tail edge of the circuit, thereby extinguishing the re-entrant circuit and terminating the arrhythmia. As with other class III agents, it exhibits reverse use dependence properties with less efficacy noted at higher heart rates and more Q-Tc prolongation and proarrhythmia noted at slower heart rates.

In addition to its bradycardic effect, amiodarone results in a drop in blood pressure probably secondary to its β -blocker, calcium channel blocker, and α_1 -blocking actions. This can result in increased cardiac output secondary to a reduction in afterload.^{63,64} In addition, its smooth muscle relaxation effect results in coronary artery vasodilation, thereby potentially decreasing coronary ischemia, which may also contribute to its antiarrhythmic properties. It does not depress left ventricular function,⁶⁵ thereby avoiding heart failure exacerbations. For these reasons, it is safe and approved for use in patients with left ventricular dysfunction.

Indications

Amiodarone is a unique antiarrhythmic agent because of its multiple class effects. It is effective in the acute treatment of both ventricular and atrial arrhythmias; however it is currently approved by the FDA for the treatment of life-threatening ventricular arrhythmias only.

The most recent ACLS guidelines recommend amiodarone for the treatment of ventricular fibrillation or pulseless ventricular

tachycardia after cardioversion shocks. It is also recommended for treatment of stable monomorphic ventricular tachycardia or stable polymorphic ventricular tachycardia with a normal Q-T interval on the baseline ECG.²⁸

Part of the controversy surrounding the use of amiodarone has been the conflicting results of different antiarrhythmic trials. For the secondary prevention of sudden cardiac death, the CASCADE trial demonstrated amiodarone to be more effective than conventional therapy.⁶⁶ On the other hand, both the EMIAT and CAMIAT studies for the primary prevention of sudden cardiac death demonstrated amiodarone reduced cardiac death compared with a placebo but had no effect on all-cause mortality.^{67,68} The GESICA trial concluded that amiodarone significantly reduced mortality in a population of mostly nonischemic cardiomyopathy,⁶⁹ but this was contradicted by the CHF-STAT study that had more ischemic cardiomyopathy patients and showed no mortality difference.⁷⁰ The more recent SCDHeFT trial had both ischemic and nonischemic cardiomyopathy patients and showed amiodarone was no more effective than a placebo in the primary prevention of sudden cardiac death.⁷¹

Amiodarone is very effective for the treatment of atrial arrhythmias, especially atrial fibrillation. In the CTAF study, amiodarone was more effective at maintaining sinus rhythm than sotalol or propafenone.⁷² This was also echoed by findings from the SAFE-T trial, which compared amiodarone to sotalol or a placebo.⁷³ The ability to use amiodarone in critically ill patients for rate control, maintaining sinus rhythm, and improving hemodynamics, makes its use even more applicable to the acute care setting. Similar to β -blocker therapy, multiple studies have shown amiodarone to be effective in decreasing the incidence of postoperative atrial fibrillation following cardiac surgery, possibly resulting in shorter hospital stays, cost reduction, and decreased morbidity.⁷⁴

Dosage and Administration

In the critical care setting, intravenous administration is the most relevant route of administration. Whether for recurrent hemodynamically unstable ventricular tachycardia or for atrial fibrillation with a rapid ventricular response, a loading dose of 150 mg given over 10 minutes is recommended. This is followed by an intravenous infusion at a rate of 1 mg/min for 6 hours and then 0.5 mg/min, delivering a total of 1050 mg in 24 hours. Central venous access catheter delivery is preferable since concentrations above 2 mg/mL can result in significant peripheral vein phlebitis.

Oral administration of amiodarone is associated with a delayed onset of action of approximately 2 to 3 days because of its highly lipophilic nature, resulting in a very large volume of distribution. This is also the reason for its prolonged half-life, which can be up to 25 to 100 days.

Pharmacokinetics

Amiodarone undergoes deiodination and is metabolized in the liver to desethylamiodarone, an active metabolite with properties similar to the parent drug but a much longer elimination half-life. It is subsequently excreted via hepatic and gastrointestinal routes. Dose adjustment is necessary in patients with hepatic impairment and routine hepatic liver function monitoring is required. Renal metabolism or elimination does not occur at all and amiodarone is not removed by either peritoneal or hemodialysis. Consequently no dosage adjustment is

required in patients with renal insufficiency or in those receiving hemodialysis.

Intravenous amiodarone can achieve peak drug levels in as little as 30 minutes to a few hours following administration. With oral long-term administration it may take several weeks or months to achieve a steady state. This is due to amiodarone's highly lipophilic nature causing it to have a large volume of distribution. Consequently, complete saturation of peripheral tissues, such as adipose, muscle, liver, and spleen, needs to occur before achieving a steady state.

Side Effects

In the acute care setting, amiodarone is typically given to critically ill patients with significant arrhythmias. Hemodynamic and arrhythmia monitoring is the rule in such patients to detect potential side effects such as significant hypotension with intravenous administration of the drug. Regular Q-Tc monitoring is important to detect rare episodes of torsades de pointes (1% to 2% incidence). Telemetry allows the detection of bradyarrhythmias because of decreased automaticity or AV node refractoriness, although this is less common with the intravenous form of amiodarone.

Long-term oral therapy with amiodarone is associated with a host of potential side effects. These include cardiac bradyarrhythmias, pulmonary fibrosis, hepatic dysfunction and cirrhosis, hyperthyroidism and hypothyroidism, skin discoloration, optic neuritis, CNS dysfunction, peripheral neuropathy, and many others. This underscores the need for routine physical examinations and biannual blood tests.

Ibutilide

Ibutilide is a class III agent that is available only in an intravenous formulation because of extensive first pass metabolism making an oral formulation ineffective.⁷⁵ It blocks I_{Kr} during phase 3 of the action potential with a resultant increase in action potential duration and refractoriness of both atrial and ventricular tissue. This is manifested by Q-Tc prolongation and the potential risk for proarrhythmia. It also blocks a slow sodium current during the repolarization phase of the action potential. Like other class III agents, it exhibits reverse use dependence with longer Q-Tc prolongation at slower heart rates.

Clinical Effects

Ibutilide has minimal effects on heart rate and its major effect on the surface ECG is prolongation of the Q-Tc. It is very well tolerated hemodynamically and is not associated with hypotension.

Indications

Ibutilide is indicated for the acute conversion of atrial fibrillation or atrial flutter to sinus rhythm. Although electrical cardioversion is far more successful, ibutilide can be used to achieve chemical cardioversion without necessitating anesthesia typically required for electrical cardioversion. It is most successful in treating atrial fibrillation or atrial flutter of relatively short duration.⁷⁵ It can also be given to facilitate electrical cardioversion in patients that are difficult to cardiovert electrically and have required multiple shocks or exhibit early recurrence of atrial fibrillation after electrical cardioversion.⁷⁶ In addition, ibutilide has been shown to be as effective as procainamide in terminating atrial fibrillation with WPW syndrome.⁷⁷

Dosage and Administration

Due to its potential for proarrhythmia, ibutilide should be administered with continuous telemetry. Electrolytes should be optimized (especially serum magnesium and potassium levels), and an external defibrillator should be available in case of polymorphic ventricular tachycardia.

The typical dose is 1 mg to be infused over 10 minutes, which can be repeated again in 10 minutes if the first dose was ineffective and if there is no significant lengthening of the Q-Tc. In patients less than 60 kg, the recommended dose is 0.01 mg/kg. If marked prolongation of the Q-Tc is noted during administration of the infusion, or if cardioversion occurs, the infusion should be stopped. Continuous telemetry monitoring is mandatory for at least 4 hours and preferably 6 hours following the end of the infusion.

Pharmacokinetics

Available only in an intravenous form, it is metabolized hepatically into many metabolites, although only one has a weak antiarrhythmic effect. These metabolites are renally excreted. The half-life ranges between 2 to 12 hours and can be quite prolonged in hepatic dysfunction.

Side Effects

The most common side effect of this intravenous agent is proarrhythmia. Torsades de pointes has been observed in various studies with an incidence that varied between 3.6% and 8.3%, with episodes requiring emergency cardioversion occurring in 1.7% to 2.4%.^{78,79} The risk of developing proarrhythmia was highest in patients with heart failure.

Class IV

Only the nonhydropyridine agents in this group of medications, verapamil and diltiazem, appear to exert electrophysiologically significant cardiac effects. Their effects are mediated through their ability to block the slow calcium channel in slow response cardiac tissue (SA and AV nodes), resulting in slow phase 4 depolarization and decreased conduction velocities. This property makes them ideal for slowing the ventricular response in atrial arrhythmias, such as atrial fibrillation or atrial flutter. In addition they seem to have antiadrenergic properties very similar to those seen with β -blockers, which also contributes to slowing of the heart rate. Although they typically do not affect ventricular tissue, they have been noted to affect calcium flux across the cell membrane in conditions of metabolic disturbance. This milieu is thought to be responsible for the occurrence of early after depolarizations (EADs), which are the arrhythmic mechanism of torsades de pointes. This property seems directly related to their ability to shorten the plateau phase of the ventricular action potential.

Clinical Effects

Calcium channel blockers cause slowing of phase 4 depolarization in the SA and AV node, in addition to increasing refractoriness of the AV node. Both the sinus and the ventricular response rate slow down. Sinus slowing and P-R interval prolongation are noted on the surface ECG. Typically there are no other changes in the duration of the QRS complex and Q-T interval. They exhibit use dependence properties with increasing efficacy at higher heart rates.

Calcium channel blockers can also induce peripheral vasodilation through their smooth muscle relaxation properties. This

is noted slightly more with diltiazem than it is with verapamil and may result in hypotension. They also exert a mild negative inotropic effect, making them unsuitable in the management of hemodynamically unstable patients or patients with heart failure exacerbations having supraventricular tachycardias.

Indications

The most common indication for using calcium channel blockers is for the treatment of supraventricular tachycardia. Intravenous verapamil or diltiazem are probably equally effective. They are also commonly used for slowing the ventricular rates in atrial fibrillation or atrial flutter.

Although they are typically not used in the treatment of ventricular tachycardias, they do have a role in the treatment of certain ventricular tachycardia entities, such as right ventricular-outflow tract tachycardia or rare tachycardias, such as verapamil-sensitive ventricular tachycardia or familial catecholaminergic polymorphic ventricular tachycardia.

Dosage and Administration

Both verapamil and diltiazem can be administered intravenously with equal efficacy when rapid control of ventricular rate in atrial arrhythmias, or termination of paroxysmal supraventricular tachycardia, is desirable.⁸⁰ The verapamil loading dose is 5 to 20 mg administered over 2 minutes and lasts for up to 6 hours. A maintenance intravenous infusion at a rate of 0.005 mg/kg/min can be administered in patients who cannot take the oral form. Short acting or extended release tablets are available and the daily dose ranges between 240 mg to 480 mg daily. Diltiazem can be loaded with a 20 mg bolus administered over 2 minutes, and a maintenance infusion of 5 to 15 mg can then be used if required. Repeated boluses can be given, if necessary, 15 minutes following the initial bolus. Extended release oral tablets are available starting at a dose of 180 mg up to a maximum of 540 mg daily.

Pharmacokinetics

Both verapamil and diltiazem undergo extensive first pass effect, with only 35% to 40% bioavailability noted with the oral formulations. Both are metabolized in the liver but diltiazem is only partially excreted by the kidney (35%), and the rest is excreted through the gastrointestinal tract. Verapamil on the other hand is mostly excreted by the kidney.

Side Effects

Both drugs are generally well tolerated orally with only mild effects noted as a result of mild hypotension, such as facial flushing or dizziness. Intravenous administration can cause significant hypotension. Diltiazem does not appear to have the same drug interaction noted with verapamil, which interacts with amiodarone and dofetilide, resulting in excessive sinus rate slowing and possible sinus arrest. Both drugs can potentiate the hypotensive effects of β -blockers and increase the degree of AV node refractoriness in patients receiving digoxin.

Atypical Antiarrhythmics

Digoxin

Digoxin is the most readily available form of digitalis and is derived from the foxglove plant. The use of this cardiac glycoside has been documented for hundreds of years. It is listed as an atypical antiarrhythmic agent because its electrophysiologic

effects do not conform to any of the other previously described antiarrhythmic classes.

Digoxin has direct actions such as decreasing automaticity of the SA node and increasing the refractoriness of the AV node. Its most prominent effects, however, are its indirect effects of increasing parasympathetic activity and inhibiting sympathetic activity.⁸¹ This explains why it has little or no effect in transplanted hearts and has decreased efficacy in critically ill patients with elevated levels of sympathetic activity commonly encountered in the critical care setting.

In the atria it shortens the plateau phase, which results in decreased refractoriness with resultant increased atrial depolarization rates. It can also decrease the refractory period of accessory pathways. This combination of effects makes it contraindicated in patients with Wolff-Parkinson-White syndrome because it may facilitate an accelerated ventricular response to atrial fibrillation in these patients, which may precipitate ventricular fibrillation.

Clinical Effects

At therapeutic doses there are typically no obvious ECG effects. Sinus rate, P-R, and QRS intervals are usually unchanged. Patients with significant sinus rate slowing are those with pre-existing sinus node dysfunction. A well-known positive inotropic agent, this property has been attributed to digoxin's ability to inhibit Na^+/K^+ ATPase, which results in increased intracellular calcium that affects excitation-contraction coupling favorably. This may also be the basis for some of the drug's proarrhythmic effect. This positive inotropic activity can result in diuresis in patients treated with digoxin. Although digoxin may improve the symptoms of heart failure and decrease hospitalizations, it has been shown not to decrease mortality in heart failure patients.⁸²

Indications

The most common indication for digoxin is to slow the ventricular rate of atrial fibrillation or atrial flutter. In this modern era, however, it should not be used as first-line therapy for this indication. An understanding of the electrophysiologic effects of this medication reveals why it is not ideally suited for treatment of patients in the acute care setting. Furthermore, better and more reliable rate control can be achieved with other medications, such as β -blockers or calcium channel blockers, which can be more tightly titrated and are readily available. Infrequently, digoxin can be used as adjunctive therapy in patients with atrial fibrillation and rapid ventricular response refractory to a combination of β -blocker and calcium channel blocker therapy. Also, in patients who are hemodynamically intolerant of β -blocker therapy or calcium channel blocker therapy due to hypotension, digoxin may be useful because it generally does not cause significant hypotension.

Dosage and Administration

When rapid therapeutic serum levels are required, digoxin can be loaded with a dose of 0.5 to 1.0 mg intravenously to be divided over 18 to 24 hours, with a resultant peak effect in 2 to 4 hours. Typically the first administered dose is 0.5 mg followed by 2 doses of 0.25 mg. Daily maintenance doses are 0.125 to 0.25 mg orally, but the equivalent intravenous dosage should be reduced by 20% to 25%. These doses should be reduced in the elderly and in patients with renal insufficiency. Digoxin serum

levels can be helpful initially to ascertain that a therapeutic level has been achieved after loading. Serum concentrations of 0.8 to 2.0 ng/mL are the goal. A serum concentration higher than 2.0 indicates toxicity and the potential for proarrhythmia.

Pharmacokinetics

Oral administration results in absorption by the stomach and small intestine with resultant bioavailability of 60% to 80%. Although digoxin is metabolized in the liver, it is excreted by the kidney almost unchanged. It has a 36 to 48 hour half-life, but this may be longer in patients with renal insufficiency. Digoxin levels are not significantly altered by hemodialysis because it is extensively protein-bound.

Side Effects

Digoxin has significant drug-to-drug interactions with a host of medications but notably with amiodarone and verapamil because both decrease its metabolism and can result in elevated levels of digoxin. Digoxin toxicity is more likely to occur in the presence of renal failure, advanced age, and electrolyte abnormalities such as hypomagnesemia and hypokalemia. The latter does so by decreasing renal tubular secretion of digoxin and increasing tissue binding of the drug. Elevated levels of calcium can predispose to increased delayed afterdepolarizations, which is one of the main proarrhythmic mechanisms of digoxin, in addition to increased sympathetic activity with enhanced automaticity.

Noncardiac manifestations of digoxin toxicity include anorexia, nausea, and vomiting. Gastrointestinal symptoms are typically early signs of toxicity. Central nervous system symptoms include headaches and visual disturbances, such as halo vision, scotoma, and altered color perception.

Cardiac toxicity is typically in the form of various arrhythmias. Almost any type of arrhythmia has been reported with digoxin toxicity; however, classical examples include atrial tachycardia with advanced AV block and accelerated junctional rhythms, in addition to bidirectional ventricular tachycardias.

Treatment of toxicity usually involves stopping the medication in patients who are hemodynamically stable along with correction of electrolyte abnormalities. Administering calcium should be avoided as this can precipitate life-threatening arrhythmias by further increasing potassium levels in a setting of preexisting hyperkalemia secondary to digoxin toxicity. In patients who are unstable as a result of their arrhythmias, digoxin immune FAB antibody can be administered to bind digoxin, which can be lifesaving.⁸³ Cardioversion should be avoided in digoxin toxicity and if absolutely necessary, should be done at low energy as this may precipitate ventricular fibrillation because of the pre-existing myocardial increased excitability.

Adenosine

Adenosine is an endogenous nucleoside found throughout the whole body. It has become the drug of choice for aiding in the diagnosis of supraventricular tachycardias and terminating both AV reciprocating tachycardia and AV nodal re-entrant tachycardia.

It plays an important role as a biochemical intermediate and regulator of cellular metabolism. Its actions are mediated through its interaction with A1 and A2 receptors, in addition to G proteins, to exert effects on potassium and calcium channels.

Adenosine primarily activates the I_{KAdo} outward potassium current, which is absent in ventricular tissue but present in atrial tissue,⁸⁴ causing shortening of the action potential in the atria. It inhibits the “funny” channel (I_f), which results in decreased sodium influx in SA and AV node tissue. This decreases automaticity in these tissues and therefore has a negative chronotropic effect. Its indirect actions include inhibition of intracellular cAMP generation, which in turn decreases the catecholamine driven inward calcium current and transient inward current. These essentially anti-adrenergic effects may play a role in its antiarrhythmic properties. It also has the ability to decrease the sinus node rate by decreasing sinus node and atrial automaticity, in addition to decreasing both sinus node and AV node conduction properties.

Indications

Adenosine is indicated for the rapid termination of supraventricular re-entrant tachycardias. It affects the antegrade slow pathway more readily than the retrograde fast pathway in patients with dual pathway physiology. Similarly, it affects the antegrade fast pathway limb of bypass mediated tachycardias more than the retrograde bypass limb of the tachycardia. This means that administration of adenosine can terminate both types of these re-entrant supraventricular tachycardias, which are AV node dependent, by affecting the antegrade limb of the tachycardia. Typically the last cardiac activation noted is atrial activity manifested by a nonconducted P wave at the break of the tachycardia before resumption of normal sinus rhythm. This may be difficult to see, however, as sometimes the P wave is obscured by the preceding QRS complex.

In atrial tachycardias or atrial flutter, the typical response to an adenosine bolus is the occurrence of complete AV node block, which can be profound sometimes, without termination of the atrial arrhythmia itself. The atrial arrhythmia may now be seen more clearly because of the absence of QRS complexes. The caveat is that approximately 10% of atrial tachycardias are adenosine sensitive and can terminate with administration of adenosine resulting in a misleading diagnosis of the mechanism of the arrhythmia.

Adenosine is also useful in terminating a type of idiopathic ventricular tachycardia that typically has left bundle inferior axis morphology and occurs in structurally normal hearts.⁸⁵ These tachycardias originate from the right ventricular outflow tract and are adrenergically driven. They are thought to be due to delayed afterdepolarizations caused by cAMP-mediated triggered activity.

Although adenosine can be given to differentiate hemodynamically stable wide complex tachycardia into supraventricular tachycardia with aberrancy and ventricular tachycardia, this can be misleading and is no substitute for expert electrocardiographic consultation.

Dosage and Administration

Intravenous boluses are given at a dose of 12 mg in a peripheral vein but should start at 6 mg when administered via a central venous catheter. Tachycardia termination is typically seen within 15 to 30 seconds of administering the bolus. If the initial dose is ineffective at terminating the arrhythmia or producing transient complete AV block, it can be repeated at the same dose or at a higher dose up to 18 mg. Its half-life of 6 seconds allows such rapid clearance of the drug that it can be readministered

within 30 seconds without accumulation of the drug. Hypotension is not typically noted as the drug has usually been cleared before it reaches the systemic circulation.

Pharmacokinetics

Adenosine undergoes immediate and rapid clearance in the bloodstream secondary to cellular uptake and enzymatic degradation. Although its half-life is difficult to determine, it has been estimated to be between 0.5 to 6 seconds.⁸⁶ Therefore, it is best suited for rapid bolus administration for termination of arrhythmias or potentially to aid in the diagnosis for arrhythmias as opposed to ongoing therapy for arrhythmias.

Side Effects

Adenosine's short half-life makes side effects very mild and transient. Most patients report facial flushing, which is related to transient vasodilation, and chest pain. It can also precipitate bronchospasm, resulting in dyspnea, and should be used with caution in patients with significant bronchial airway disease. Frequent premature atrial or ventricular contractions have been observed in addition to precipitation of atrial fibrillation in up to 15% of patients.⁸⁷

Conclusion

Antiarrhythmics have an important role in the treatment of a wide variety of arrhythmias that are associated with significant morbidity and mortality. It is important to remember, however, that these drugs are also associated with a host of side effects and limitations. Novel antiarrhythmics are constantly being evaluated in search of the holy grail of combined high efficacy and high safety in the treatment of cardiac arrhythmias. In the meantime, we will have to continue to rely on currently available medicines and use them in a targeted way to derive the greatest therapeutic benefit coupled with the highest safety in the management of critically ill patients.

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Analgesics, Tranquilizers, and Sedatives

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CHAPTER 41

Opioid Analgesics

Antipsychotic Agents

THE CORONARY CARE UNIT (CCU) has evolved drastically over the past several decades from an area primarily limited to the management of the acute coronary insufficiency patient to a full-fledged cardiac intensive care unit (CICU) concerned with a multitude of life-threatening cardiovascular diseases. With this development has also occurred the parallel need for more adequate and flexible analgesia and sedation because many of these critically ill patients undergo invasive procedures, such as balloon angioplasty and placement of intra-aortic balloon pumps, pulmonary artery catheters, and ventricular assist devices. In addition, many require long-term mechanical ventilation. The goal of therapy in the CICU is frequently more complicated than the simple relief of myocardial ischemia or infarction pain and the anxiety that accompanies it. For example, today's CICU practitioner is more likely to encounter an older and frailer patient, and although the elderly may benefit greatly from analgesic or sedative medications, they are also more likely to suffer the side effects of these medications.¹ Likewise, CICU practitioners today are likely to encounter patients who require sedation for long-term mechanical ventilation.

Only a few decades ago, the options for analgesic and sedative therapy in the CICU were essentially limited to the narcotic morphine sulfate and the benzodiazepine chlordiazepoxide. Since that time, many new agents have been developed for the treatment of pain, anxiety, and delirium, and these often possess more desirable pharmacokinetic and pharmacodynamic properties than their predecessors. Although some of the older agents, especially morphine, have retained clinical usefulness because of their unique and beneficial pharmacokinetic and hemodynamic properties, many agents have been replaced by new drugs that have improved efficacy and safety.

This chapter describes the analgesic and sedative agents available for use in the critical care setting, with special attention paid to those drugs of greatest usefulness in the CICU. Intramuscular and other injection routes of administration are not discussed here because the absorption, bioavailability, and pharmacokinetic properties of agents not administered by intravenous injection are highly unpredictable in critically ill patients. Agents used specifically for the induction of anesthesia also are not discussed in detail. Readers are referred to more standard anesthesia texts for information regarding these drugs.

Within each classification of medication discussed, basic mechanisms of drug function (e.g., receptor physiology, site of action) are reviewed, and the pharmacokinetics and pharmacodynamics of each agent are discussed. Clinical uses of the

agents, with special attention paid to those indications most germane to the CICU, are addressed. Finally, established agents that have found new clinical applications in the CICU patient are described.

Opioid Analgesics

Morphine

History and Structure

Morphine has been used for analgesia and sedation for many centuries, but it has only been used by the intravenous route for approximately 150 years.⁴ Morphine is the only naturally occurring opiate agent obtained from the poppy plant, *Papaver somniferum*, still used with frequency in the critical care setting. Its proper chemical class is the phenanthrene group, which it shares with the agent codeine.⁵ Morphine occurs in essentially a rigid, pentacyclic type of structure.

Site of Action and Receptor Physiology

Since the first description of the opiate receptor in 1973, the mechanism for sedation and pain relief has been investigated.⁶ The initial system included only the μ -receptor; since then, a number of different opiate receptors have been discovered and named, including β -, κ -, σ -, and ϵ -receptors (Table 41-1).⁷⁻⁹ Additional investigations have shown that the μ -receptor system actually includes two subtypes: the μ_1 -receptor and the μ_2 -receptor. Although research is ongoing, it appears that the μ_1 -receptor is responsible primarily for analgesia and sedation, whereas the μ_2 -receptor may be responsible for euphoria and addiction in addition to analgesia.^{9,10} Both the δ - and κ -receptors may be responsible for mediating respiratory depression. The σ -receptor seems to be related to those physiologic responses usually associated with acute withdrawal syndromes, specifically dysphoria, hallucinations, mydriasis, tachycardia, and hypertension.¹¹ Based on these findings, opioid agents have been designed as selective agonists of certain receptors to maximize beneficial physiologic effects while minimizing deleterious ones. The greater μ -specificity of the synthetic opioid fentanyl compared with morphine is an example. Furthermore, agents with partial antagonist properties (e.g., nalbuphine) have been designed to simultaneously act on several opiate receptors, in this case the κ - and μ -receptors, to prevent respiratory depression while allowing analgesia.

The different opiate receptors are located in diverse anatomic sites throughout the central nervous system so it is apparent

Table 41-1. Characteristics of Opioid Receptors

Receptor	Tissue Bioassay	Agonists	Major Actions
Mu			
Mu ₁	Guinea pig ileum	Morphine Meptazinol Phenylpiperidines	Analgesia Bradycardia Sedation
Mu ₂	Guinea pig ileum	Morphine Phenylpiperidines	Respiratory depression Euphoria Physical dependence
Delta	Mouse vas deferens	d-Ala-d-Leu Enkephalin	Analgesia (weak) Respiratory depression
Kappa	Rabbit vas deferens	Ketocyclazocine Dynorphin Nalbuphine Butorphanol	Analgesia (weak) Respiratory depression Sedation
Sigma		SKF 10.047 Pentazocine	Dysphoria-delirium, mydriasis Hallucinations Tachycardia Hypertension
Epsilon	Rat vas deferens	β-Endorphin	Stress response Acupuncture

Adapted from Bailey PL, Stanley TH: Narcotic intravenous anesthetics. In Miller RD (ed): Anesthesia, 3rd ed, vol 1. New York, Churchill Livingstone, 1990, p 281.

that anatomy and receptor type dictate the pharmacodynamic effects of opiate agents. Whereas opiate receptors are located in a number of distinct areas in the brain and spinal cord, the highest density of receptors is located in the substantia gelatinosa of both the cerebral cortex and spinal cord, the periaqueductal gray areas, the thalamus, and the hippocampus.¹² Of these areas, laminae II through V of the substantia gelatinosa and the periaqueductal gray areas appear to have the highest concentrations of μ -receptors and hence the greatest input with respect to analgesia. As a general rule, the gray matter of the central nervous system contains more opiate receptors than does the white matter.¹³

Pharmacokinetics, Pharmacodynamics, and Metabolism

Morphine has a rapid initial redistribution phase of 1 to 1.5 minutes and an initial elimination half-life ($t_{1/2\alpha}$) of 10 to 20 minutes. Its terminal elimination half-life ($t_{1/2\beta}$) is much longer (between 2 and 4.5 hours).¹⁴ Morphine is unique compared with the other commonly used opioid agents in that it has relatively low lipid solubility (Table 41-2). Interestingly, the shape of the morphine elimination curve is nearly identical to that of fentanyl, even though it is well known that the clinical behavior of the two drugs (e.g., onset time, offset time, duration of action) is quite different. This is explained by the following comparison between fentanyl and morphine, which is intended to illustrate how two drugs with similar pharmacokinetic properties can have different pharmacodynamic profiles. Compared with fentanyl, morphine has low lipid solubility (it is approximately 40 times less lipid soluble than fentanyl) and therefore has slow penetration of the blood-brain barrier.⁵ In contrast, the high lipid solubility of fentanyl allows rapid penetration of the blood-brain barrier, which leads to a peak effect within several minutes. Conversely,

it is this same property (lipid solubility) that allows fentanyl's rapid redistribution away from the brain and hence its short duration of action. Morphine, with its greater water solubility, crosses the blood-brain barrier much more slowly than fentanyl, resulting in a slower time to peak effect (20 to 30 minutes; Fig. 41-1). Similarly, once morphine has entered the brain, its lower lipid solubility prevents rapid redistribution and hence allows a longer clinical duration of action than fentanyl. Even though morphine appears to be pharmacokinetically similar to fentanyl, it typically has a slower onset time and longer duration of action.

Morphine is metabolized by both the liver and the kidneys. Although the liver is responsible for the majority of its metabolism, 40% is metabolized by the kidneys.¹⁵ The major metabolic byproduct of morphine metabolism is morphine-3-glucuronide, which is known to have intrinsic opiate activity roughly one half that of morphine.¹⁶ When using morphine in patients with renal failure, the presence of this compound is important because cases of prolonged sedation do occur.^{17,18}

Cardiovascular and Hemodynamic Effects

For many years, morphine has been used in the management of acute myocardial ischemia and infarction pain and for sedation in patients with underlying myocardial disease.¹⁹ Morphine has distinct pharmacodynamic and hemodynamic properties that make it advantageous in cardiac patients. Perhaps the most important of these is morphine's ability to decrease venous and arterial tone.^{20,21} It appears that the increase in venous capacitance produced by morphine is relatively greater than the decrease in arterial resistance.²² This effect on venous capacitance is dose-related, and with large doses it is possible to decrease preload to the point of hypotension.²³ In certain cardiac patients, a modest decrease in preload, as occurs with a dose of

Table 41-2. Physicochemical and Pharmacokinetic Data of Commonly Used Opioid Agonists

	Morphine	Meperidine	Fentanyl	Sufentanil	Alfentanil
pKa	8	8.5	8.4	8	6.5
Percent un-ionized at pH 7.4	23	<10	<10	20	90
Octanol/H ₂ O partition coefficient	1.4	39	813	1778	145
Percent bound to plasma protein	20-40	70	84	93	92
$t_{1/2\pi}$ (min)	1-2.5		1-2	1-2	1-3
$t_{1/2\alpha}$ (min)	10-20	5-15	10-30	15-20	4-17
$t_{1/2\beta}$ (hr)	2-4	3-5	2-4	2-3	1-2
V_{doc} (L/kg)	0.1-0.4	1-2	0.5-1.0	0.2	0.1-0.3
V_{dss} (L/kg)	3-5	3-5	3-5	2.5-3	0.4-1
Clearance (L/min/kg)	15-30	8-18	10-20	10-15	4-9
Hepatic extraction ratio	0.8-1	0.7-0.9	0.8-1	0.7-0.9	0.3-0.5

Abbreviations: $t_{1/2\pi}$, first distribution half-life; $t_{1/2\alpha}$, second distribution half-life; $t_{1/2\beta}$, elimination half-life; V_{doc} , volume of distribution at central compartment; V_{dss} , volume of distribution at steady state.

Adapted from Bailey PL, Stanley TH: Narcotic intravenous anesthetics. In Miller RD (ed): Anesthesia, 3rd ed, vol 1. New York, Churchill Livingstone, 1990, p 281.

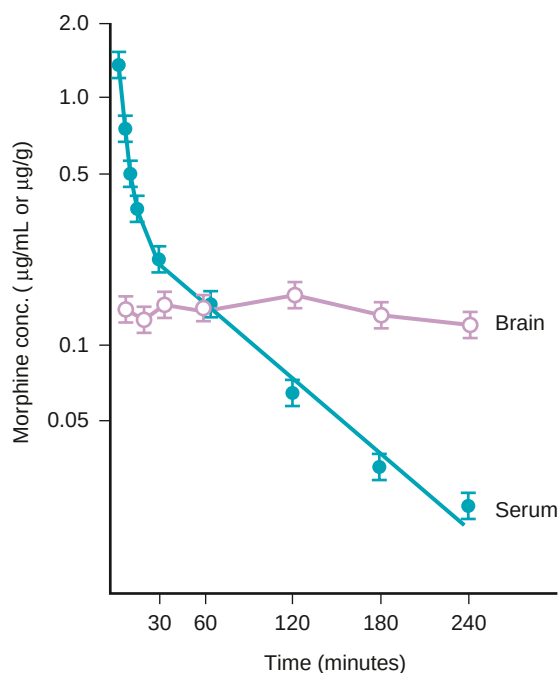


Figure 41-1. Serum and brain decrement curves in normocarbic dogs show the relationship of morphine concentrations in the brain to morphine concentrations in serum. Serum and brain morphine decrement curves intersect at approximately 1 hour. Vertical bars are standard error ($n = 7$). (From Nishitaten K, Ngai SH, Finck AD, Berkowitz BA: Pharmacokinetics of morphine: concentrations in the serum and brain of the dog during hyperventilation. *Anesthesiology* 1979;50:520-523.)

intravenous morphine, is desirable. It appears that in the dosages commonly used in the critical care setting, morphine has no direct effect on the inotropic state of the heart.²⁴ An exception to this is the negative inotropic state caused by histamine release when morphine is administered rapidly or when large

doses are given (discussed later).⁵ Finally, the net chronotropic effect of morphine is to slow the heart rate under usual conditions. The exact mechanism by which morphine achieves this action is not certain, but it is thought to involve both a stimulation of the central vagal nucleus and a direct depressive effect on the sinoatrial node.^{25,26} Morphine has also been observed to secondarily increase heart rate by causing histamine release (discussed later).

Side Effects, Complications, and Toxicity

Many of morphine's side effects are dose-related and can be minimized by reducing the size of doses administered to patients. The most important and potentially dangerous side effect of morphine administration is respiratory depression. The opiate agonists all share the ability to depress ventilation; this is primarily accomplished by decreasing the central ventilatory response to CO_2 .⁵ Specifically, the ventilatory response curve to an increasing PaCO_2 is shifted to the right, and the slope is decreased (Fig. 41-2). This means that for a given rise in PaCO_2 , the patient compensates with a less-than-expected minute ventilation rate.⁵ The typical breathing pattern is one of slow respiratory rate with preserved or even increased tidal volume. This effect is dose-related, and although apnea can occur with high doses, it is usually preceded by a period of progressive hypoventilation and therefore can be identified early and prevented.

The central nervous system side effects of morphine include drowsiness, lethargy, and potentially excessive sedation. In addition to the direct central respiratory depression described previously, excessive sedation with morphine can worsen respiratory compromise by causing upper airway obstruction and obstructive apnea. Euphoria with morphine use has been noted but is less common than that occurring with some other opioid agents. Dysphoria can also occur. As in respiratory depression, the central depressant effects are dose-related and progressive.

The other organ systems most commonly affected by morphine (or any of the opioid agents) are the gastrointestinal (GI)

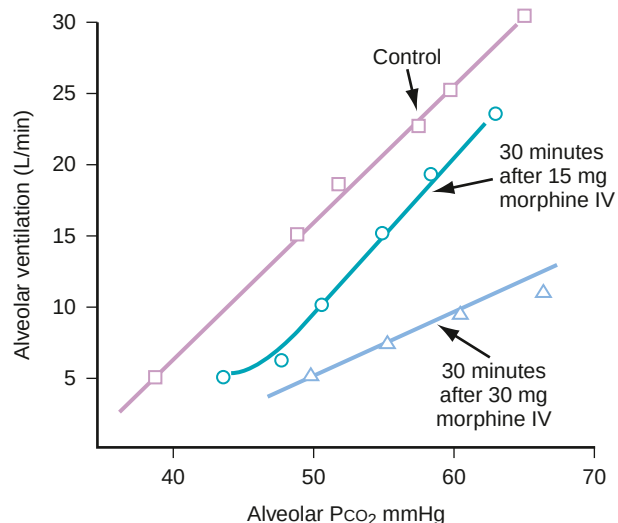


Figure 41-2. Ventilatory responses to CO₂. In control subjects, increases in alveolar PCO₂ produce increases in alveolar ventilation. After morphine administration, the response to CO₂ is shifted to the right, and the slope of the response is decreased.

and genitourinary (GU) systems. Morphine has many GI effects, including nausea, emesis, constipation, generalized slowing of the GI tract, and spasm of the sphincter of Oddi. Morphine has been reported to cause urinary retention by increasing urethral sphincter and detrusor tone.²⁷ Hyponatremia secondary to the syndrome of inappropriate secretion of antidiuretic hormone is also occasionally seen with the administration of large doses of morphine.²⁸ When morphine is given to patients with renal failure, prolonged narcotic effect from the accumulation of the active metabolite morphine-3-glucuronide can cause excessive sedation or respiratory depression.¹⁷

Although true allergic reactions to morphine are quite rare, morphine is known to cause the release of histamine.²⁹ The release of histamine is from mast cells rather than the basophils, and the mechanism, although not thoroughly understood, is nonimmunologic.³⁰ The release of histamine can lead to a warm flushing sensation, intense pruritus, hypotension, and tachycardia. When hypotension related to histamine release occurs, treatment includes discontinuing morphine infusion, ruling out other causes of anaphylactic or anaphylactoid type of reactions, administering intravenous fluids for hypotension, and administering histamine type 1 and type 2 blocking agents.⁵ One study has demonstrated that pretreatment with histamine type 1 and type 2 receptor antagonists in patients who have received morphine and tubocurarine (another agent associated with histamine release) significantly decreases hypotension when compared with similar patients pretreated with a placebo, although skin flushing was not reduced.³⁰ Other side effects, including respiratory depression, sphincter of Oddi spasm, excessive sedation, and pruritus, can be reversed by the administration of the opiate antagonist naloxone. By titrating small doses of naloxone, it is possible to reverse the side effects of morphine without completely reversing the analgesia. It is prudent to avoid giving large doses of naloxone to cardiac patients because complete reversal of opiate effect can result in dangerous increases in sympathetic tone and, rarely, has been reported to cause pulmonary edema.³¹

Clinical Indications

The main reason to administer intravenous morphine in the CICU is to produce analgesia and sedation, especially in the setting of acute myocardial ischemia or infarction or acute cardiogenic pulmonary edema. As mentioned previously, the acute venodilatory effects of intravenous morphine, combined with its analgesic and sedative properties, make it useful in cardiac patients. In contrast to fentanyl, morphine, with its long clinical duration and low lipid solubility, is best suited to administration by intermittent boluses rather than continuous infusion. Morphine may best be avoided altogether in the hemodynamically unstable patient because it is more likely to induce hypotension than is fentanyl.

Fentanyl

History and Structure

Fentanyl and meperidine are probably the best known of the synthetic opioid analgesic agents. These agents, along with sufentanil and alfentanil, are members of the phenylpiperidine class of opiate agents. They are named for the phenylpiperidine skeleton in their chemical structure.⁵ In terms of analgesic properties, fentanyl is approximately 80 times more potent than morphine because of its greater affinity for the μ -opiate receptor.¹⁵

Fentanyl was introduced in 1959 and has been in clinical use since the early 1960s, when it was first used in a combination preparation with the butyrophenone agent droperidol (Innovar) for the technique of neuroleptanesthesia.^{32,33} For many years, fentanyl was used almost exclusively in the operating room by anesthesiologists because of safety concerns related to its high potency and rapid onset. In the past few decades, fentanyl has found greater use as an analgesic and sedative in the critical care setting.

Pharmacokinetics, Pharmacodynamics, and Metabolism

The initial redistribution half-life for fentanyl is short (1 to 2 minutes), the $t_{1/2\alpha}$ is longer (10 to 30 minutes), and the $t_{1/2\beta}$ is 2 to 4.5 hours.¹⁴ Therefore, pharmacokinetically, fentanyl behaves similarly to morphine; this fact is supported by the nearly identical elimination curve shared by the two drugs. Fentanyl is approximately 40 times more lipid-soluble than morphine, leading to significant differences in the pharmacodynamics between these two drugs. Fentanyl's great lipid solubility allows rapid entry of this drug into the brain, causing a peak effect minutes after a bolus administration.⁵ Peak effect parallels the serum level for this agent.¹⁴ As a corollary, fentanyl redistributes away from the brain very quickly, resulting in a short clinical duration of action of only 30 to 60 minutes after a bolus dose. For these reasons, fentanyl administered by constant infusion leads to more consistent analgesia.³⁴ Prolonged narcotic effect may be observed with fentanyl after prolonged infusions or frequent bolus dose administration.³⁵ The reason for this prolongation of half-life with long-term infusion of fentanyl is thought to be that the high lipid solubility of this agent allows absorption of large amounts of drug into poorly perfused fatty tissue. When this occurs, termination of effect no longer depends on redistribution but rather is dependent on the terminal half-life of the drug. In a situation analogous to that seen with prolonged infusions of sodium thiopental, fatty uptake leads to a prolonged $t_{1/2\beta}$ and a long clinical duration of effect.^{5,36,37}

Fentanyl is metabolized primarily by the liver and somewhat by the kidney. Active metabolites of fentanyl are probably of minimal or no clinical significance.¹⁵

Cardiovascular and Hemodynamic Effects

When used in analgesic doses, fentanyl has developed a reputation for causing minimal hemodynamic effects. It has been demonstrated that fentanyl does not have negative inotropic effects.^{38,39} Although its occurrence is unusual, fentanyl can cause hypotension. The etiologies of fentanyl-related hypotension are likely fentanyl-induced bradycardia and a decrease in central sympathetic tone. The cause of the bradycardia is thought to be direct stimulation of the central vagal nucleus by fentanyl.⁴⁰ Furthermore, the magnitude of the bradycardia is believed to be related to both the total dose administered and the rate of infusion.^{5,40} Fentanyl is also known to cause hypotension indirectly by decreasing central sympathetic outflow.⁴¹ This mechanism is supported by the observation that patients with high basal levels of sympathetic tone are more likely to become hypotensive when given fentanyl.⁵ Patients with relative or absolute hypovolemia are more prone to hypotension after receiving fentanyl. Although fentanyl administration has minimal hemodynamic effects, it is important to note that reports have suggested that the combination of synthetic opioids and benzodiazepines, especially midazolam, can cause significant decreases in blood pressure.⁴² It is possible that lorazepam combined with fentanyl may cause less hypotension than does the combination of midazolam and fentanyl.⁴³

Side Effects, Complications, and Toxicity

The side effect and toxicity profile of fentanyl is similar to that of morphine, with several exceptions. The cardiovascular and hemodynamic effects of fentanyl have been discussed previously. The respiratory, central nervous system, GI, and GU side effects are similar to those previously discussed for morphine. The pharmacodynamic properties of fentanyl result in apnea and oversedation quickly; therefore, this drug should be used only in a monitored situation. Fentanyl does not release histamine from mast cells in humans.⁴⁴ It has been rarely reported to cause true anaphylactic reactions in humans.⁵ The respiratory, GI, and GU side effects of fentanyl are responsive to treatment with the narcotic antagonist naloxone. The same cautions described for the use of naloxone with morphine also apply to its use with fentanyl.

Clinical Indications

There are few studies that formally address the role of fentanyl in the CICU. Although this is also technically true with morphine, that agent, in comparison with fentanyl, has a long history of safety and familiarity in the CICU. Furthermore, the beneficial hemodynamic effects of morphine in the setting of myocardial ischemia or acute cardiogenic pulmonary edema have also strengthened its role as the primary opiate analgesic-sedative for the cardiac patient. Even so, it appears that those properties that make fentanyl a desirable agent in the operating room also make it attractive in the critical care setting. Fentanyl's rapid onset and short duration of action make it a useful analgesic and sedative agent for invasive procedures, with the caveat that it *must* be administered by experienced personnel in a monitored setting. Pharmacokinetically, fentanyl is more suitable for constant-infusion administration than is morphine, and it can be

easily and rapidly titrated to the desired analgesic effect. During long infusions of fentanyl, $t_{1/2\beta}$ increases as poorly perfused tissues are saturated. Adjustments in infusion rate must be made to compensate for this effect to prevent an undesired prolonged narcotic effect. The resulting bradycardia seen after fentanyl administration is a beneficial effect in some medically managed cardiology patients. Finally, the more neutral hemodynamic profile of fentanyl may make it a better choice for analgesia-sedation in the hemodynamically unstable patient.

Benzodiazepines

History and Structure

The benzodiazepines, which are the most commonly used sedative agents in the critical care unit, have been in use for several decades. The first benzodiazepine, chlordiazepoxide, was formulated in 1955, but it was not noted to have sedative properties until 1957 and was not released for clinical use until 1959.⁴⁵ Chlordiazepoxide was followed in 1959 by the synthesis of diazepam, in 1971 by the formulation of lorazepam, and in 1976 by the synthesis of midazolam.^{46,47} In addition to its unique pharmacologic properties (discussed later), midazolam is of great interest to intensivists and anesthesiologists in that it is the first benzodiazepine formulated primarily for use in anesthesia and the critical care setting. The benzodiazepines as a group are relatively small, lipid-soluble molecules that act as agonists at the benzodiazepine receptor.⁴⁶

Site of Action and Receptor Physiology

In 1977, 18 years after their clinical introduction, it was discovered that the site of action of the benzodiazepines was at a receptor complex that it shared with another important class of central nervous system depressants, the barbiturates.⁴⁸ This receptor, named the BNZ receptor, along with the barbiturate receptor, forms part of a larger receptor system known as the γ -aminobutyric acid (GABA) receptor complex.¹⁴ The benzodiazepines act agonistically at this receptor. GABA, one of the primary inhibitory neurotransmitters of the human central nervous system, acts as an agonist at the GABA complex, causing a net influx of chloride ion into the cell, which results in hyperpolarization and resistance to excitation.⁴⁹ It appears that there are two main GABA receptors in the central nervous system: a GABA_A complex and a GABA_B complex. The benzodiazepines appear to have their main activity at the GABA_A complex.¹⁴ When a benzodiazepine binds at its BNZ receptor, the conformation of the GABA_A complex is altered such that the binding of the neurotransmitter GABA is facilitated.⁴⁶ Benzodiazepine receptors are found in greatest concentration in the olfactory bulb, cerebral cortex, cerebellum, hippocampus, substantia nigra, and inferior colliculus.⁴⁶

Pharmacokinetics, Pharmacodynamics, and Metabolism

In the United States, the three benzodiazepines most widely available for intravenous administration, and hence most commonly used in the CICU, are diazepam, lorazepam, and midazolam. Although these agents work similarly at the receptor level, they are quite different with respect to their pharmacology and physical properties (Table 41-3). For example, these agents differ in potency. Midazolam is roughly three times more potent than diazepam, whereas lorazepam is five times more potent than diazepam.⁴⁶ In general, all three compounds are highly lipid soluble, but lorazepam is less so than diazepam or midazolam.⁵⁰

Table 41-3. Physicochemical Characterization of Three Benzodiazepines

	Diazepam	Lorazepam	Midazolam
Molecular weight	284.7	321.2	362
pKa	3.3 (20° C)	11.5 (20° C)	6.2 (20° C)
Water soluble	No*	Almost insoluble	Yes*
Lipid soluble	Yes,* highly lipophilic	Yes, relatively less lipophilic	Yes,* highly lipophilic

*pH dependent: pH >4 = lipid soluble, pH <4 = water soluble.

Adapted from Sasajima M: Analgesic effect of morphine-3-glucuronide. Keio Ogaka 1970;47:421.

The initial $t_{1/2\alpha}$ of these agents is similar: 1 to 2 minutes for midazolam and diazepam and about 3 minutes for lorazepam.^{51,52} The onset of peak clinical activity mirrors these half-lives; the slightly slower onset of lorazepam is related to its lower lipid solubility. The $t_{1/2\beta}$ is quite different among these three drugs and is related to a number of factors (discussed later). The absolute range in $t_{1/2\beta}$ is large; midazolam has a relatively short half-life of 2 to 3 hours, lorazepam has an intermediate half-life of 10 to 20 hours, and diazepam has a long half-life of 20 to 50 hours.⁴⁶

The benzodiazepines are metabolized in the liver where the parent compounds undergo extensive biotransformation. This often results in metabolic products that have significant benzodiazepine activity. Diazepam, the archetypal compound, undergoes biotransformation to a number of products, two of which (oxazepam and desmethyldiazepam) are potent and long-acting BNZ receptor agonists.¹⁴ This fact helps to explain the long $t_{1/2\beta}$ and prolonged sedative effect frequently seen with the use of diazepam.⁵³ Lorazepam is also highly metabolized, but it appears that none of its metabolic compounds have significant activity and that these products are rapidly excreted by the kidneys.⁵¹ Midazolam is biotransformed to compounds known as hydroxymidazolams, but controversy exists regarding whether these compounds have any intrinsic benzodiazepine activity.⁵⁴ As mentioned earlier, there have been many case reports of prolonged sedation from long-term use of diazepam, and this has been traditionally thought to be an effect of accumulation of active metabolites.⁵³ There are reports of prolonged sedation with midazolam infusions. Several studies have shown a prolongation of $t_{1/2\beta}$ and duration of sedation with midazolam administration in elderly patients and in the critically ill.^{55,56} These studies have shown a prolongation of the elimination half-life of about 2.5 times; this is thought to be caused by several factors, including increased volume of distribution and extensive fatty tissue uptake after prolonged infusion (recall that midazolam is highly lipid-soluble). One study investigating the effect of prolonged midazolam infusions in critically ill patients found that the mean time from administration to awakening in patients with renal failure was approximately 44 hours (control, 13 hours), and the time to awakening in two patients with renal and hepatic failure was greater than 120 hours.⁵⁷ Although these same principles could also theoretically apply to lorazepam, with its lower lipid-solubility and inactive metabolites, it appears less likely to cause prolonged sedation.¹⁴

Diazepam and lorazepam are water-insoluble and therefore require vehicles for intravenous injection. Diazepam injection is prepared with propylene glycol, alcohol, and benzyl alcohol as vehicles, whereas lorazepam is prepared with polyethylene glycol and benzyl alcohol vehicles.⁴⁶ The specific toxicities of these agents are discussed later. Midazolam for injection is a simpler solution to commercially prepare and administer because of the drug's pH-dependent water solubility.

A study of prolonged midazolam infusion in critically ill patients has noted a need for a progressive increase in dose that appears consistent with the development of acute benzodiazepine tolerance.⁵⁸ A convincing model for acute benzodiazepine tolerance has also been developed in the dog, showing tolerance with very short-term, albeit high-dose, benzodiazepine exposure.⁵⁹ The clinical significance of this phenomenon, especially with respect to how it may relate to benzodiazepine addiction in critically ill patients, is uncertain.

Cardiovascular and Hemodynamic Effects

With respect to hemodynamics, the benzodiazepines have a reputation of safety in patients with cardiac disease of various etiologies, especially coronary artery disease.^{60,61} High doses of these agents have been found to be safe for the induction of anesthesia in aortic stenosis patients.⁶² When administered alone, the benzodiazepines cause a mild decrease in arterial blood pressure, which is related to a decrease in systemic vascular resistance.⁴⁶ Other cardiac indices are minimally affected, and it is believed that a maintenance of normal compensatory cardiovascular reflexes is responsible for this relative preservation in blood pressure.⁴⁶ It is notable that midazolam has a more potent blood pressure-lowering effect than the other intravenous benzodiazepines.⁶³ As was alluded to previously, it is known that when a combination of a benzodiazepine and an opioid agent are administered, there is a synergistic effect in lowering blood pressure.⁶⁴ This effect appears to be super-additive and has been demonstrated with several different combinations of benzodiazepines and opioids. The effect appears to be related to a reduction in central sympathetic tone.⁶⁵ With respect to agents commonly used in the CICU, this synergism has been demonstrated for the combinations of midazolam-fentanyl and lorazepam-fentanyl.^{66,67} Although the majority of these data are taken from the cardiac anesthesia literature and may be related to the high doses of these drugs routinely used in this setting, common sense dictates that care must also be practiced in the CICU when these combinations are used, even when the doses are significantly lower.

Side Effects and Toxicity

When used with care, the benzodiazepines are safe sedative agents, largely because of their high therapeutic index.¹⁴ The cardiovascular and hemodynamic effects of benzodiazepines were discussed previously. The main side effects of the benzodiazepines applicable to critical care populations are excessive sedation and respiratory depression. Excessive sedation is generally a dose-related phenomenon. It is of greatest concern in the scenario of awake sedation in the nonintubated patient, when it may lead to inability to protect or maintain a patent airway. Central respiratory depression occurs with the benzodiazepines, but again, it appears to be a dose-related phenomenon that is relatively infrequent with reasonable dosages. Although the benzodiazepines flatten the ventilatory response curve to

hypercarbia, they do not shift the curve to the right as do opioids.^{46,68} Apnea does occur with benzodiazepines, but it is most commonly seen with the administration of large doses, as in the induction of anesthesia, and is not common with lower sedative doses used in the CICU.

Analogous to the blood pressure–lowering effect seen with opioid-benzodiazepine combinations, it is likely that these combinations also have a synergistic central respiratory depressive effect.⁴⁶ The sedative and respiratory side effects of benzodiazepines can be reversed by the BNZ receptor antagonist flumazenil, which has a very high affinity for the BNZ receptor.⁶⁹ Flumazenil has proved effective at acutely reversing benzodiazepine toxicity, but it must be used with caution. It has a relatively short elimination half-life compared with the longer-acting benzodiazepines; therefore, its reversal effect may be short-lived in comparison to the sedative effects of these agents, allowing the patient to become resedated after the flumazenil effect has terminated.⁴⁶ Additionally, seizures and acute withdrawal symptoms have been reported in patients with benzodiazepine tolerance treated with flumazenil.⁷⁰

The solvents used to provide an intravenous vehicle for the water-insoluble agents diazepam and lorazepam are known to cause phlebitis with peripheral intravenous injection.⁴⁶ Propylene glycol toxicity has also been reported with high-dose intravenous diazepam administration.⁷¹

Recently, it has been found that the prolonged administration of benzodiazepines to critically ill patients, particularly lorazepam, was found to be an independent risk factor for the development of delirium.⁷² Furthermore, plasma concentrations of benzodiazepines, or other sedatives, did not correlate well with sedation scores, suggesting that the effects of the drug are influenced by other factors, including age.^{72a} These reports should decrease practitioners' enthusiasm for infusions of benzodiazepines in critically ill elderly patients.

Clinical Indications

The benzodiazepines have three main uses in the CICU: as anxiolytics, as sedatives for mechanically ventilated patients, and as anticonvulsants.⁵⁸ Benzodiazepines are also useful for the treatment of acute alcohol withdrawal and may be useful in the treatment of acute cocaine intoxication.¹⁴ A secondary but beneficial property of the benzodiazepines in the critical care setting is amnesia, especially when painful invasive procedures or prolonged mechanical ventilation is necessary. Benzodiazepines do not, by themselves, have analgesic properties. Therefore, if painful procedures (e.g., placement of intra-aortic balloon pump or central lines) are anticipated, the benzodiazepines should be used in conjunction with an opioid analgesic. With respect to anxiolysis, the three commonly used benzodiazepines are equally efficacious and differ only with respect to their potency. The same statement also applies to their efficacy when used for sedation during mechanical ventilation. As discussed previously, because of its pharmacokinetic and pharmacodynamic properties, midazolam may be the best choice for long-term sedation in the mechanically ventilated patient if an intravenous infusion is to be used.⁵⁸ All of the benzodiazepines are effective when used for the acute termination of seizures. It is believed that lorazepam may be the drug of choice in the termination of status epilepticus because its longer half-life allows treatment with another longer-acting anticonvulsant (i.e., phenytoin) to be begun before seizures can recur.^{72b}

With respect to amnesia, all three of these agents appear to be efficacious. Lorazepam maintains a reputation for being a more potent amnestic than either diazepam or midazolam, but this is not fully supported by the literature. Lorazepam and midazolam have been compared in a randomized, controlled fashion with respect to anterograde amnesia, and it is clear that lorazepam provides a longer period of amnesia.⁷³ Likewise, diazepam was compared with midazolam in a similar study that demonstrated that at equal doses, midazolam was a more potent amnestic agent⁷⁴; however, the doses of midazolam and diazepam were equal but not equipotent in this study. Another study demonstrated the amnestic efficacy and safety of lorazepam when used for procedures in the critical care setting.⁷⁵ It appears that flumazenil is not as effective at reversing the amnestic effects of the benzodiazepines as it is at reversing the other side effects.⁷⁶

Propofol

History and Structure

Propofol is a unique hypnotic agent that was first introduced into clinical use in 1977.⁷⁷ It has an alkylphenol structure that is water-insoluble at room temperature. Because of this water-insolubility, propofol was first formulated in a Cremophor solution for anesthetic use, but was then changed to a lipid vehicle because of anaphylactic responses to cremophor.^{46,78} Since its introduction as an anesthetic agent, propofol has enjoyed progressively greater use in clinical areas outside of the operating room. Propofol is a rapid-acting, highly lipid-soluble central nervous system depressant with hypnotic and amnestic properties, but its exact site and mode of action are not fully understood.

Pharmacokinetics, Pharmacodynamics, and Metabolism

When administered by bolus or infusion, propofol follows a two-compartment pharmacokinetic model with a rapid $t_{1/2\alpha}$ of 2 to 8 minutes and a slower $t_{1/2\beta}$ of 1 to 3 hours.⁷⁹ A three-compartment model with a prolonged $t_{1/2\beta}$ of 4 to 7 hours has been postulated, implying uptake of propofol by poorly perfused fatty tissue.^{80,81} Although this would seem to imply that a prolonged period of sedation would occur with constant infusions (as is known to occur with fentanyl and midazolam, discussed previously), this does not seem to be the case with propofol. A study using propofol for sedation in mechanically ventilated CICU patients demonstrated a rapid time to extubation and full recovery (1 and 2 hours, respectively) in patients who were receiving infusions of propofol.⁸² This rather unique ability is thought to be related to extremely high clearance, which is higher than liver blood flow.⁷⁹ Therefore, although propofol has high hepatic clearance, it appears that other routes of elimination must exist to explain its short clinical duration of action. It is postulated that respiratory elimination may be partially responsible for this phenomenon.⁸³

Cardiovascular and Hemodynamic Effects

The majority of the data regarding the cardiovascular and hemodynamic effects of propofol have been generated in the setting of general anesthesia or sedation for surgery. The most prominent effect of propofol on hemodynamics is a decrease in arterial blood pressure, and several studies have found the average decrease in systolic blood pressure with an induction dose of propofol to be in the range of 25 to 40 mm Hg.^{84,85} During the maintenance phase of anesthesia with propofol infusion

(a situation more similar to propofol sedation in the CICU), systolic blood pressure was maintained at a level 20% to 30% below preinduction levels.^{84,85} This hypotension appears to be related to both peripheral vasodilation and a negative inotropic effect of the drug.⁴⁶ Propofol infusions appear to decrease both myocardial blood flow and myocardial oxygen demand.⁸⁶ These decreases are of roughly equal magnitude.⁴⁶ Various chronotropic responses have been reported in patients receiving propofol, including an increase, a decrease, and no change in heart rate.⁸⁶⁻⁸⁸

Side Effects, Complications, and Toxicity

Propofol is an agent of high potency that was previously used almost exclusively in the operating room by trained personnel (usually anesthesiologists) in a closely monitored setting. In many aspects, propofol behaves similarly to sodium thiopental. Propofol, like sodium thiopental, has a narrow therapeutic range between desired clinical effect and serious toxicity. The most serious of these side effects include arterial hypotension and central apnea; this apnea may be more prolonged than that seen with thiopental.⁸⁹ Propofol is a potent compound with a narrow therapeutic index and several dose-related effects, which if managed incorrectly, are potentially life-threatening. Propofol use should be limited to experienced personnel in a closely monitored setting. If propofol is used in nonintubated patients, it can lead to apnea or airway obstruction. Additionally, patients anesthetized with propofol have reported intense dreams in the immediate postoperative period.⁹⁰ Patients emerging from propofol anesthesia have also been observed to commonly display adventurous or merry behavior compared with patients who have been anesthetized with thiopental.⁹¹ Dystonic or choreiform movements not associated with abnormal EEG activity are observed in patients anesthetized with propofol.⁹²

An irritating side effect of propofol is pain at the site of infusion. This can be prevented by avoiding infusion into small hand veins.⁹³ Phlebitis is also occasionally seen.⁴⁶

Another important possible toxicity is seen after infusion of propofol: the propofol infusion syndrome, PRIS, is associated with some or all of the following: metabolic acidosis, refractory heart failure, progressive and refractory bradycardia, fever, lipemia, and increased creatine phosphokinase, myoglobinemia, and/or myoglobinuria.^{93a} The maximum recommended dose from the manufacturer is 4 mg/kg/hr for adults and all reported cases of PRIS apparently received higher doses than this.^{93b} Propofol infusions are no longer used in many pediatric intensive care units because of PRIS,^{93c} and all practitioners have been encouraged to adhere to the maximum limits suggested and to be watchful for signs of PRIS.^{93b}

Clinical Indications

The two most common indications for propofol in the CICU have been sedation for elective electrical cardioversion and sedation for mechanical ventilation.⁹⁴ A study comparing propofol, methohexital, and midazolam as sedatives for the elective electrical cardioversion of patients with supraventricular arrhythmias demonstrated that all three agents were efficacious, but that time to awaken was much more rapid in the propofol and methohexital groups.⁹⁵ It is notable that in this study two patients in the propofol group experienced recall of their cardioversion, whereas no patients in the methohexital or midazolam treatment groups reported awareness. Although hemodynamics

were well maintained in this group of stable patients, it seems prudent to avoid the use of propofol in the setting of cardioversion accompanied by hemodynamic instability because of propofol's known cardiovascular depressive effects.

There have been no randomized, controlled studies specifically investigating the safety or efficacy of propofol for sedation in the CICU patient. There are, however, a number of studies addressing its use in the medical-surgical intensive care unit (ICU) patient⁹⁶⁻¹⁰¹ and in the postoperative cardiac surgery patient.¹⁰²⁻¹⁰⁵ The experience from these studies suggests that when propofol is used in sedative doses ranging between 3 and 50 $\mu\text{g/kg/min}$, there is excellent patient tolerance and minimal side effects.

In a study directly comparing propofol and midazolam for short-term sedation of mechanically ventilated patients after coronary artery bypass graft (CABG) surgery, there was no difference in the number of hypotensive episodes during the maintenance phase of the study, although there was a significantly higher number of hypotensive episodes in the propofol group during propofol loading.¹⁰⁵ In addition, despite the mild to moderate degree of hypotension that accompanies the use of this agent, ICU patients sedated with propofol appear to have no compromise in oxygen transport.¹⁰¹ Furthermore, in a study by Stephan and colleagues,⁸⁶ patients treated with propofol were found to have a parallel and equal decrease in myocardial oxygen supply and demand, implying that this agent may be safe in the setting of coronary artery disease.

Despite the fact that propofol is not noted to possess analgesic properties, ICU patients sedated with propofol were noted to have a lower supplemental narcotic requirement than patients sedated with midazolam.^{99,105} Several studies including patients sedated for prolonged periods show a significantly more rapid awakening time and time to extubation with propofol than with midazolam.^{82,95} In a study by Carrasco and colleagues,⁸² the time to extubation in ICU patients treated with propofol was 2 hours as opposed to 37 hours in patients sedated with midazolam for more than 7 days. This experience has not been universal, and in two studies comparing propofol with midazolam in postoperative CABG patients, there was no significant difference in time to extubation.^{102,105} It is notable that in these studies, the duration of sedation was relatively short, perhaps preventing the fatty tissue uptake of midazolam, which seems to result in the pharmacodynamic changes responsible for prolonged sedation with this agent (discussed previously).

The absolute mechanism by which patients awaken so rapidly after prolonged propofol infusions is not clear because several studies have shown a dramatic increase in $t_{1/2\beta}$ when these agents are infused for long periods.^{98,100} Even so, Bailie and colleagues¹⁰⁰ showed an impressive decrease in plasma propofol level of 50% in the first 10 minutes after termination of propofol infusions in critically ill patients sedated for a mean of 86 hours.

Propofol infusions for mechanically ventilated patients provide a good option in the area of critical care and sedation. In terms of applicability to the cardiology patient, the published experience is limited. Experience in the medical-surgical and postoperative CABG patient population suggests that this therapy is safe and efficacious. As described previously, the literature suggests that propofol's main advantage over standard sedative agents is rapid awakening, but this improvement in time to awakening may only be significant in patients treated with prolonged infusions. In addition, there is a general consensus

in the literature that the minute-to-minute control of sedation is improved with propofol compared with standard sedative agents.⁹⁴ The available literature supports the use of sedative doses of propofol in the CICU for mechanical ventilation only.

Dexmedetomidine

History and Structure

Dexmedetomidine is the active dextro-isomer of medetomidine and is a highly selective α_2 -adrenergic receptor agonist. The α_2 -adrenergic agonist class of drugs can be divided into three groups: imidazolines, phenylethylamines, and oxalozepines. Clonidine, a more commonly used α_2 -agonist, and dexmedetomidine are both imidazole compounds. They exhibit a high ratio of specificity for the α_2 - versus the α_1 -receptor. Dexmedetomidine has eight times the potency as clonidine at the α_2 -receptor, and therefore is considered a full agonist at the α_2 -receptor.¹⁰⁶ As an α_2 -adrenergic agonist, dexmedetomidine exhibits sedative, anxiolytic, and analgesic properties.¹⁰⁷ It was granted FDA approval in December of 1999 for use as a short-term sedative (<24 hours) in ICU patients.

Site of Action and Receptor Physiology

Dexmedetomidine works at α_2 -receptors both peripherally and centrally. The sedative and anxiolytic effects of the drug are mediated through stimulation of central α_2 -receptors. Activation of these receptors attenuates central nervous system excitation, especially in the locus coeruleus.¹⁰⁸ Stimulation of central α_2 -receptors also leads to a decrease in sympathetic outflow and augmentation of cardiac vagal activity.¹⁰⁹ In addition, α_2 -receptors modulate pain pathways within the spinal cord. Activation of the α_{2c} -receptor subtype produces an analgesic effect by accentuating the action of opioids.³ Finally, α_2 -receptors are located on blood vessels and sympathetic terminals where they mediate vasoconstriction and inhibit norepinephrine release, respectively.¹⁰⁹

Pharmacokinetics, Pharmacodynamics, and Metabolism

Dexmedetomidine has an onset of action of approximately 15 minutes with peak concentrations reached within 1 hour following continuous infusion. It exhibits a rapid distribution phase with a $t_{1/2\alpha}$ of approximately 6 minutes and a $t_{1/2\beta}$ of approximately 2 hours. The drug is highly protein bound and has a large volume of distribution.¹¹⁰

Dexmedetomidine is highly metabolized by the liver. It undergoes glucuronidation and cytochrome P450 mediated metabolism. Therefore, patients with severe hepatic insufficiency may require lower doses of dexmedetomidine.¹¹⁰ The by-products of dexmedetomidine metabolism are excreted by the kidneys.¹¹¹

Cardiovascular and Hemodynamic Effects

The manufacturer's recommended dose of dexmedetomidine is 1 $\mu\text{g}/\text{kg}$ loading infusion over 10 minutes, followed by a continuous intravenous infusion of 0.2 to 0.7 $\mu\text{g}/\text{kg}/\text{hr}$.¹⁰⁸ A bolus of dexmedetomidine (1 $\mu\text{g}/\text{kg}$ over 10 minutes) may result in a transient increase in blood pressure and a reflex decrease in heart rate, especially in young patients.¹¹² This response is likely related to direct vasoconstriction of peripheral vessels. Animal studies show that the pressor response to bolus doses of α_2 -agonists is enhanced after autonomic denervation.¹¹⁰ In other words, when sympathetic inhibition from the central effects of α_2 -agonists are absent, the peripheral effects predominate, and

vasoconstriction leading to high blood pressure occurs.^{109,110} Alternatively, patients may experience profound hypotension and bradycardia with the bolus dose.^{112a} Most intensivists simply start a continuous infusion of dexmedetomidine between 0.2 and 0.7 $\mu\text{g}/\text{kg}/\text{hr}$ since omitting the bolus dose may avoid undesirable hemodynamic effects without compromising sedation.^{112b} During a continuous infusion of dexmedetomidine (0.2 to 0.7 $\mu\text{g}/\text{kg}/\text{hr}$), patients typically experience a slight decrease in blood pressure, heart rate, and cardiac output.¹⁰⁹ Sympatholysis from dexmedetomidine is involved in decreasing the heart rate as evident by the fact that patients taking β -blockers do not experience heart rate slowing.¹⁰⁹

Side Effects, Complications, and Toxicity

Giving a bolus dose of dexmedetomidine before initiation of a continuous infusion may cause hypertension or hypotension and bradycardia as noted above. Patients may experience hypotension and bradycardia during the continuous infusion of dexmedetomidine as well. This hypotension may be more severe in patients who are hypovolemic. Significant bradycardia and sinus arrest may occur in patients with high vagal tone or during rapid intravenous or bolus administration. Dexmedetomidine should be avoided in patients with advanced heart block and ventricular dysfunction because bradycardia and hypotension may be more pronounced.¹¹¹ Doses of the drug should be reduced in patients with hepatic impairment because the drug is highly metabolized by the liver. As noted above, the metabolites are excreted in the urine, and although the effects of the metabolites have not been studied, cautious dosing with renal failure may be prudent because these metabolites may accumulate. Mild respiratory depression is seen with bolus dosing of dexmedetomidine. This likely occurs as a result of sedation and is not due to any direct respiratory effects of the drug.¹⁰⁹

Clinical Indications

Dexmedetomidine is FDA approved for use as a sedative in the intensive care unit for less than 24 hours duration. Studies in intensive care patients have shown that compared with propofol, dexmedetomidine produces similar levels of sedation and time to extubation with less opioid requirements.¹⁰⁸ One study by Herr and colleagues examined dexmedetomidine versus propofol-based sedation regimens in post-coronary artery bypass graft patients. The results showed that dexmedetomidine provided safe and effective postoperative sedation in this patient population and reduced the need for analgesics, β -blockers, antiemetics, epinephrine, and diuretics.^{112c} Since dexmedetomidine provides sedation without decreasing respiratory drive, it can be used as a sedative during weaning from mechanical ventilation and throughout the extubation period. This can be particularly useful in anxious patients who otherwise might require large doses of propofol or benzodiazepines to tolerate the endotracheal tube during spontaneous breathing trials. In addition, dexmedetomidine may be beneficial in patients who have a high tolerance to opioids. Finally, current studies are evaluating whether dexmedetomidine is associated with less delirium than other types of sedatives.

In the cardiac care unit, many patients may have pre-existent bradycardia, cardiac conduction problems, or reduced ventricular ejection fractions. Patients may also be hypotensive or hypovolemic for a variety of reasons. Caution should be used in choosing dexmedetomidine as a sedative in these patient

populations. The risk of the side effects may outweigh the benefits in some patients.

Antipsychotic Agents

The occurrence of delirium in the intensive care unit is associated with adverse outcomes including lengthened ICU and hospital stay and increased 1-year mortality.^{113,114} Antipsychotic administration is broadly accepted as a treatment for delirium not associated with hypoglycemia, hypoxemia, or other treatable causes. The hope is that severity and duration of symptoms will be decreased.^{115,116} Two commonly used antipsychotic agents used to treat delirium in the critical care setting include haloperidol and olanzapine.

Haloperidol

Haloperidol is a member of the butyrophenone class of neuroleptic major tranquilizers. It has a moderately rapid rate of onset, with a $t_{1/2\alpha}$ of 3 to 19 minutes and a $t_{1/2\beta}$ of 10 to 19 hours.¹⁴ It is a more potent neuroleptic compared with the phenothiazines, with less severe side effects. Haloperidol is reputed to have fewer extrapyramidal, anticholinergic, and α -blocking effects than the other commonly used major tranquilizers.¹¹⁸ In addition, respiratory depression is rare with this agent, as is hypotension.¹⁴ Initially developed as an oral neuroleptic agent, haloperidol has gained favor as an intravenous agent for the acute treatment of psychosis and delirium in the critically ill medical patient.¹¹⁹ The intravenous route of administration seems to decrease the incidence of extrapyramidal side effects compared with the usual oral route of administration.¹²⁰ Intermittent bolus administration with rapid bolus escalation is recommended and commonly used to treat acute delirium.¹⁴ Standard doses range from 2 to 10 mg administered every 10 to 15 minutes until the desired effect is obtained. If around the clock dosing is desired the patient may be started on a divided intravenous dose based on the loading dose.¹⁴

Although haloperidol is an effective agent for the treatment of delirium it is not without serious side effects that may adversely affect CICU patients. A prolonged Q-T interval, torsades de pointes, ventricular arrhythmias, and cardiac arrest have been reported in patients treated with intravenous haloperidol.^{121,122} Daily electrocardiograms are warranted to follow the Q-T interval in all patients receiving haloperidol for the treatment of acute delirium. In addition to the cardiovascular effects, haloperidol may cause extrapyramidal effects, such as akathisia and oropharyngeal dysfunction.^{116,123} Neuroleptic malignant syndrome and dystonic reactions may also occur.^{118,124} In spite of these side effects, haloperidol has been investigated as a safe and efficacious treatment of agitation and delirium associated with the intra-aortic balloon pump.¹²⁵

Olanzapine

Olanzapine is a second-generation antipsychotic agent that belongs to the thienobenzodiazepine class. It is a selective monoaminergic antagonist with a high affinity for multiple receptors including serotonin 5HT₂/2C and 5HT₆, dopamine D₁-4, histamine H₁, and adrenergic α_1 -receptors. The mechanism of action of olanzapine is largely unknown.¹²⁶ It is available in oral and intramuscular forms, but is more commonly given by mouth in the intensive care setting. The oral form of Olanzapine is well absorbed with good bioavailability. It reaches

peak concentrations in approximately 6 hours and its $t_{1/2\beta}$ is approximately 21 to 54 hours. The drug undergoes direct glucuronidation and cytochrome P450 mediated oxidation. Renal dysfunction does not likely impact pharmacokinetics.¹²⁶ If a patient is able to take medications by mouth it is a good alternative to haloperidol for the treatment of ICU delirium, and in fact may be better tolerated with fewer side effects. In one study of olanzapine versus haloperidol, the group taking olanzapine had no extrapyramidal side effects.¹¹⁶ The drug is typically administered orally in doses that range from 5 to 10 mg daily.¹²⁶

Side effects of olanzapine include orthostatic hypotension that is likely the result of antagonism of adrenergic α_1 -receptors. Q-T prolongation has been reported with atypical antipsychotics such as olanzapine, however, the occurrence rate is lower than that seen with haloperidol.¹²⁷ Some studies indicate that olanzapine should be avoided in patients with dementia-related psychosis as there may be an increased risk of stroke and death compared to placebo.^{126,128} A recent prospective study, however, reported that neither the use of atypical antipsychotics nor the use of conventional neuroleptics increased mortality among elderly patients with dementia.¹²⁹ Nonetheless, olanzapine is not approved for the treatment of patients with dementia-related psychosis and should be avoided in this patient population.¹²⁶ Other side effects include hyperglycemia, neuroleptic malignant syndrome, and hyperlipidemia.

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Pharmacologic Interactions in the CICU

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CHAPTER

42

Vasodilators
Angiotensin-Converting Enzyme Inhibitors and
Angiotensin Receptor Blockers

Inotropic Drugs
Antiarrhythmic Drugs

CONCOMITANT ADMINISTRATION of several drugs is common in the treatment of cardiovascular diseases. Often, combinations of drugs are necessary and result in increased efficacy of therapy, but with a large number of medications there is also an increased concern about drug interactions. Although the number of potential interactions is great, many are inconsequential. Conversely, drug interactions can have a significant adverse effect or even be lethal.^{1,2}

Many drug interactions can be prevented by recognizing the drugs and the patients at risk. Situations with a high likelihood for clinically significant adverse drug interactions include the following¹⁻⁴:

1. A large number of drugs. The risk is significantly higher when more than 10 drugs are concurrently administered.
2. Drugs with a steep dose-response relation, so that even small changes in the drug level lead to profound changes in its action.
3. Drugs with a narrow therapeutic index.
4. Concomitant administration of drugs known as liver enzyme inducers or inhibitors (e.g., rifampin and cimetidine).
5. Elderly patients.
6. Critically ill patients.

It is important to be aware of the possibility of drug interactions in the CICU because many of these patients receive high-risk drugs, are elderly, and may have circulatory failure or be critically ill. It is also important to inquire about the use of herbal supplements and medicines, as many of these products can interact with drugs and cause adverse events. Drug interactions may mimic worsening or progression of the underlying disease, with manifestations such as arrhythmia or heart failure.

Mechanisms of interactions may be pharmacokinetic, affecting drug absorption, bioavailability, metabolism, or renal excretion; or pharmacodynamic, occurring at the sites of action in the heart such as sinoatrial and atrioventricular nodes, the intraventricular conduction system, and the smooth muscle.⁴

This chapter discusses interactions of drugs commonly used in CICU, with emphasis on interactions with other cardiovascular drugs.

Vasodilators

Nitrates

The chief interactions of nitrates are pharmacodynamic. Nitrates (e.g., nitroglycerin, isosorbide dinitrate, isosorbide mononitrate) are widely used both in patients with angina

and in those with congestive heart failure. A limitation in nitrate therapy is the development of tolerance, which is time-dependent.⁵ Many theories are proposed to explain this phenomenon⁶⁻⁸ including nitrate resistance,⁹ pseudotolerance (i.e., activation of counter-regulatory responses, such as secretion of catecholamines, angiotensin II, and endothelin)¹⁰ and “true” tolerance resulting from impaired bioconversion to nitric oxide (NO)^{11,12} and increased generation of superoxide.⁸

There are several reports of agents that limit or reverse nitrate tolerance when coadministered with nitroglycerin to isosorbide dinitrate. These include *N*-acetylcysteine, ACE inhibitors,^{13,14} angiotensin receptor blockers (ARBs),¹⁵ carvedilol,¹⁶ hydralazine,¹⁷ ascorbic acid,¹⁸ folic acid,¹⁹ and L-arginine.²⁰ However, there are not enough data to make definite recommendations on drug combinations to prevent nitrate tolerance.

The combination of nitrates with hydralazine has been long known to be beneficial in congestive heart failure and is still used in patients who are intolerant of ACE inhibitors and in African-American patients who have reduced capacity for endogenous production of nitric oxide.²¹ These drugs may interact at the site of smooth muscle, involving inhibition of pyridoxal-dependent enzymes by hydralazine and resulting in an increased availability of sulfhydryl groups and prevention of nitrate tolerance by decreasing superoxide production and scavenging of reactive oxygen species.^{17,22}

A clinically significant interaction occurs between nitrates and phosphodiesterase type 5 (PDE5) inhibitors, such as sildenafil and tadalafil, commonly used to treat erectile dysfunction.²³⁻²⁵ Inhibition of PDE5 results in increased cGMP levels, which are generated from endogenously derived NO. Nitrates exert their effect via biotransformation to NO and generation of cGMP. Coadministration of nitrates and PDE5 inhibitors causes significant reduction of blood pressure via a synergistic increase in cGMP levels, resulting in symptomatic hypotension and even death.²³⁻²⁵ PDE5 inhibitors are contraindicated for patients treated with nitrates. Conversely, nitrates should not be started within 24 hours of using sildenafil and 48 hours of using tadalafil.²⁶

Another pharmacodynamic interaction occurs when nitrates are used with β -blockers, calcium channel blockers, or both as part of an intensive antianginal regimen, resulting in hypotension with reduced coronary flow. The result may be worsening of angina.²⁷

Table 42-1. Drug Interactions with Angiotensin-Converting Enzyme Inhibitors (ACEI)

Interacting Drug	Effect	Mechanism	Comments
Potassium supplements or potassium-sparing diuretics	Hyperkalemia	Inhibition of aldosterone release	Avoid combinations, monitor potassium levels
Angiotensin receptor blockers	Hyperkalemia Hypotension Renal failure	Dual inhibition of RAS	Monitor potassium levels, blood pressure, and renal function
Diuretics	Hypotension Renal failure	Inhibition of angiotensin II-mediated response to hypovolemia	Reduce dose or temporarily discontinue the diuretic before starting ACE inhibitor
NSAIDs	Inhibition of hypotensive effect of ACEI	Inhibition of kinin-mediated prostaglandin synthesis	Monitor blood pressure
Lithium	Lithium toxicity	Reduction of Na concentration in the proximal tubules by ACEI, causing increased lithium reabsorption	Reduce lithium dose by 50%, monitor lithium blood levels
Sulfonylurea	Hypoglycemia	Increased sensitivity to insulin	Monitor blood glucose

Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs; RAS, renin-angiotensin system.

Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

ACE inhibitors (Table 42-1) are widely used for the treatment of heart failure and hypertension, and to prevent remodeling after myocardial infarction.

Interactions involving ACE inhibitors are primarily pharmacodynamic and are based on their mechanism of action. The principal mechanism of action is lowering of angiotensin II levels, resulting in vasodilatation and suppression of aldosterone release. ACE inhibitors also inhibit the degradation of bradykinin and increase prostaglandin synthesis, both of which may contribute to vasodilation.

The main interaction of concern is between ACE inhibitors and potassium supplements or potassium-sparing diuretics. These combinations can result in rapid development of hyperkalemia, especially in the presence of diminished renal function.

There is a beneficial effect in the synergism between ACE inhibitors and diuretics (e.g., thiazides and furosemide) in the treatment of hypertension and heart failure, but in a sodium-depleted patient or one with high renin levels, the combination can result in hypotension and worsening of renal failure. In such patients, the physician should start with a lower than normal dose of ACE inhibitor, temporarily lower the dose of diuretic, or discontinue the diuretic before administration of an ACE inhibitor.²⁸ There is no evidence of a significant pharmacokinetic interaction between ACE inhibitors and diuretics.²⁹ A synergistic effect on blood pressure reduction was also observed between various ACE inhibitors and calcium antagonists without pharmacokinetic interactions.²⁸

No significant interactions were found between ACE inhibitors and β -blockers or digoxin.^{28,29}

Among the interactions with noncardiovascular drugs, the most notable is with nonsteroidal anti-inflammatory drugs (NSAIDs) because of these drugs' opposing effects on prostaglandin synthesis. The result is an attenuation of the

antihypertensive effects of ACE inhibitors, predisposition to renal failure, or both.^{30,31} There are conflicting reports on the interactions between ACE inhibitors and low-dose aspirin.^{32,33} However, a retrospective analysis did not demonstrate an adverse effect of aspirin on the survival of patients with left ventricular systolic dysfunction treated with ACE inhibitors.³⁴

There are reports of lithium toxicity when patients on chronic lithium therapy were started on ACE inhibitors. Because renal excretion of lithium is dependent on glomerular filtration and on sodium concentration in the proximal tubule, the possible mechanism of interaction may be the reduction of both by ACE inhibitors, especially in volume-depleted patients.^{28,29}

A life-threatening anaphylactoid reaction has been described in a patient treated with ACE inhibitors while on hemodialysis with a polyacrylonitrile membrane (AN69). The possible mechanism of this interaction is activation of the kinin-kallikrein system by the surface of the AN69 membrane, resulting in an increased production of bradykinin, the breakdown of which is inhibited by ACE inhibitors.²⁸ No adverse reactions were reported with other dialysis membranes.

ACE inhibitors increase insulin sensitivity, and there have been several reports of hypoglycemia when captopril or enalapril was given to patients receiving glibenclamide, although others did not observe this effect.³⁵⁻³⁷ It seems prudent to monitor for possible hypoglycemia when ACE inhibitors are given to patients who are already receiving oral antihypoglycemic agents.

Angiotensin receptor blockers (ARBs) have low potential for interaction with other drugs. Among ARBs, only losartan and irbesartan undergo significant metabolism by cytochrome P-450 enzymes (CYP 2C9 and CYP 3A4). Rifampin significantly reduces the AUC and the half-life of losartan and of its active metabolite, and dose increase of losartan may be indicated during concomitant administration.³⁸ However, no clinically significant interactions were found between losartan and erythromycin, digoxin, or warfarin, and between irbesartan and digoxin, nifedipine, or hydrochlorothiazide.³⁹ There was a report of a significant interaction between valsartan and lithium resulting in lithium toxicity.⁴⁰

Attenuation of the hypertensive effect of ARBs may result from concomitant administration of NSAIDs, via mechanisms similar to the interaction with ACE inhibitors.³⁹

Combination of ACE inhibitors and ARBs provides a dual and more effective blockade of the renin-angiotensin system (RAS). The combination was shown to be more effective in patients with diabetic and nondiabetic nephropathy and in patients with congestive heart failure.^{41,42} However, there are more adverse effects of hypotension, hyperkalemia, and renal dysfunction in patients on combination therapy.⁴² There are conflicting data on the use of dual RAS blockade with β -blockers in patients with CHF. Val-HeFT trial suggested an increased mortality in patients treated with triple therapy compared with an ACE inhibitor and β -blocker alone, while the CHARM and VALIANT trials did not find any increase in mortality in patients on triple therapy.⁴³⁻⁴⁵ The combination therapy of ACE inhibitor and ARB seems prudent in patients with CHF with highly activated RAS despite full-dose ACE inhibition, and in diabetic patients with nephropathy.⁴¹

Inotropic Drugs

Dopamine and Dobutamine

Vasoactive amines are used in the CICU to treat heart failure and shock. Both drugs are metabolized in the liver: dopamine by catechol-*O*-methyltransferase and monoamine oxidase; dobutamine by catechol-*O*-methyltransferase. Dopamine is inactivated in alkaline pH and therefore should not be administered in the same infusion as bicarbonate.⁴⁶

Although there are not many reports in the literature about drug interactions involving vasoactive amines, such interactions could be expected in patients treated with monoamine oxidase inhibitors, requiring lowering the dose of dopamine. The dose of vasoactive amines should be adjusted in patients treated with tricyclic antidepressants because of the possibility of an increased pressor effect.

Changes in blood pressure and in blood flow to the liver will affect the metabolism of high-extraction drugs, such as lidocaine and lipophilic β -blockers (e.g., propranolol, metoprolol). As a result, doses of inotropic drugs that increase cardiac output will also increase liver blood flow and accelerate the clearance of lidocaine, requiring an increased dose of lidocaine. Conversely, when dopamine is used in high doses, resulting predominantly in α -activation and vasoconstriction, the liver blood flow decreases, and lidocaine clearance would be expected to do the same.

Low-dose dopamine prevented norepinephrine-induced decreases in renal plasma flow in healthy volunteers.⁴⁷ However, it is not clear whether the same effect is found in critical-care patients. A multicenter study of low-dose dopamine use in critical care patients did not find any improvement in renal outcomes, and there were more adverse effects in patients on dopamine.^{48,49}

There is a report of interaction between dobutamine and low-dose carvedilol resulting in severe hypotension.⁵⁰ The proposed mechanism is a fall in systemic vascular resistance due to excessive β_2 -receptor activation caused by a selective β_1 -receptor blockade by low-dose carvedilol. This interaction may be expected with other selective β_1 -blockers.

Digoxin

Digoxin is a drug with a narrow therapeutic range and is subject to many drug interactions, both pharmacokinetic and pharmacodynamic (Table 42-2).

Interactions Affecting Absorption and Bioavailability

Digoxin tablets are absorbed slowly; therefore, agents that increase gastrointestinal motility (e.g., metoclopramide) may decrease its absorption, whereas agents that slow gastrointestinal transit (e.g., propantheline, other anticholinergic agents) may increase its absorption.⁵¹ Elixir preparations are usually not subject to these interactions because their absorption is more rapid.

Treatment with high-dose chemotherapeutic agents resulting in intestinal mucosal injury can reduce digoxin absorption from tablets by as much as 50% but does not significantly affect absorption from elixir.⁵²

In about 10% of patients, digoxin that is not absorbed in the upper gastrointestinal tract or that is excreted in the bile is reductively metabolized by the anaerobic bacteria *Eubacterium Lentum*, which is part of the normal flora of the colon. Such metabolism can account for about 40% of digoxin elimination. These patients may be recognized by the characteristic of needing higher than usual doses of digoxin to achieve therapeutic levels. In this group of patients, treatment with broad-spectrum antibiotics (e.g., erythromycin, tetracycline) can result in significantly increased bioavailability and digoxin toxicity.⁵³

Cholesterol-binding resins (e.g., cholestyramine, colestipol) bind digoxin in the gut and may reduce its absorption by 20% to 30%. This effect can be avoided by giving digoxin at least 1 hour before the resins.⁵⁴

Sucralfate has been reported to decrease the absorption of digoxin.⁵⁵ No significant interaction has been found between digoxin and antacids.⁵⁶

Intestinal P-glycoprotein (P-gp) plays an important role in bioavailability of digoxin.⁵⁷ Rifampin increases P-gp content in the intestine and decreases digoxin bioavailability, resulting in significantly lower digoxin AUC after oral administration.⁵⁸ On the other hand, drugs that inhibit intestinal P-gp increase digoxin bioavailability and AUC. Dipyridamole was shown to increase digoxin bioavailability in vitro and in vivo; however, the effect on AUC was slight and clinically insignificant.⁵⁹ Carvedilol significantly decreased oral clearance of digoxin in children, resulting in digoxin toxicity in some cases.⁶⁰ However, in adults carvedilol caused only a modest increase in digoxin bioavailability and AUC.⁶¹

St. John's wort (*Hypericum perforatum*) is an herbal medicine frequently used for treatment of depression. *Hypericum* induces intestinal P-gp, resulting in a 1.4-fold increased expression of duodenal P-gp in humans.⁶² Coadministration of St. John's wort and digoxin caused a 25% decrease in AUC and a 33% reduction in trough and C_{max} concentrations of digoxin.⁶³

Interactions Affecting Elimination

Digoxin is eliminated primarily by renal excretion via the ATP-dependent efflux pump P-glycoprotein (P-gp).^{57,64-66} Basic drugs, among them amiodarone, clarithromycin, itraconazole, quinine, quinidine, verapamil, spironolactone, cyclosporine A, propafenone, and ritonavir decrease the renal clearance of digoxin by inhibiting P-gp in the kidney.⁶⁷⁻⁷² Carvedilol caused significant increases in digoxin AUC and C_{max} in men, but not in women.⁷³ The explanation may be that men have a higher P-gp activity compared to women, and thus are more sensitive to the effects of inhibiting drugs.

Because the combination of digoxin with drugs that inhibit its elimination results in increased toxicity, the physician should

Table 42-2. Drug Interactions with Digoxin

Interacting Drug	Serum Digoxin Levels	Mechanism	Comments
Cholestyramine, colestipol	D	Decreased absorption	Wait 1 hr after digoxin administration
Metoclopramide	D	Decreased absorption due to increased GI motility	Monitor digoxin levels; substitute elixir for tablets
Erythromycin	I (only in small percentage of patients)	Increased bioavailability due to decreased gut metabolism	Monitor digoxin levels, adjust dose
Anticancer drugs	D	Decreased absorption due to mucosal injury	Monitor digoxin levels; substitute elixir for tablets
Sucralfate	D	Decreased absorption	Do not administer within 1 hr of digoxin
Amiodarone	I	Decreased clearance (P-gp inhibition)	Decrease digoxin dose, monitor levels
Cyclosporine	I	Decreased clearance of digoxin (P-gp inhibition)	Monitor digoxin levels, decrease dose
Diuretics	I	Decreased renal clearance in hypovolemia; increased toxicity due to hypokalemia/hypomagnesemia	Monitor serum potassium and magnesium levels; monitor digoxin levels
Itraconazole	I	Decreased clearance (P-gp inhibition)	Decrease digoxin dose, monitor levels
Propafenone	I	Decreased renal clearance	Monitor digoxin levels, adjust dose
Quinine, quinidine	I	Decreased renal clearance (P-gp inhibition)	Decrease digoxin dose, monitor blood levels
Spironolactone	I	Decreased renal clearance (P-gp inhibition)	Monitor levels
Verapamil	I	Decreased renal excretion (P-gp inhibition)	Decrease digoxin dose, monitor levels
Rifampin	D	Increased bioavailability (intestinal P-gp induction)	Monitor levels

Abbreviations: D, decrease; GI, gastrointestinal; I, increase; P-gp, P glycoprotein.

reduce the digoxin dose by 50% when starting another drug such as quinidine or amiodarone. Because of the long half-life of digoxin, even after dose reduction there is still a potential for toxicity during the first week after adding another drug to the regimen, and patients must be monitored closely during this period.

Pharmacodynamic Interactions

Digitalis effect and toxicity are enhanced in the presence of hypokalemia and hypomagnesemia, and toxicity may be present even with digoxin blood levels within the therapeutic range. Because digoxin is often used with diuretics, which can cause electrolyte abnormalities, it is important to monitor and correct deficiencies, even though potassium and magnesium blood levels do not always accurately reflect body stores.⁷⁴ Concomitant administration of digoxin and sympathomimetic or vagolytic drugs may mask digitalis toxicity because of opposing effects on cardiac conduction. This effect is used therapeutically when digoxin is administered at the beginning of quinidine therapy to prevent rapid atrioventricular node conduction as a result of the vagolytic effect of quinidine.

Coadministration of digoxin with sympatholytic drugs (e.g., β -blockers) or calcium antagonists (e.g., verapamil, diltiazem) may result in additive atrioventricular block or bradyarrhythmia.

Antiarrhythmic Drugs

Drug interactions with antiarrhythmic drugs are presented in Table 42-3. A detailed review was published by Trujillo and Nolan.⁷⁵

Class 1A

Quinidine

Quinidine is a drug with many adverse side effects, and it interacts with many other drugs.

Pharmacokinetic Interactions

Quinidine is primarily metabolized in the liver, and only about 20% is excreted in urine. Thus it is subject to interactions with drugs that either induce or inhibit liver enzymes. Among the enzyme inducers, phenobarbital, phenytoin, and rifampin accelerate the metabolism of quinidine, resulting in decreased blood levels. Therefore, when any of these drugs is added, the quinidine dose should be increased, and when these drugs are stopped, the quinidine dose should be decreased. The dose adjustment may be as great as threefold.⁷⁶

There have been conflicting reports about the effect of nifedipine on quinidine blood levels.⁷⁷ However, quinidine

Table 42-3. Drug Interactions with Antiarrhythmic Drugs

Drug	Interacting Drug	Effect	Mechanism	Comments
Quinidine (Q)	Rifampin	Decrease in Q levels	Induction of Q metabolism	Increase Q dose, monitor Q levels
	Phenytoin Phenobarbital Cimetidine	Increase in Q levels	Inhibition of Q metabolism	Decrease Q dose, monitor Q levels
	Amiodarone Verapamil Antacids	Increase in Q levels	Alkalinization of urine, reduced Q tubular secretion	Monitor Q levels, change can be minor
	Procainamide	Proarrhythmic effect	Additive Q–T prolongation	Use combination with caution; monitor Q–T and potassium levels
	Disopyramide Amiodarone Sotalol Succinylcholine	Torsades de pointes		
		Prolonged neuro-muscular blockade	Inhibition of neuromuscular transmission (muscarinic receptors)	
Procainamide (P)	Cimetidine Trimethoprim Levofloxacin	Increased P levels	Reduced tubular secretion of P	Reduce P dose, monitor P levels
Disopyramide (Di)	Rifampin	Decreased Di levels	Acceleration of Di metabolism	Increase Di dose or avoid combination (increased anticholinergic effects with Di metabolite)
	Phenytoin Macrolides	Increased Di levels	P-450 inhibition	Decrease Di dose or avoid combination
Lidocaine (L)	Cimetidine Amiodarone Fluvoxamine Phenobarbital β -blockers	Increased L levels Decreased L levels Increased L levels	Inhibition of L metabolism Acceleration of L metabolism Decrease in L clearance due to reduction in hepatic blood flow	Reduce L infusion rate Increase L dose Reduce L infusion rate
Mexiletine (M)	Quinidine	Increased M levels	Inhibition of M metabolism	Reduce M dose or avoid combination
	Rifampin Phenytoin	Decreased M levels	Acceleration of M metabolism	Increase M dose
Flecainide (F)	Cimetidine Amiodarone Quinine Antacids	Increased F levels Increased F levels	Inhibition of F metabolism Alkalinization of urine, decrease in tubular secretion	Decrease F dose Minor effect
Encainide (E)	Quinidine	Increased E levels; diminished efficacy due to reduced formation of active metabolite	Inhibition of E metabolism	Avoid combination
	Cimetidine	Increased E levels; enhanced activity due to inhibition of active metabolite clearance	Inhibition of E metabolism	Avoid combination

Continued

Table 42-3. Drug Interactions with Antiarrhythmic Drugs—*cont'd*

Drug	Interacting Drug	Effect	Mechanism	Comments
Propafenone (Pr)	Quinidine	Increased Pr levels and β -blockade	Inhibition of Pr metabolism	Decrease Pr dose or avoid combination
Amiodarone (A)	Digoxin	Increased levels of the interacting drugs	Inhibition of the drug's metabolism by A	Monitor serum A levels, adjust dosages
	Flecainide			
	Lidocaine			
	Procainamide			
	Quinidine			
	Simvastatin			
	Cyclosporine			
	Phenytoin			
	Warfarin			
	Class 1A and 1C drugs	Proarrhythmic effect, torsades de pointes	Additive Q-T prolongation	Avoid combination or monitor Q-T
	β -blockers Ca channel blockers	Hypotension, bradycardia, AV	Additive depression of conduction	Monitor blood pressure and pulse rate; avoid combination in conduction disorders and heart failure
Adenosine (Ad)	Theophylline (T)	Antagonizes Ad effect	Competition for Ad receptors	Ad ineffective for patients on T
	Dipyridamole	Increased Ad levels and effect	Inhibition of Ad reuptake	Decrease Ad dose by 50%-75%

pharmacokinetics do not appear to be significantly changed by nifedipine or felodipine.⁷⁷

Cimetidine, verapamil, and amiodarone inhibit quinidine metabolism and necessitate downward dose adjustment.⁷⁸⁻⁸⁰

Even though renal excretion accounts for only 20% of quinidine clearance, clearance is influenced by urine pH, and alkalinization of urine (e.g., with intensive antacid therapy) may result in a moderate increase in quinidine levels.⁸¹

Pharmacodynamic Interactions

The combination of quinidine with other class 1A drugs (e.g., disopyramide, procainamide) or with class 3 drugs (e.g., amiodarone, sotalol) can result in Q-T prolongation and increased risk of torsades de pointes.^{82,83}

Moxifloxacin, a methoxyquinolone antibiotic, prolongs Q-T interval, and must be used with caution with class 1A or class 3 drugs.⁸⁴ Hypokalemia, hypomagnesemia, or both, common with diuretic treatment, can increase Q-T prolongation and the risk of torsades de pointes from quinidine or other drugs.⁸⁵

A proarrhythmic effect of combining amiloride and quinidine together has been described, probably resulting from a synergistic increase in sodium channel blockade.⁸⁶

Quinidine has also been reported to potentiate the anticoagulant effects of warfarin by direct inhibition of clotting factor synthesis in the liver.^{81,87} Quinidine inhibits neuromuscular transmission and prolongs the duration of anesthesia when used with curare or succinylcholine.⁸⁸

Procainamide

Procainamide is both metabolized and excreted renally, and its active metabolite, *N*-acetyl procainamide (NAPA), is cleared primarily by renal excretion. The major mechanism is tubular

secretion with little reabsorption; therefore, urine pH changes do not cause significant changes in blood procainamide concentration. Conversely, other basic drugs that are secreted by renal tubules (e.g., cimetidine, ranitidine, trimethoprim) significantly inhibit procainamide secretion.^{89,90} Levofloxacin, but not ciprofloxacin, was found to significantly inhibit renal clearance of procainamide and of NAPA.⁹¹

Additive effects of combined treatment with other class 1A or class 3 drugs, or other drugs that cause Q-T prolongation, are the same as for quinidine.

Disopyramide

Disopyramide is metabolized by liver enzymes. Enzyme inducers (e.g., rifampin, phenytoin, barbiturates) enhance the metabolism of disopyramide and may cause subtherapeutic blood levels.⁹² Enzyme inhibitors such as cimetidine are expected to decrease disopyramide clearance and to increase blood levels. Macrolide antibiotics, including erythromycin, clarithromycin, and azithromycin, inhibit P450 enzymes and there are reports of disopyramide toxicity during concomitant administration.⁹³⁻⁹⁵

Class 1B

Lidocaine

Lidocaine is extensively metabolized by the liver, with a high extraction ratio; therefore, its clearance is dependent on hepatic blood flow. Lidocaine is usually administered as a bolus followed by continuous intravenous infusion. The distribution of a bolus to the tissues is slowed in patients with severe heart failure and shock and may result in high blood levels and toxicity.⁹⁶ To avoid this, a bolus dose of lidocaine in these situations should be given slowly.

Drugs that decrease hepatic blood flow (e.g., β -blockers) decrease lidocaine clearance, whereas drugs that increase

hepatic blood flow (e.g., dopamine and dobutamine) can be expected to increase clearance.⁹⁷

Lidocaine clearance changes with liver enzyme inducers and inhibitors; it decreases with cimetidine and increases with phenobarbital.⁹⁸ Amiodarone has been reported to reduce lidocaine clearance, resulting in high lidocaine plasma levels and seizures.⁹⁹ Fluvoxamine, a CYP 1A2 inhibitor, significantly reduced lidocaine clearance.¹⁰⁰ An interaction with mexiletine, resulting in increase in plasma lidocaine levels and toxicity, was reported.¹⁰¹ The purported mechanism is displacement of lidocaine from tissue binding sites. It is recommended that the rate of lidocaine infusion be adjusted by 25% to 50% in the presence of potential drug interactions.

Increased cardiotoxicity resulting in sinoatrial block has been reported with concomitant use of lidocaine and quinidine or procainamide.^{81,102}

Mexiletine

Mexiletine is extensively metabolized by the liver, mainly by cytochrome P-450 isozyme 2D6, the activity of which is genetically determined, and in part by isozyme 1A2. Mexiletine metabolism is inhibited by quinidine.¹⁰³ Fluvoxamine, a CYP 1A2 inhibitor, caused significant increases in mexiletine AUC.¹⁰⁴ The enzyme inducers rifampin and phenytoin have been shown to enhance its metabolism.¹⁰⁵

Class 1C

Flecainide

Flecainide is eliminated by renal excretion and hepatic metabolism. Changes in urine pH are expected to affect its clearance; alkalization of urine will result in higher plasma concentrations. Cimetidine, quinine, and amiodarone have been reported to inhibit the clearance and increase plasma concentrations of flecainide.^{106,107}

Encainide

Encainide is extensively metabolized by the liver with significant first-pass effect, and its metabolism is genetically determined. Its metabolites are active and are responsible for the majority of its pharmacologic activity.¹⁰⁸ Quinidine inhibits encainide metabolism, resulting in diminished pharmacologic activity.¹⁰⁹ Cimetidine inhibits the metabolism of the active metabolites of encainide even more than it inhibits encainide metabolism, resulting in enhanced pharmacologic activity.¹¹⁰

Propafenone

Propafenone is metabolized by cytochrome P-450 isozyme 2D6; thus its metabolism is subject to genetic polymorphism of 2D6; about 10% of whites are poor metabolizers of this drug. When propafenone is administered to extensive metabolizers, quinidine, a potent inhibitor of 2D6 enzyme, inhibits its clearance, resulting in higher blood levels and a significant increase in pharmacologic effect.^{111,112} Conversely, rifampin, a P-450 inducer, increases propafenone clearance.¹¹³ Propafenone has been reported to inhibit the metabolism of theophylline.¹¹⁴

Class 3

Amiodarone

Amiodarone has a number of significant pharmacokinetic and pharmacodynamic drug interactions.

Pharmacokinetic Interactions

Amiodarone is an inhibitor of certain cytochrome P-450 enzymes. Amiodarone potentiates the effect of warfarin and causes enhanced anticoagulation.^{115,116} Because the half-life of amiodarone is very long, this effect may take up to several weeks to reach maximum intensity. Conversely, after amiodarone is discontinued, its effect on warfarin metabolism can persist for several months. Amiodarone also elevates the blood levels of digoxin, quinidine, procainamide, flecainide, lidocaine, metoprolol, simvastatin, cyclosporine, and phenytoin.^{99,117-120} It is recommended that dosages of warfarin and digoxin should be decreased by half when amiodarone is added.⁷⁵

Pharmacodynamic Interactions

The combination of amiodarone with class 1A or 1C drugs can result in enhanced antiarrhythmic efficacy. However, when combined with class 1A drugs such as quinidine, amiodarone can result in marked Q-T prolongation and an increased risk of torsades de pointes.⁷⁴ Another pharmacodynamic interaction with calcium antagonists or β -blockers may result in sinoatrial node depression, with excessive bradycardia or sinus arrest.¹²¹ This effect may persist for weeks after discontinuing amiodarone. However, the combination of amiodarone and β -blockers is usually safe, and may be beneficial in post-MI patients.¹²²

Sotalol

The administration of aluminum and magnesium hydroxide decreased sotalol absorption.¹²³ Separation of the drugs by 2 hours avoided the interaction. Sotalol is excreted primarily unchanged by the kidneys. The same pharmacodynamic effects for the combination with class 1A drugs would be expected for sotalol as with amiodarone. Hypokalemia can aggravate the risk of torsades de pointes with this combination.¹²⁴ Torsades de pointes was reported after the combination of sotalol and terfenadine.¹²⁵ The combination of sotalol with other β -blockers may produce bradycardia, atrioventricular block, or exacerbation of heart failure.¹²⁶

Class 4

Adenosine

Adenosine is used for acute treatment of supraventricular tachycardia. Dipyridamole inhibits adenosine reuptake, causing increased blood concentrations. Patients on dipyridamole should receive one fourth the standard dose of adenosine. Theophylline competes with adenosine for the same receptors and thus inhibits its action.¹²⁷

Calcium Channel Blockers

The most commonly used calcium channel blockers (Table 42-4) (e.g., verapamil, diltiazem, nifedipine) are extensively metabolized by the liver; therefore, their metabolism is dependent on hepatic blood flow. Because of their extensive hepatic metabolism, they undergo significant first-pass metabolism in the liver, with a low level of bioavailability.¹²⁸ Verapamil and diltiazem also inhibit some P-450 enzymes, thus affecting the metabolism of other drugs.

Pharmacokinetic Interactions

Cytochrome P-450 enzyme inducers (e.g., rifampin, phenytoin, phenobarbital) decrease the bioavailability and increase the clearance of verapamil and diltiazem. St. John's wort also

Table 42-4. Drug Interactions with Calcium Channel Blockers

Drug	Interacting Drug	Effect	Mechanism	Comment
Verapamil Diltiazem	β -blockers	Bradycardia, sinus arrest, heart block, heart failure	Additive effect on myocardial contractility and conduction	Avoid combination in elderly patients and in those with heart failure or conduction abnormalities
	Cimetidine	Increased bioavailability	Inhibition of metabolism	Decrease dose of Ca blockers
Felodipine Nitrendipine	Grapefruit juice	Increased bioavailability	Inhibition of metabolism	Monitor blood pressure and side effects
Verapamil (V) Diltiazem (D)	Rifampin	Decreased levels	P-450 induction; decreased bioavailability and increased clearance	Increase V and D dose
Verapamil (V)	Clarithromycin	Increased V levels	Inhibition of metabolism	Decrease V dose
Verapamil	Digoxin (D)	Increased D levels, heart block, asystole in D toxicity	Inhibition of P-gp, additive depression of conduction	Decrease D dose, monitor serum levels, avoid Ca blockers in digitalis toxicity
Verapamil	Prazosin (Pz)	Increased Pz levels, excessive hypotension	Inhibition of metabolism, additive α blockade	Monitor blood pressure
Verapamil Diltiazem	Simvastatin (S) Atorvastatin (A)	Increased S and A levels Increased risk of myotoxicity	CYP 3A4 inhibition	Avoid high S and A doses; use another statin
	Theophylline (T)	Increased T levels	Inhibition of T metabolism	Decrease T dose, monitor T levels
Verapamil	Quinidine	Hypotension (after verapamil IV)	Additive α -blockade	Use verapamil IV cautiously
	Clonidine	Complete AV block, hypotension	Additive myocardial depression	Use combination cautiously
	Halothane	Excessive bradycardia	Additive myocardial depression	Avoid combination if possible
	Cyclosporine (Cy)	Increased Cy levels	Inhibition of Cy metabolism	Decrease Cy dose, monitor serum levels
Verapamil	Phenytoin (Ph)	Increased Ph and C levels	Inhibition of Ph and C metabolism	Decrease anticonvulsant dose, monitor levels
	Midazolam (Md)	Increased Md levels and effect	Inhibition of Md metabolism	Reduce Md dose
	Disopyramide	Heart failure	Additive negative inotropic effect	Avoid combination
Diltiazem	Sirolimus (Sir) Tacrolimus (Tac)	Increased Sir and Tac levels	Inhibition of metabolism	Decrease dose, monitor levels
Nifedipine	Magnesium sulfate	Neuromuscular blockade	Additive effect on depletion of intracellular calcium	
	Quinidine (Q)	Decreased Q levels	Increased clearance of Q(?); effect found in men with left ventricular failure	Monitor Q levels

significantly decreases verapamil bioavailability through induction of first-pass metabolism in the gut.¹²⁹ Conversely, the enzyme inhibitor cimetidine increases the bioavailability and decreases the clearance of calcium antagonists.¹³⁰⁻¹³² Macrolide antibiotics clarithromycin and telithromycin also inhibit CYP 3A4, and their combination with verapamil resulted in significant verapamil toxicity.^{133,134} Felodipine metabolism was inhibited by itraconazole and erythromycin resulting in significant increases in plasma concentrations and AUC.^{135,136}

Grapefruit juice, which inhibits some P-450 enzymes, has been found to increase the bioavailability of some dihydropyridine calcium antagonists. The most significant interaction was with felodipine and nitrendipine, whereas nifedipine bioavailability was

not significantly affected.¹³⁷ Verapamil increases digoxin concentration by inhibiting its renal excretion through P-glycoprotein.¹³⁸ Diltiazem has been reported to increase digoxin concentration, but this effect is not always present, and digoxin levels are affected to a lesser degree than with verapamil.¹³¹ Nifedipine does not have a significant effect on digoxin concentration.¹³⁹

Verapamil and diltiazem are inhibitors of CYP 3A4, and thus are expected to inhibit the clearance of drugs metabolized by this enzyme. Verapamil and diltiazem significantly increase peak plasma levels and AUC of simvastatin and atorvastatin,¹⁴⁰⁻¹⁴² and there are reports of rhabdomyolysis with these combinations.^{143,144} Verapamil and diltiazem have been reported to increase cyclosporine plasma levels, thus necessitating reduction of cyclosporine

doses.^{145,146} The same interaction was observed between diltiazem and sirolimus¹⁴⁷ and diltiazem and tacrolimus.^{148,149} Verapamil has also been reported to increase blood levels of prazosin. This pharmacokinetic interaction, along with a possible pharmacodynamic interaction, may result in hypotension.¹⁵⁰ Verapamil inhibits theophylline metabolism.¹⁵¹ Verapamil and diltiazem significantly decrease the metabolism of midazolam, potentially causing excessive sedation; they also inhibit the metabolism of the anticonvulsants carbamazepine and phenytoin.^{152,153}

Because verapamil is highly bound to plasma proteins, its displacement can result in transient toxicity. Complete atrioventricular block has been precipitated by ceftriaxone and clindamycin, which are also highly bound drugs, in a patient receiving verapamil.¹⁵⁴

Pharmacodynamic Interactions

Many calcium antagonists depress cardiac contractility and conduction and thus can cause sinus bradycardia or arrest, atrioventricular block, asystole, hypotension, and heart failure.¹⁵⁵ There is a greater risk of these events when calcium channel blockers are coadministered with other drugs that can have similar effects on the heart, such as β -blockers. Verapamil and diltiazem have the greatest effect on conduction and contractility and thus the most reported interactions with β -blockers, but nifedipine has also been implicated in such interactions.^{131,155-158} The combination of calcium antagonists and β -blockers can be desirable and necessary to control angina, but patients should be closely monitored. The probability of adverse interactions is increased in the elderly and when the patient has underlying heart failure or conduction disorders. Intravenous verapamil should be avoided in patients treated with β -blockers because asystole has been reported as a complication of such therapy.¹⁵⁸ Development of heart failure is also a risk when administering verapamil with other negative inotropic agents, such as disopyramide. Hypotension with verapamil and quinidine has been described, possibly as a result of additive α -adrenergic blocking effects.¹⁵⁹ An interaction between verapamil and clonidine that resulted in severe hypotension and atrioventricular block has been reported.¹⁶⁰

Verapamil is contraindicated in patients with digitalis toxicity because of additive depression of the sinoatrial and atrioventricular nodes.¹⁶¹

An interaction between nifedipine and intravenous magnesium sulfate was reported in a woman with preeclampsia, resulting in neuromuscular blockade in the presence of normal magnesium blood levels. The possible mechanism is depletion of intracellular calcium by the additive actions of the calcium antagonist and magnesium.¹⁶²

Interactions between calcium channel blockers and anesthetic agents have been described, notably a pronounced bradycardia when halothane was given to a patient on verapamil.¹³¹

Calcium can negate some of the effects of calcium antagonists and has been used to treat their overdose or adverse effects. Calcium reverses the negative inotropic effect and partly reverses atrioventricular conduction depression caused by calcium channel blockers but does not offset sinus node depression or vasodilation.^{155,163}

β -blockers

β -blockers (Table 42-5) can be divided into two groups based on their disposition: the lipophilic drugs (e.g., propranolol, metoprolol, timolol) and the more hydrophilic drugs (e.g., atenolol,

nadolol, pindolol). The lipophilic drugs are extensively metabolized by the liver and are subject to a significant first-pass metabolism. The hydrophilic drugs have little first-pass metabolism, although absorption is less complete. The hydrophilic β -blockers are mostly excreted unchanged by the kidneys.

Pharmacokinetic Interactions

Absorption of all β -blockers is reduced by concomitant administration of antacids or cholesterol-binding resins. For the drugs with high first-pass metabolism (e.g., propranolol, metoprolol), rifampin, phenytoin, and phenobarbital decrease bioavailability and increase clearance, resulting in low blood concentrations. Cimetidine has the opposite effect.¹⁶⁴⁻¹⁶⁷

Hydralazine has an effect on propranolol and metoprolol disposition whereby it increases the bioavailability of these β -blockers by increasing hepatic blood flow, saturating the metabolizing enzymes. By the same token, by increasing hepatic blood flow, hydralazine increases propranolol clearance, but the increase in bioavailability exceeds the increase in clearance; therefore the net result is an increase in propranolol blood levels.¹⁶⁸ Metoprolol is metabolized by the cytochrome P-450 isozyme 2D6, and its metabolism is genetically determined. Quinidine inhibits metoprolol clearance in extensive metabolizers.¹⁶⁹ There is some evidence that desethylamiodarone, a metabolite of amiodarone, can increase metoprolol serum concentration by inhibiting CYP 2D6.¹⁷⁰ β -blockers themselves, by decreasing hepatic blood flow, reduce clearance of other extensively metabolized drugs, such as lidocaine. Carvedilol and propranolol significantly inhibit P-glycoprotein, and can lead to an increase in serum concentrations of drugs such as digoxin and cyclosporine.^{73,171} Doses of both drugs should be adjusted if combined with carvedilol.

Pharmacodynamic Interactions

Because the major effects of β -blockers are depression of cardiac contractility and conduction, their combination with drugs exerting similar effects may result in excessive bradycardia, sinus arrest, atrioventricular block, heart failure, and hypotension. Especially implicated is a combination of β -blockers with verapamil, but adverse effects with diltiazem and nifedipine have also been reported, especially in patients with heart failure or conduction disorders.^{157,158} The combination of β -blockers and disopyramide, which has a significant negative inotropic effect, may precipitate heart failure.

The interaction between β -blockers and epinephrine can be very serious. Nonselective β -blockers, and also selective ones in high doses, also block β_2 -receptors, which mediate arterial vasodilation. Administration of epinephrine to a patient receiving nonselective β -blockers can result in unopposed action on α -receptors and cause a serious increase in blood pressure that could be catastrophic.¹⁷²

Chronic treatment with β -blockers has also been shown to increase sensitivity to pressor effects of norepinephrine and angiotensin about twofold; the mechanism is unclear.¹⁷³

Antithrombotic and Anticoagulant Drugs

Aspirin

Aspirin is a mainstay of antithrombotic therapy in patients with ischemic heart disease. Most aspirin interactions are pharmacodynamic. The most significant interaction is with warfarin, resulting in excessive bleeding by producing additive effects

Table 42-5. Drug Interactions with β -blockers

Drug	Interacting Drug	Effect	Mechanism	Comments
All β -blockers	Antacids Verapamil	Decreased concentrations Bradycardia, AV block, sinus arrest, hypotension, heart failure	Reduced absorption Additive effect on myocardial contractility and conduction	Separate dosing by 1 hr Avoid combination in elderly and in patients with heart failure or conduction disturbance
	Diltiazem Amiodarone Epinephrine (adrenalin)	Severe hypertension	Unopposed effect on α -receptors	Avoid epinephrine with patients on β -blockers
Propranolol (Pp)	Rifampin	Reduced bioavailability	Accelerated metabolism	Increase the doses of Pp and Me
Metoprolol (Me)	Phenytoin Phenobarbital Cimetidine Hydralazine	Increased bioavailability Increased bioavailability and clearance; usually, increase in Pr levels	Inhibition of metabolism Increased hepatic blood flow, accelerated metabolism, and saturation of first-pass metabolism	Decrease the dose Adjust Pr dose to achieve β -blockade
Metoprolol (Me)	Quinidine	Increased levels	Inhibition of metabolic clearance	Decrease the dose of Me
Carvedilol	Digoxin (D) Cyclosporine (Cy)	Increased D and Cy levels	Inhibition of P-gp	Decrease D and Cy dose, monitor levels

through their different effects on hemostasis. This additive effect is diminished when both drugs are used in low doses.¹⁷⁴

Concomitant use of low-dose aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) may increase gastrointestinal bleeding; and use of aspirin with selective COX-2 inhibitors may abolish their gastroprotective effect.¹⁷⁵ In addition, NSAIDs, and in particular ibuprofen, may interfere with the antithrombotic effects of low-dose aspirin, especially when the ibuprofen dose is given before aspirin or with chronic use.^{176,177} However, short-term use of over-the-counter ibuprofen did not result in a clinically meaningful loss of cardioprotection.¹⁷⁸

Thienopyridines

Ticlopidine

Ticlopidine has a different antithrombotic action than aspirin; ticlopidine's mechanism is inhibition of ADP-dependent platelet aggregation. It is cleared primarily through hepatic metabolism. Ticlopidine has been shown to inhibit some P-450 enzymes. It reduces theophylline clearance.^{179,180} Contrary to expectations, ticlopidine was reported to significantly decrease plasma cyclosporine levels; the mechanism responsible for this action is unknown.¹⁸¹

Clopidogrel

Clopidogrel has largely replaced ticlopidine because of lower incidence of neutropenia. Clopidogrel is a prodrug, and is metabolized to an active drug by CYP 3A4. Concerns have been raised about potential interaction causing decreased efficacy of clopidogrel with some statins that inhibit CYP 3A4, such as atorvastatin and simvastatin. Indeed, there are several reports of the reduced antiplatelet effect of clopidogrel with atorvastatin in vitro.^{182,183} However, other studies did not find this effect,¹⁸⁴ and

no adverse effect on cardiovascular outcomes was found when clopidogrel was administered with CYP 3A4-inhibiting statins compared with statins with no effect on CYP 3A4.¹⁸⁵⁻¹⁸⁷

Addition of clopidogrel to aspirin has a synergistic effect on platelet inhibition, and in some patients was shown to overcome aspirin resistance assessed by aggregometry, flow cytometry, and platelet resistance index.¹⁸⁸

Warfarin

Warfarin (Tables 42-6 and 42-7) is subject to many drug interactions, both pharmacokinetic and pharmacodynamic. As many as 80 interactions have been described; most of these have been known for many years. The consequences of warfarin interactions can be catastrophic (e.g., bleeding, thrombosis). Most consequences can be avoided by checking the concomitant medications and adjusting the warfarin dose accordingly, especially when starting or discontinuing another drug. Warfarin metabolism is stereo-selective. The more potent S isomer is metabolized by CYP 2C9, whereas the less potent R isomer is metabolized by CYP 1A2 and CYP 3A4. CYP 2C9 is subject to genetic polymorphism, and *2 and *3 alleles are associated with poor warfarin metabolism.¹⁸⁹ CYP 2C9 polymorphism contributes to the variability in warfarin dosage also in the presence of drug-drug interactions.¹⁹⁰

Pharmacokinetic Interactions

Enhancing the Anticoagulant Effect Drugs that enhance the anticoagulant effect of warfarin (see Table 42-6) do so by inhibiting warfarin metabolism. Among drugs that inhibit warfarin metabolism are anti-infectives (metronidazole, macrolides, trimethoprim-sulfamethoxazole, fluoroquinolones, and azole antifungals), cardiovascular drugs (amiodarone, diltiazem,

Table 42-6. Drug Interactions with Warfarin: Increased Anticoagulation

Interacting Drug	Mechanism	Comment
Allopurinol	Inhibition of warfarin metabolism	Reduce warfarin dose, monitor PT
Amiodarone		
Propafenone		
Diltiazem		
Cimetidine		
Ranitidine		
Omeprazole		
Quinolones		
Macrolides		
Co-trimoxazole		
Metronidazole		
Azole antifungals		
Lovastatin		
Gemfibrozil		
Fenofibrate		
Fluvoxamine		
Sertraline		
Phenylbutazone		
Sulfinpyrazone		
Broad-spectrum antibiotics	Reduction in vitamin K availability	Primarily in malnourished patients
Acetaminophen	Inhibition of vitamin K-dependent carboxylase	Variable effect
Quinidine	Inhibition of clotting-factor synthesis	Adjust warfarin dose, monitor PT
NSAIDs	Depression of platelet function	Avoid combination; monitor
Clopidogrel		
SSRIs		
Cefamandole		
Moxalactam		

Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs; PT, prothrombin time; SSRIs, selective serotonin reuptake inhibitors.

propafenone), lipid-lowering drugs (fenofibrate, gemfibrozil, lovastatin), antidepressants (selective serotonin inhibitors, such as fluvoxamine and sertraline), GI drugs (cimetidine, ranitidine, omeprazole), and other drugs such as allopurinol, anabolic steroids, and tamoxifen.^{191,192} The time course of the interactions is difficult to predict because it depends on the half-lives of the interacting drug and warfarin and the vitamin K–dependent clotting factors II, VII, IX, and X. For most drugs, the interactions start within 2 to 3 days after administration and reach their maximal effect at 1 to 2 weeks.

Inhibiting the Anticoagulant Effect Drugs such as cholestyramine and colestipol inhibit the anticoagulant effect of warfarin by decreasing its absorption (see Table 42-7). Most of the drugs that antagonize the anticoagulant response do so by accelerating warfarin metabolism. Among these drugs are rifampin, phenytoin, barbiturates, and carbamazepine.^{191,192}

Table 42-7. Drug Interactions with Warfarin: Decreased Anticoagulation

Interacting Drug	Mechanism	Comments
Barbiturates	Accelerated metabolism of warfarin	Increase warfarin dose, monitor PT
Carbamazepine		
Griseofulvin		
Phenytoin		
Nafcillin		
Rifampin		
Cholestyramine	Decreased absorption of warfarin	Allow at least 1 hr after warfarin administration
Colestipol		
Vitamin K	Antagonizes warfarin action	Avoid combination

Abbreviation: PT, prothrombin time.

Nafcillin and dicloxacillin also accelerate warfarin metabolism, and high doses of warfarin may be required to achieve prothrombin time prolongation in the presence of these drugs.¹⁹³

Pharmacodynamic Interactions

Warfarin acts by inhibiting the synthesis of vitamin K–dependent clotting factors. Most of the vitamin K is obtained from food, with a small amount synthesized by intestinal bacteria. Treatment with antibiotics may reduce the amount of vitamin K produced by intestinal flora and thus cause an enhanced sensitivity to warfarin. However, the degree of INR change following this interaction is highly variable.¹⁹¹ Acetaminophen was reported to potentiate warfarin effect by inhibiting vitamin K–dependent carboxylase. There is a significant inter-individual variation in the magnitude of this effect.¹⁹⁴ Drugs that depress the synthesis of clotting factors (e.g., quinidine, salicylate in high doses) also enhance the anticoagulant effect of warfarin.⁸⁷

The most significant interactions are those resulting from the additive effects of other drugs affecting hemostasis by a different mechanism and thus creating an increased risk of bleeding. Such drugs include aspirin, NSAIDs, clopidogrel, some third generation cephalosporins, which inhibit platelet function, and heparin, which affects other clotting factors.^{195,196} Selective serotonin reuptake inhibitors may inhibit platelet aggregation by depleting platelet serotonin levels, and cause additive risk of bleeding with warfarin.¹⁹⁷ Drugs that injure gastrointestinal mucosa, such as NSAIDs and to lesser degree COX-2 inhibitors, also increase the risk of gastrointestinal hemorrhage.^{195,198}

Some herbal preparations, such as garlic, ginger, ginseng, ginkgo biloba, and the Chinese herb danshen, have been shown to have antiplatelet activity and may increase the risk of bleeding when used concomitantly with warfarin.¹⁹⁹

Drugs that antagonize the effects of warfarin are vitamin K analogues and foods, and enteral formulas containing high amounts of vitamin K. Oral contraceptives inhibit the anticoagulant effect by increasing the synthesis of clotting factors VII and X.

Table 42-8. Drug Interactions with Lipid-Lowering Drugs

Drug	Interacting Drug	Effect	Comments
Simvastatin Lovastatin Atorvastatin	Macrolides Fluconazole Amiodarone Diltiazem Verapamil	Rhabdomyolysis via increased statin levels (CYP 3A4 inhibition)	Avoid combination if possible; otherwise, monitor CPK
Simvastatin Lovastatin	Gemfibrozil	Rhabdomyolysis via increased statin levels (CYP 2C8 and OATP1B1 inhibition)	Avoid combination if possible; otherwise, monitor CPK
HMG-CoA reductase inhibitors	Cyclosporine Clarithromycin Ritonavir Saquinavir Indinavir	Rhabdomyolysis via increased statin plasma levels (OATP1B1 inhibition)	Avoid combination if possible; otherwise, monitor CPK; decrease dose when combined with cyclosporine
HMG-CoA reductase inhibitors	Fibrates	Rhabdomyolysis	Avoid combination if possible; otherwise, monitor CPK
Clofibrate Gemfibrozil	Warfarin	Increased anticoagulation (inhibition of warfarin metabolism)	Monitor PT, adjust warfarin dose
Probucol	Class 1A antiarrhythmics	Additive Q–T prolongation; risk of torsades de pointes	Avoid combination
Cholestyramine Colestipol	Digoxin Ezetimibe Thiazide diuretics Warfarin Sulfonylurea Thyroid hormones	Binding in the gut and decreased absorption of the interacting drugs	Separate administration of bile acid sequestrants by 2–3 hr

Abbreviations: CPK, creatine phosphokinase; PT, prothrombin time.

Heparin and Low Molecular Weight Heparins (LMWHs)

The significant interactions of heparin and LMWHs are with other drugs that affect hemostasis, such as aspirin in high doses, NSAIDs, and warfarin. Concomitant use of glycoprotein IIB/IIIA antagonists, particularly in elderly patients, is also associated with increased risk of major bleeding.²⁰⁰ There have been reports of interactions with intravenous nitroglycerin, in which the anticoagulant effect of heparin is reduced and therefore higher heparin doses are required, but subsequent studies did not support this observation.^{201–203}

Lipid-Lowering Drugs

Drug interactions with lipid-lowering drugs are displayed in Table 42-8. The significant interactions with hydroxymethylglutaryl-coenzyme A reductase inhibitors (e.g., lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, and rosuvastatin) are pharmacokinetic, leading to high statin concentrations in the peripheral blood and muscle tissue, and pharmacodynamic, leading to additive or synergistic muscle toxicity.

Concomitant use of simvastatin, lovastatin, and atorvastatin with CYP 3A4 inhibitors, such as erythromycin, clarithromycin, fluconazole, verapamil, diltiazem, and amiodarone, results in significantly increased AUC of statins, and particularly when high doses of statins are used, in myotoxicity and rhabdomyolysis.^{204,205} CYP 3A4 inhibitors have no appreciable effect on plasma levels of pravastatin and rosuvastatin, which are not metabolized by CYP 3A4.²⁰⁵ Cytochrome P-450 inducers, such

as rifampin and carbamazepine, can significantly reduce the AUC of simvastatin and atorvastatin.

The uptake of statins into the liver is mediated by organic anion transporter OATP1B1. This mechanism is particularly significant for hydrophilic statins, such as pravastatin and rosuvastatin. Inhibitors of OATP1B1 include cyclosporine, clarithromycin, and protease inhibitors ritonavir, saquinavir, and indinavir. Coadministration of these drugs with statins results in increased AUC of statins and increased risk of rhabdomyolysis.²⁰⁵

Concomitant use of statins and fibrates results in increased risk of myopathy and rhabdomyolysis because of their additive risk. The risk of interaction with gemfibrozil is the greatest because, in addition to the pharmacodynamic interaction, gemfibrozil also inhibits CYP 2C8, which metabolizes the active form of simvastatin and lovastatin, and OATP1B1.²⁰⁵ Gemfibrozil also increases plasma levels of other CYP 2C8 substrates, particularly the glucose-lowering drugs repaglinide, rosiglitazone, and pioglitazone.²⁰⁵

Clofibrate and gemfibrozil increase the anticoagulant effect of warfarin by inhibiting its hepatic metabolism.

Cholesterol-binding resins (e.g., cholestyramine, colestipol) bind to acidic drugs such as digoxin, warfarin, thiazide diuretics, thyroid hormones, and sulfonylurea in the gut, thereby interfering with their absorption.²⁰⁶ Cholestyramine also decreases the bioavailability of ezetimibe.²⁰⁵ Probucol can prolong the Q–T interval and thus create an additive risk for torsades de pointes when administered with class 1A or class 3 drugs.²⁰⁷

Diuretics

Most of the drug interactions with diuretics are pharmacodynamic. There is a synergistic effect when a loop diuretic is administered with a thiazide, and this combination is used in refractory edematous states (e.g., severe heart failure), in which loop diuretic efficacy is limited because of enhanced sodium reabsorption in the distal tubules. Because this combination may result in massive fluid and electrolyte loss, the thiazide should be started at low doses.²⁰⁸ Care should be exercised when an ACE inhibitor is added to a diuretic because the inhibition of angiotensin II response may result in profound hypotension and renal failure. Reduction in the diuretic dose or temporary withdrawal of the diuretic is prudent before starting an ACE inhibitor.^{28,29} NSAIDs and COX-2 selective inhibitors raise blood pressure and significantly increase the incidence of congestive heart failure, and thus can be expected to diminish the response to loop and thiazide diuretics.^{209,210} There are reports of indomethacin inhibiting the antihypertensive actions of the diuretics, although other NSAIDs, specifically diclofenac and sulindac, did not have this effect.²¹¹

Diuretics reduce the renal excretion of lithium because sodium depletion causes enhanced tubular reabsorption of lithium. Lithium doses should therefore be reduced by 25% when adding diuretics, and plasma levels should be monitored. There is a risk of additive ototoxicity when loop diuretics are used with aminoglycosides, especially with high doses of the diuretic and in patients with renal failure.

Concomitant use of potassium-sparing diuretic with ACE inhibitors or angiotensin receptor blockers can result in severe hyperkalemia, particularly in patients with spironolactone doses higher than 25 mg/day, the elderly, and patients with impaired renal function and diabetes mellitus.²¹²

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Advanced Diagnostic and Therapeutic Techniques: Indications and Technical Considerations

SECTION

VI

Echocardiography in the CICU

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CHAPTER

43

**Evaluation of Patients with Chest Pain
Pulmonary Embolism
Aortic Diseases**

**Pericardial Effusion
Infective Endocarditis**

ECHOCARDIOGRAPHY PROVIDES critical diagnostic information in the care of patients in the CICU. It is an easy, safe, portable, and readily available tool for thoroughly evaluating patients who are hemodynamically unstable and require intensive monitoring. It provides information on cardiac structure, function, and hemodynamics. Echocardiography can diagnose, detect complications, evaluate reperfusion therapy, and can assist in risk stratification in patients having myocardial infarction.

Advances in echo technology and the ability to digitally store data enable acquisition of accurate information that can easily be displayed and compared with prior studies for serial comparison. Echocardiography has increasing utility in guiding management of a wide spectrum of cardiovascular

disorders. It has been shown to influence therapeutic decision making in critically ill patients and provide supplemental information beyond that obtained by pulmonary artery catheterization.^{1,2}

This section is divided into the following categories:

- Evaluation of patients with chest pain
- Echocardiography in patients with acute coronary syndrome
- Evaluation of left ventricular (LV) function
- Exclusion and evaluation of LV aneurysm
- Exclusion of apical clot
- Exclusion of right ventricular (RV) involvement
- Ischemic mitral regurgitation (MR)
- Left ventricular outflow tract (LVOT) obstruction

- Mechanical complications
- Guidance of placement and monitoring of assist devices
- Assessment of the aorta
- Evaluation of patients with suspected or documented pulmonary embolism
- Evaluation of pericardial effusion and tamponade physiology
- Evaluation of patients with suspected or documented infective endocarditis

Evaluation of Patients with Chest Pain

Each year 6 million patients in the United States come to the emergency room with chest pain.³ The sensitivity of electrocardiography in diagnosing acute myocardial infarction (MI) is relatively low.⁴ Detection of regional wall motion abnormalities by echocardiography is a very sensitive method for diagnosing an acute MI. If no regional wall motion abnormalities are present during chest pain, ischemic risk is very low.^{5,6,7} Although not approved by the U.S. Food and Drug Administration for this indication, numerous studies have demonstrated the incremental value of perfusion echo in identifying the presence of ischemia. Kaul and colleagues⁶ compared contrast echocardiography with a modified Thrombolysis In Myocardial Infarction (mTIMI) score for triage of nearly 1000 patients having chest pain and nondiagnostic ECG before troponin levels became available. Both regional myocardial function and perfusion were analyzed by rest contrast echocardiography and related to early (in the first 24 hours), intermediate (at 30 days), and late (1 year) events. Only 0.4% of patients with normal regional function had a primary event consistent with an excellent negative predictive value of contrast echo. Contrast echocardiography was able to classify patients with an intermediate mTIMI score into low and high risk for acute coronary syndrome (ACS). When the troponin level was not available, the mTIMI score failed to identify approximately 4% of patients with ACS, consistent with previous data. The regional function provided incremental prognostic information beyond the mTIMI score for predicting intermediate and late events. Myocardial perfusion provided additional prognostic information beyond the mTIMI score and regional function in patient with abnormal regional function. The complete TIMI score did not provide incremental prognostic benefit when compared with the combination of mTIMI, regional function, and myocardial perfusion in the prediction of early and intermediate events. Therefore, in patients with chest pain and nondiagnostic ECG, rapid identification of regional function and myocardial perfusion help to risk stratify patients even before troponin levels are known.

Echo can be used to differentiate ischemic chest pain from other mimicking abnormalities, such as aortic dissection, pulmonary embolism, and pericardial effusion, which will be described later in the chapter.

Echocardiography in Patients with Acute Coronary Syndrome

Once the diagnosis of acute coronary syndrome is made, echocardiographic evaluation of the location and extent of regional wall motion abnormalities can be used to assess the results of reperfusion therapy, infarct expansion, extension, or remodeling.

Evaluation of Left Ventricular Function

Accurate assessment of left ventricular systolic function and ejection fraction are critical in patients with myocardial infarction (MI) since further interventions, such as placement of an AICD or BiV pacemaker, require a certain ejection fraction (EF) as an indication. In addition, LV ejection fraction provides important prognostic information in patients with ST elevation myocardial infarction (STEMI). LV function has been shown to be an important determinant of mortality and subsequent development of congestive heart failure, and development of ventricular arrhythmias and sudden cardiac death.⁸⁻¹¹ Figure 43-1 demonstrates the recommended method for calculation of EF by the American Society of Echocardiography.

In patients in whom accurate quantification of systolic function cannot be obtained with 2D echo, new techniques such as 3D echo can be used. Multiple studies have confirmed the accuracy and feasibility of a 3D echocardiogram for assessment of LV volumes and function,¹²⁻¹⁵ and demonstrated good correlation between these parameters and those obtained by MRI.¹⁶⁻¹⁸ Because a data set comprises the entire LV volume, the greatest advantage of 3D echo over 2D echo is that there is no need for any assumption on the shape of the ventricle, which is required for volume calculation obtained from two planes only. As a result volume calculations using 3D echo are more accurate. This is especially true in patients in whom the geometry and shape of the LV is distorted secondary to MI and the presence of wall motion abnormalities and or an aneurysm. In these patients, direct measurements of full volume acquired by 3D will result in a more accurate analysis of structure and function than by making erroneous assumption using 2D data. Advances in technology now enable 3D data acquisition to be performed at the bedside. (Fig. 43-2 demonstrates 3D reconstruction of the LV). If image quality is limited, acquisition can be combined with infusion of contrast to improve the delineation of the endocardial border.

LV Aneurysm

Aneurysm is defined as a discontinuity in the left ventricular contour that is present during both systole and diastole. It is formed when normal myocardium is replaced by necrotic myocardium and fibrous scar tissue, and is therefore a potential complication of transmural infarction. Mechanically, the aneurysm is a reservoir of blood that is not ejected, thus reducing the overall stroke volume, which could lead to the development of heart failure. Other potential consequences of the presence of an aneurysm are the development of a clot due to stagnation of blood and intractable arrhythmias due to the presence of scar tissue. Heart failure is a common indication for surgical resection of the aneurysm. Patients with ejection fraction of 35% or more generated by contractility of the basal portion of the ventricle, as measured by the basal fractional shortening, derive more benefit from aneurysm resection.¹⁹ Echocardiography plays a major role defining the size and location of an aneurysm and excluding the presence of a clot. It is instrumental in distinguishing it from a pseudoaneurysm by demonstrating the presence of a wide neck communicating with the ventricular cavity. Use of contrast echocardiography can clearly delineate the aneurysm better (Fig. 43-3). Three-dimensional echocardiography has a role in accurate determination of EF in these patients with abnormal geometry as outlined in detail previously.

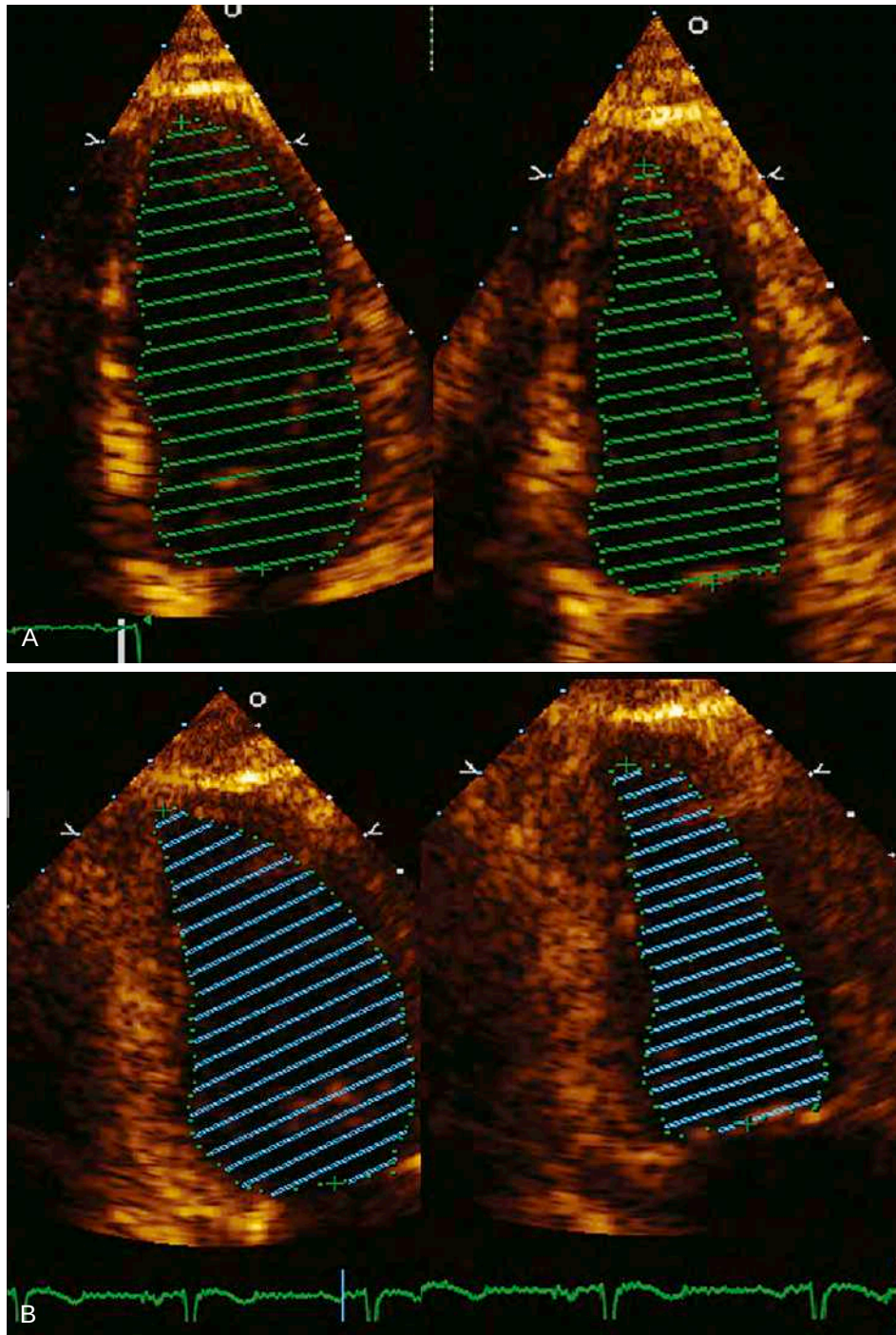


Figure 43-1. Ejection fraction calculation using biplane method of disks. **A**, Diastolic (*left*) and systolic (*right*) frames obtained from apical four-chamber view. **B**, Diastolic (*left*) and systolic (*right*) frames obtained from apical two-chamber view.

Apical Clot

Left ventricular thrombus usually occurs in anteroapical infarction although it can infrequently be seen in inferior myocardial infarction as well (Fig. 43-4). A thrombus can be mobile, pedunculated, or laminar in nature. It occurs in areas of extensive regional wall motion abnormalities, where stagnation of flow is expected, or within an aneurysm. Although the majority of clots form at least 72 hours after the onset of MI, it can occasionally

be seen much earlier and emphasis should therefore be made to exclude their presence on any echo performed in a post-MI patient. Identification of a thrombus is important because these patients require anticoagulation therapy for at least 6 months to reduce risk of embolic events. Two-dimensional echo can be repeated to assess resolution of a thrombus. The use of echo contrast has significantly increased the sensitivity of echo for detection of small clots, which appear as filling defects.²⁰ Figure 43-5.

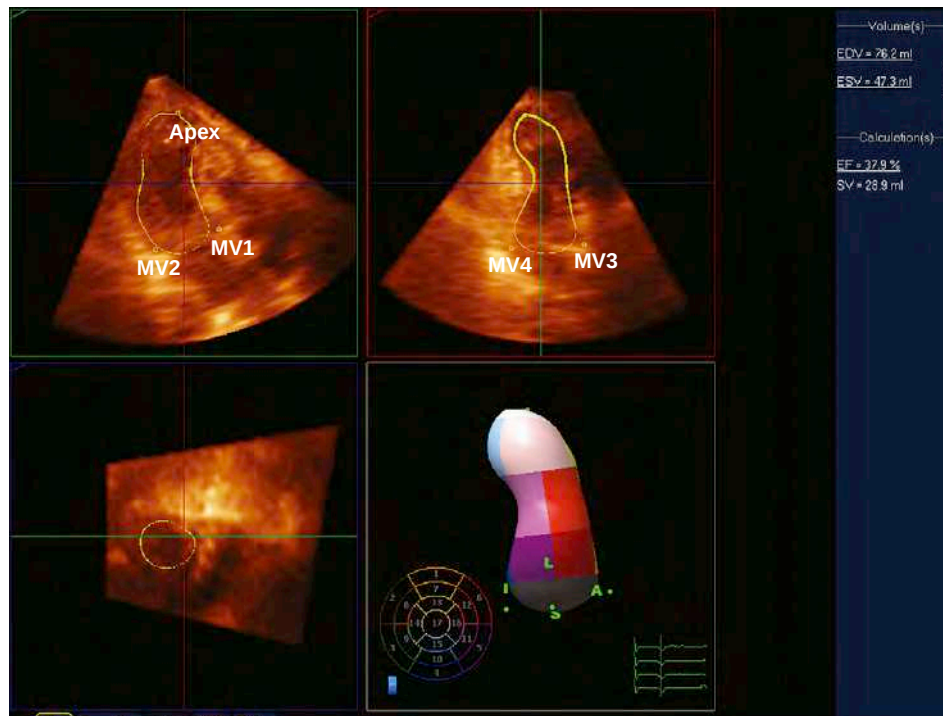


Figure 43-2. Left ventricular volume generated by three-dimensional echocardiography.

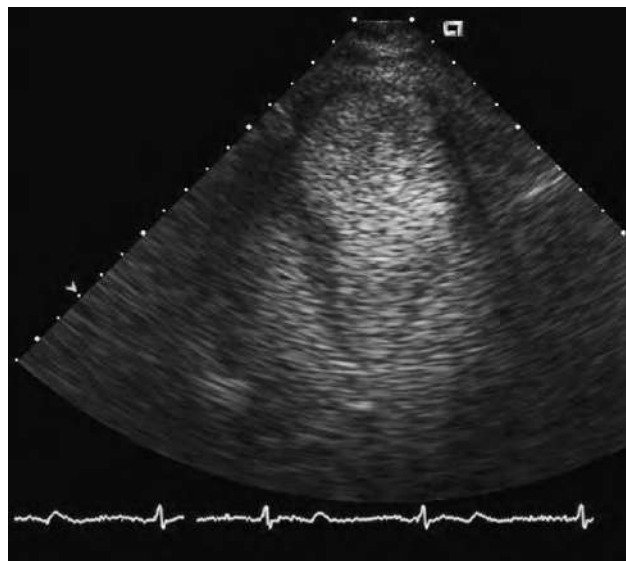


Figure 43-3. Contrast-enhanced left ventricular cavity showing the presence of an apical aneurysm.

Exclusion of Right Ventricular (RV) Involvement

The incidence of right ventricular infarction in association with left ventricular myocardial infarction ranges from 14% to 84% and is dependent on the population studied and the pathologic criteria.²¹ Right ventricular (RV) infarction usually occurs in association with inferior wall infarcts, less commonly with anterior wall infarcts, and rarely in isolation. The clinical triad characteristic of RV infarcts is: hypotension, clear lungs, and elevated jugular venous pressure. The Kussmaul sign (an increase in jugular venous pressure with inspiration) is a highly sensitive and specific clinical finding for the diagnosis

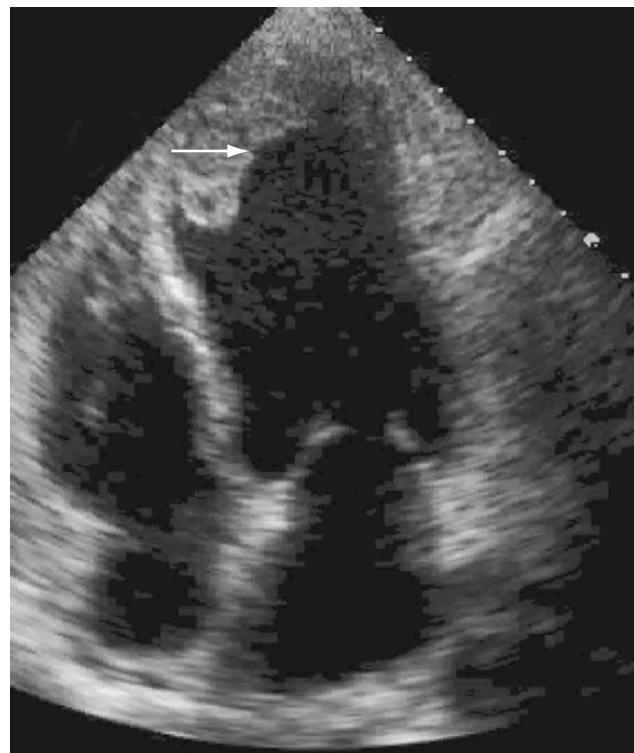


Figure 43-4. Large apical clot (arrow).

of RV infarction. These patients have normal LV filling pressures, but elevated right atrial and ventricular filling pressures. ST elevation seen on right-sided ECG leads (V_3R , V_4R , and V_5R) is very suggestive of RV involvement. Echocardiography identifies depression of right ventricular systolic function with

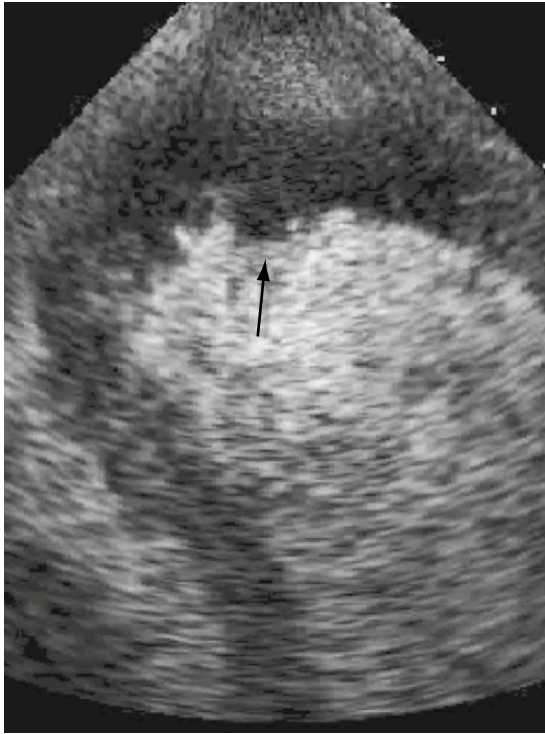


Figure 43-5. Small apical clot seen as a filling defect (arrow) with the use of contrast medium.

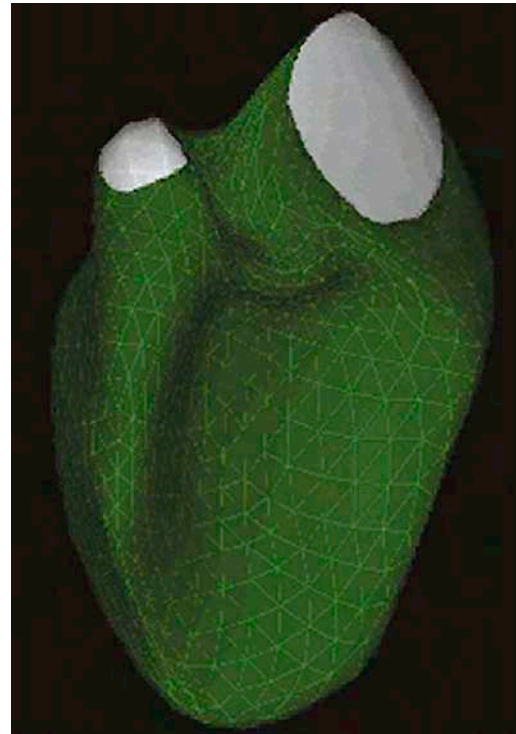


Figure 43-6. Three-dimensional reconstructions of the right ventricle.

segmental wall motion abnormalities, and dilation of the right ventricle. Abnormal interventricular septal motion is also seen due to increased right ventricular end-diastolic pressure. The parasternal short axis view has the highest sensitivity (82%) with specificity ranging between 62% to 93% for hemodynamically significant right ventricular infarction.²² Interatrial septal bowing toward the left atrium, indicative of an increased right atrial-left atrial pressure gradient, has been shown to be an important prognostic marker in right ventricular infarction. This finding is associated with hypotension, heart block, and increased mortality.²³ Recently 3D echocardiographic assessment of RV volumes in healthy adults has been shown to be reproducible, accurate, and closely correlated with the assessment of RV volumes using cardiac MRI.²⁴ Given the complex structure of the RV, 3D echo may prove to be the preferred method for accurate assessment of RV structure and function, especially in patients with dilated RV and reduced function [Figure 43-6](#). The treatment of right ventricular infarction includes aggressive maintenance of RV preload, reduction of RV afterload, inotropic support, and early reperfusion.

Ischemic Mitral Regurgitation (MR)

Myocardial infarctions (MIs) often trigger a remodeling process that leads to gross ventricular distortion, contractile dysfunction of normally perfused myocardium, symptomatic congestive heart failure (CHF), and premature death.²⁵ Depending on size, location, and transmural extent of the infarct, the remodeling process may be associated with the development of ischemic mitral regurgitation (IMR).²⁶ Mild degrees of mitral regurgitation after acute MI portend a substantially increased risk of cardiovascular mortality within 5 years, even in patients who do not initially have signs of overt CHF.²⁷ Echocardiographic features

include severe segmental hypokinesis/akinesis predominantly of the inferior wall, tethering of the mitral valve leaflets, and inadequate coaptation of the valve leaflets associated with mitral regurgitation²⁸ [Figure 43-7](#). It is critical to exclude the presence of a significant degree of ischemic MR by performing a transthoracic echocardiogram (TTE), followed by a transesophageal echocardiogram (TEE) as needed, particularly in those who are candidates for surgical revascularization since it has been shown that CABG alone does not reduce the severity of MR.²⁹ Alternative surgical and percutaneous approaches to these patients using repair and placement of devices in an attempt to restore the original shape of the annulus are now being explored.²⁹⁻³³

Innovative 3D reconstruction software have been developed recently that allow accurate evaluation of the mitral annulus. The utility of this 3D data in guiding interventions still need to be determined.³⁴

LVOT Obstruction

Recent case reports have described dynamic left ventricular outflow tract obstruction in the setting of anteroapical infarction ([Fig. 43-8](#)). In this instance, the basal portions of the myocardium are hyperdynamic compensate for the reduced stroke volume, causing systolic anterior motion of the mitral valve. Both these features can easily be recognized on TTE. This entity should be suspected in a patient having hypotension refractory to inotropes and an intra-aortic balloon pump. Since the LVOT obstruction is dynamic and caused by the hyperdynamic contractility of the basal segments, inotropic medications would worsen the hypotension and should be avoided. Similar mechanism of LVOT obstruction can also be seen in patients with left ventricular apical ballooning syndrome, also known as Takotsubo cardiomyopathy^{35,36} ([Fig. 43-9](#)).



Figure 43-7. Tethering of the mitral leaflets.

Mechanical Complications

Echocardiography is invaluable in the diagnosis of complications of acute myocardial infarction such as free wall rupture, left ventricular pseudoaneurysm, ventricular septal rupture, and acute mitral regurgitation.

Free Wall Rupture

Rupture of the free wall accounts for 10% of in-hospital deaths due to STEMI.³⁷ Free wall rupture occurs more commonly in patients who have received fibrinolytics, especially in patients who present after a long delay from the symptom onset. In the era before reperfusion, the incidence was as high as 6% of patients with STEMI.³⁸ The incidence has sharply decreased after the widespread use of primary percutaneous intervention for acute myocardial infarction, accounting for less than 1%.^{20,39} A patient can have either an acute rupture, which usually results in immediate death, or a subacute rupture, which is associated with nonspecific symptoms, including nausea, hypotension, and pericardial type of discomfort. A quarter of these patients have pericardial effusion with blood in the pericardial space (hemopericardium). Early recognition of this complication is critical because stabilization with an intra-aortic balloon pump and prompt surgical repair determines survival. Whenever suspected, an echocardiogram at the bedside should be performed immediately. The presence of pericardial effusion can be evaluated with 2D imaging, and flow into the pericardial space should be confirmed by color Doppler.³⁸

Occasionally, incomplete free wall rupture is sealed by organizing a thrombus, hematoma, and adjacent pericardial tissue, thus preventing the development of hemopericardium (Fig. 43-10). This leads to the formation of a pseudoaneurysm, which can still communicate with the left ventricular cavity. This is

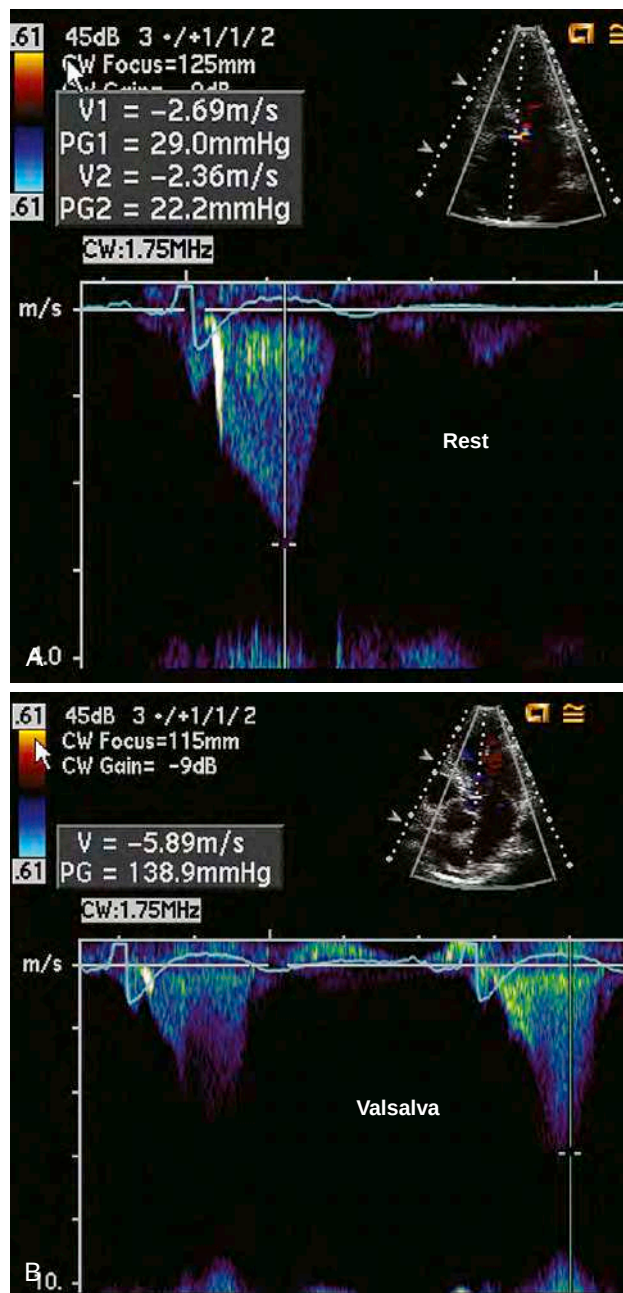


Figure 43-8. A and B, Pulsed wave Doppler at the level of the left ventricular outflow tract showing normal gradients at rest (A) and increased gradients during Valsalva maneuver (B).

distinguished echocardiographically from a true aneurysm by a narrow neck. Color flow into the pseudoaneurysm can be visualized by echocardiography and confirms the communication with the left ventricle. Unlike a true aneurysm, the wall of the pseudoaneurysm is very thin because it is composed of pericardium not myocardium and lacks all the elements of the ventricular wall. Characteristic features of a pseudoaneurysm as described by Roelandt and colleagues⁴⁰ are: (1) Saccular or globular echolucent extracardiac space; (2) discontinuity of the endocardial border at the site of the pseudoaneurysm suggestive of a communication between the left ventricle and the echo free space by a narrow neck; and (3) systolic expansion of the echo free space and displacement of the cardiac chambers.

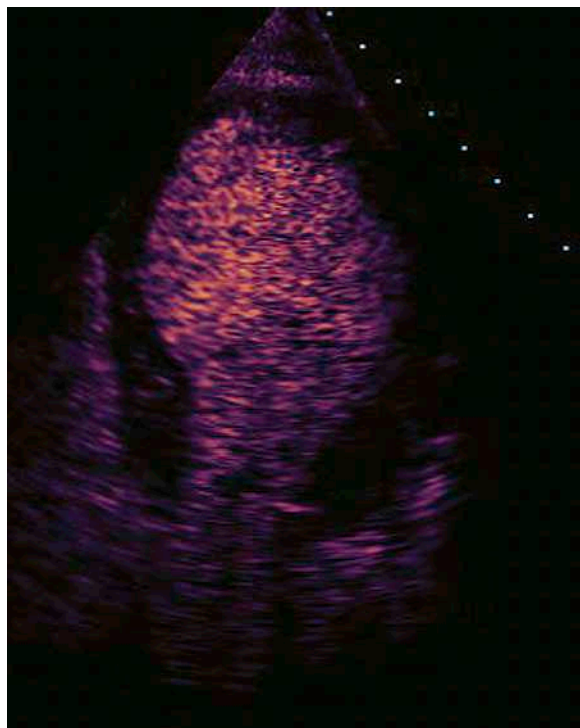


Figure 43-9. Apical ballooning cardiomyopathy enhanced with the use of contrast medium.

Ventricular Septal Rupture

This is a less frequent complication than free wall rupture. In the era before reperfusion therapy, septal rupture (VSD) complicated 1% to 3% of acute myocardial infarctions.^{37,41-43} Similar to other mechanical complications, the incidence has decreased to 0.2% in the reperfusion era as demonstrated in a retrospective review of 41,021 patients in the GUSTO-I trial.⁴⁴ It usually occurs after transmural infarctions. Biventricular failure usually occurs within hours to days. The presentation depends on the site and size of the rupture. Mortality is high; 25% of affected patients die within 24 hours and 65% die within 2 weeks without prompt surgical repair. Echocardiography is highly sensitive for the diagnosis and characterization of the type of ventricular septal rupture⁴⁵⁻⁵⁰ and in differentiating it from acute mitral regurgitation, which shares similar clinical characteristics.^{46,49,50,52} Using color flow imaging, a high-velocity mosaic jet can be seen entering the right ventricular cavity in the short axis and the apical views. Direct visualization of the defect by two dimensional imaging can be seen in 50% of the patients. Contrast imaging using agitated saline helps to identify the septal rupture in 80% of the patients. This can be seen as a negative contrast effect in the right ventricle since high-velocity flow is exiting the left ventricle into the right ventricular cavity. Addition of color flow and pulsed wave Doppler imaging increases the sensitivity to 96%⁴⁸ (Fig. 43-11). Using continuous wave Doppler, the right ventricular systolic pressure and the pulmonary artery pressure can be determined directly by interrogating the VSD jet.

Acute Mitral Regurgitation Secondary to Rupture of the Papillary Muscle

Another rare complication of AMI is a ruptured papillary muscle, which occurs in 1% of patients with MI. This complication, unless treated surgically, carries high mortality, accounting

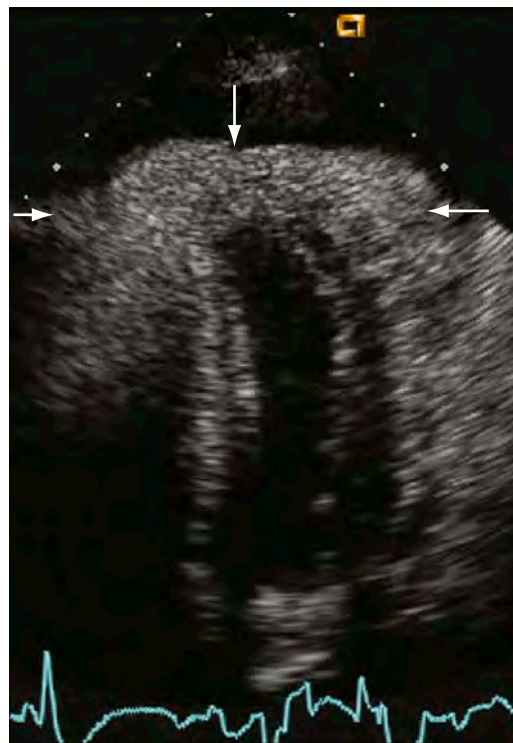


Figure 43-10. Free wall rupture and clots adjacent to the left ventricular apex (arrows).

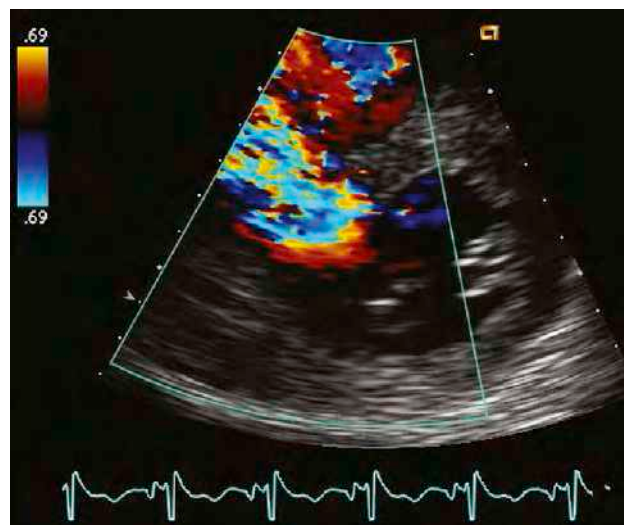


Figure 43-11. Ventricular septal defect shown by color flow across the interventricular septum.

for up to 5% of postinfarction deaths—with 50% dying within 24 hours and 90% within 1 week.⁵³ Papillary muscle rupture involves the posteromedial papillary muscle in 75% of cases and the anterolateral papillary muscle in 25% of cases. The reduced occurrence in the anterolateral papillary muscle is a result of its dual blood supply from left anterior descending and left circumflex coronary arteries. The physical examination is highly unreliable. Due to rapid equalization of pressures between the left ventricle and atrium, a murmur may not be heard. When a new holosystolic murmur is heard in a post-MI patient, an

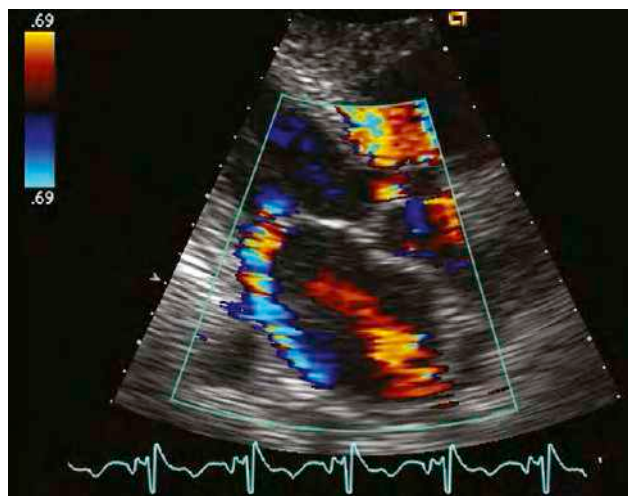


Figure 43-12. Eccentric mitral regurgitation.

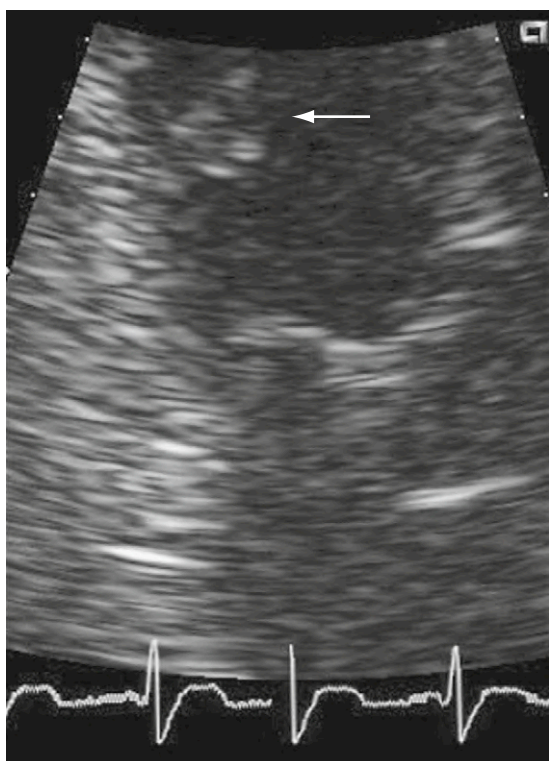


Figure 43-13. Ruptured papillary muscle, seen as a mobile tissue density in the left ventricular cavity (arrow).

emergent echocardiogram is indicated to exclude the presence of ventricular septal rupture or acute mitral regurgitation (MR). Using transthoracic echocardiography, the following features can be seen: an eccentric jet of mitral regurgitation (Fig. 43-12), a flail mitral leaflet, and a ruptured or partially ruptured papillary muscle seen as a mobile echodensity in the left ventricular cavity prolapsing back into the left atrium (Fig. 43-13). These features can be better appreciated using transesophageal echocardiography (TEE), so when a papillary muscle rupture is suspected and not confirmed on TTE, a TEE should be performed.

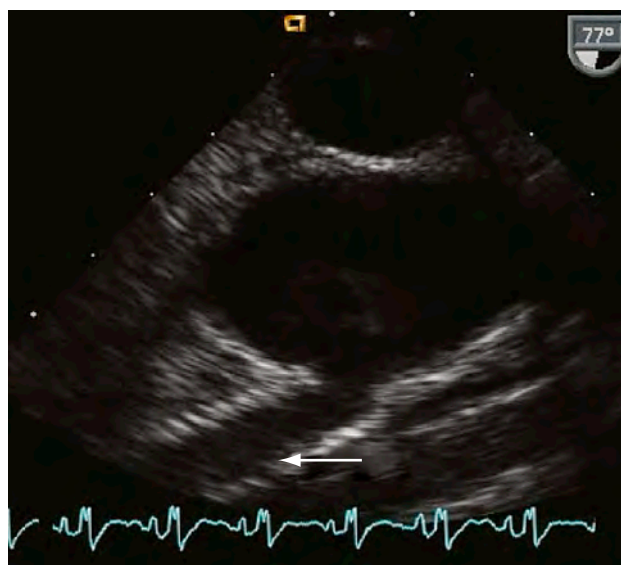


Figure 43-14. Left ventricular assist device cannula (arrow) as it can be seen with transesophageal echocardiography.

When the diagnosis is made using TTE, TEE should still be performed (preferably in the operating room) to better define the anatomy for the surgeon. In 65% of the patients described by Moursi and colleagues,⁵⁴ the papillary muscle head was seen in the left atrium. In 18 of 20 patients who did not have prolapse of the ruptured papillary muscle head into the left atrium, TEE was useful in making the diagnosis by demonstrating an erratic large amplitude motion of the papillary muscle in the left ventricle, as confirmed by surgery.

Multiple Complications

Although rare, more than one complication can be found in post-MI patients. A combination of left ventricular free wall and papillary muscle rupture has been described. Also a combination of ventricular septal rupture and papillary muscle rupture may occur in the same patient. Rapid identification of both these complications in critically ill patients who need urgent cardiac surgery is possible with transthoracic and transesophageal echocardiography.⁵⁵

Guidance of Placement and Monitoring of Assist Devices

Implantable ventricular assist devices are now approved to be used as a bridge to transplantation in transplant eligible patients with congestive heart failure. TEE is invaluable in the preoperative, intraoperative, and postoperative management of these devices. Assessment of right ventricular function and exclusion of patent foramen ovale, aortic regurgitation, aortic atheroma, and mural thrombus are important in the preoperative assessment. Intraoperatively, the function of the left ventricular and right ventricular assist device and the position of the inlet and outlet cannula position should be assessed echocardiographically (Fig. 43-14). Postoperatively, low and high pump flow states, interrogation of grafts, and patency of the cannulae can be assessed via TEE. Finally, explant of the left ventricular /right ventricular assist device is guided by TEE to prevent microperforation and air entrapment.⁵⁶

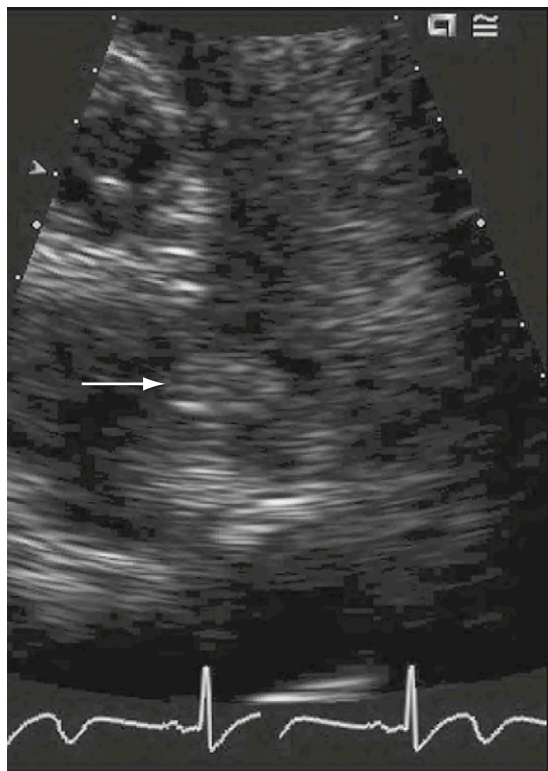


Figure 43-15. Clot seen in the right pulmonary artery (arrow).

Pulmonary Embolism

Pulmonary embolism can be a potentially life-threatening disorder. Administration of thrombolytic therapy is reserved for patients who are hemodynamically unstable; however, according to recent studies,⁵⁷ echocardiographic evidence of right ventricular strain is considered an indication for thrombolytic therapy even in patients who are hemodynamically stable.

Large clots in the pulmonary artery and the proximal branches can be visualized using TTE and TEE (Fig. 43-15), and these modalities can be performed at the bedside in patients who are hemodynamically unstable and cannot be transported to the radiology department for a confirmatory test. TEE has 70% sensitivity and 81% specificity for detection of pulmonary embolism.^{58,59} In addition, TTE enables assessment of right ventricular function, which carries prognostic information in these patients. The presence of McConnell sign—wall motion abnormality of the free wall of the right ventricle with preservation of the apex, largely due to tethering by the left ventricle—is 77% sensitive and highly specific (94%) for the diagnosis of pulmonary embolism.⁵⁸ Echocardiographic features of elevated pulmonary artery pressures, such as inferior vena cava plethora and interventricular septal flattening, can be assessed using transthoracic echocardiogram. In addition, systolic, diastolic, and mean pulmonary artery pressures can be measured noninvasively using this modality. This information can be used for diagnosing PE, guiding therapy, and following up these patients serially.

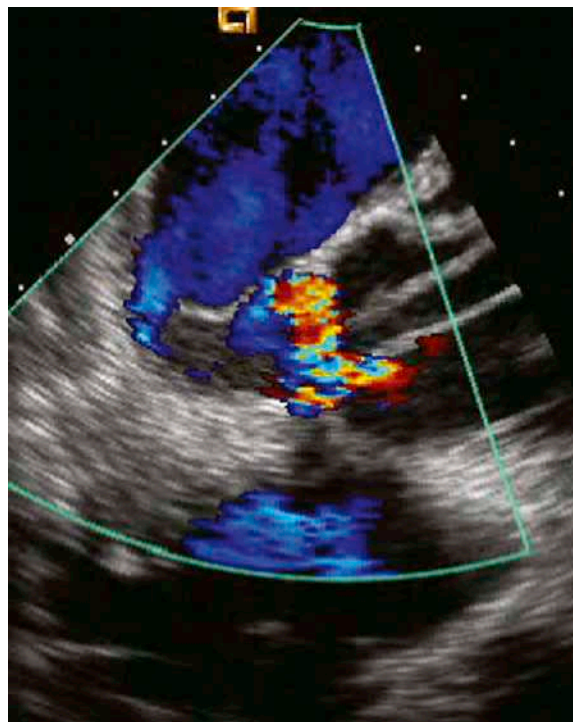


Figure 43-16. Dissection flap extending through the aortic valve resulting in severe aortic regurgitation.

Aortic Diseases

Aortic dissection is a life-threatening disorder that requires prompt treatment to reduce morbidity and mortality. These patients are critically ill, requiring invasive and intensive monitoring. An ideal imaging modality is one that is portable, readily available, and characterizes the dissection. TEE fulfills all of these criteria and also provides vital information, such as the presence of aortic valve involvement with resultant aortic regurgitation (Fig. 43-16), pericardial effusion, and LV function. TEE also helps to identify other disorders in the same spectrum, such as aortic aneurysm and intramural hematoma. Since the aortic lumen is not affected by the presence of intramural hematoma, other diagnostic modalities that image the lumen and not the wall of the aorta (computerized tomography, aortogram) frequently fail to diagnose this life-threatening pathology, which is associated with the same mortality rate as aortic dissection. TEE can also identify the presence of mobile aortic atheromas.

The sensitivity of TTE for imaging of the aorta is low because only the aortic root and a portion of the ascending aorta can be visualized; however, a proximal dissection, especially in cases in which the aortic valve is involved, can be visualized using a TTE. TEE overcomes many of the limitations of TTE and is able to image the aortic root, ascending aorta, arch, and the descending thoracic aorta. The distal portion of the ascending aorta is difficult to image because of interceding bronchus. A recent meta-analysis by Shiga and colleagues⁶⁰ reviewed all published studies of the diagnosis of aortic dissection by TEE, helical CT, and MRI and showed that all three modalities yield equally reliable diagnostic values. The sensitivities of TEE, helical CT, and MRI for diagnosing aortic dissection were 99%, 100%, and 98%, respectively, with specificities of 95%, 98%, and 98%.

In addition to demonstrating the extent of the dissection, TEE can provide additional important information for the surgeon, including the presence of entry and exit sites, extravasation of blood into the thoracic cavity and pericardial space, and assessment of LV function and aortic valve involvement, which were mentioned earlier. Conventional helical CT can identify the dissection flap but cannot elucidate the entry and exit points and can provide very limited information on LV function and the aortic valve.

Pericardial Effusion

Echocardiogram is a rapid means of identifying the size, location, and hemodynamic effects of pericardial effusions. The echocardiographic findings that are consistent with the presence of

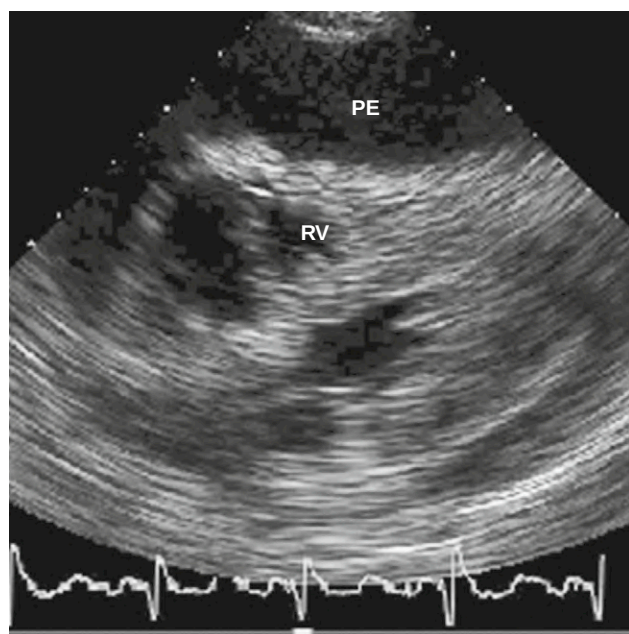


Figure 43-17. Large pericardial effusion (PE) and collapsed right ventricle (RV).

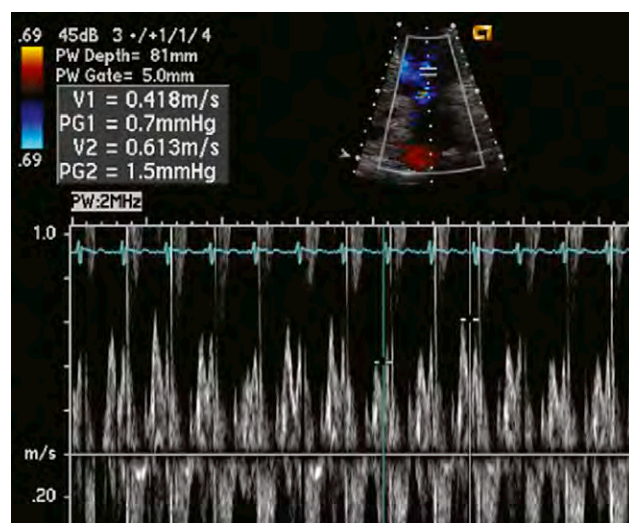


Figure 43-18. Significant respiratory variation in transmittal inflow velocities.

a hemodynamically significant effusion and tamponade physiology include the swinging motion of the heart, right ventricular diastolic collapse (Fig. 43-17), right atrial collapse, respiratory variation in mitral and tricuspid inflow velocities (Fig. 43-18), and plethora of the inferior vena cava (IVC). Early diastolic collapse of the right ventricle is a specific but not sensitive finding. Late systolic collapse of the right atrium is a more sensitive but not specific finding. Measuring the duration of right atrial collapse increases the diagnostic yield of this finding. The presence of inversion of the right atrium during more than one third of the duration of systole has 94% sensitivity and 100% specificity for the diagnosis of tamponade. The respiratory variation can be nonspecific and is seen in atrial fibrillation and lung diseases, such as chronic obstructive pulmonary disease and asthma. Plethora of the IVC, which is defined as dilated IVC that exhibits less than 50% respiratory change in its diameter, has a sensitivity of 97% and specificity of 40% for the presence of tamponade. The lack of a single marker with high sensitivity and specificity mandates a comprehensive echo examination with close attention to all the findings outlined above.

In some centers, TTE is also used to guide pericardiocentesis. After placement of a drain into the pericardial space, serial monitoring of size of the effusion using an echocardiogram is invaluable for optimal management.

Infective Endocarditis

This diagnosis carries a high mortality and morbidity rate. Frequently, patients are critically ill and early diagnosis and treatment may result in a favorable outcome. Echocardiography plays a critical role in the diagnosis and characterization of the endocarditis along with the functional consequences and presence of potential complications. TTE has a sensitivity of 60% to 70% for diagnosing endocarditis on a native valve. The sensitivity is much higher at 95% with the use of TEE.⁶¹⁻⁶³ The identification of vegetations is made by visualizing a mobile, irregularly shaped echodensity usually attached to the free edge of the valve leaflet (Fig. 43-19). TEE is instrumental in identification of potential

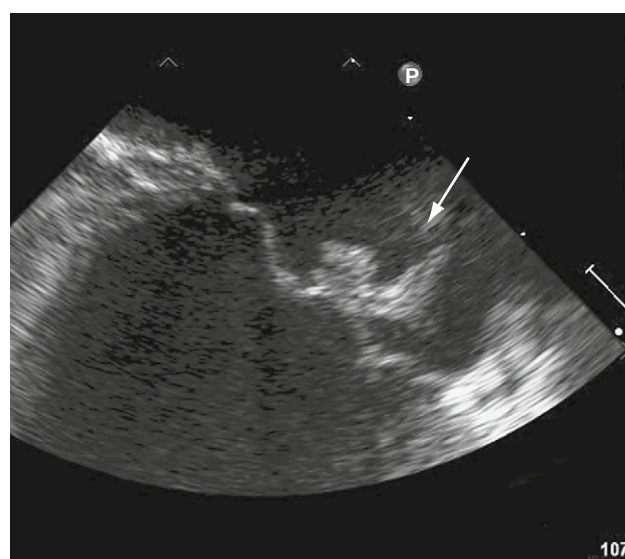


Figure 43-19. Large vegetation (arrow) attached to the atrial surface of the mitral valve, as seen on transesophageal echocardiography.

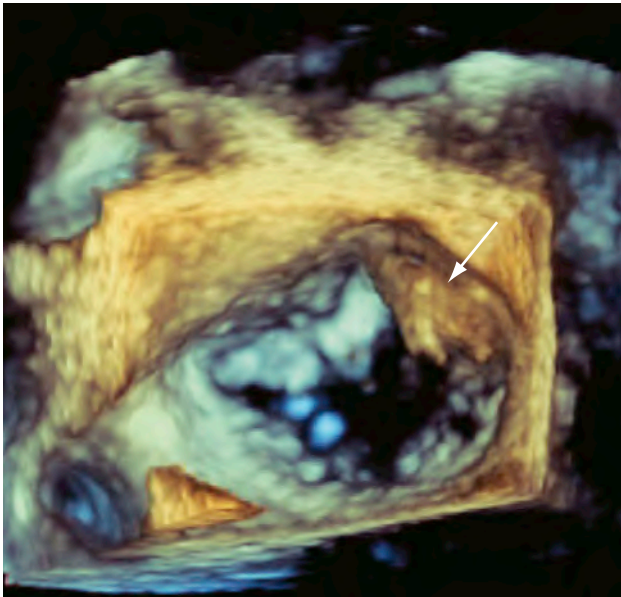


Figure 43-20. Large vegetation (arrow) attached to the mitral valve annulus, as seen from the left atrium using three-dimensional transesophageal echocardiography.

complications, such as valve perforation, periannular abscesses, and fistula formation, which are indications for valve replacement. In addition, it can be used for evaluation of the effect of the endocarditis on valvular function, and both mechanical obstruction to flow across the valve and regurgitation can be thoroughly evaluated using a combination of TTE and TEE. TEE is the mainstay for the assessment of prosthetic heart valves due to multiple artifacts seen on transthoracic images. A recent study demonstrated the potential role of transthoracic 3D echocardiography in evaluation of prosthetic valves in patients with suspected endocarditis.⁶⁴ A transesophageal 3D probe was recently added to the armamentarium of diagnostic tools available and may be instrumental for earlier and more precise diagnosis of endocarditis and its potential complications (Fig. 43-20).

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Vascular Access in the Intensive Care Unit

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CHAPTER 44

Peripheral Intravenous Line

Radial Arterial Line

Brachial Arterial Line

Femoral Arterial Line

Femoral Central Venous Line

Internal Jugular Central Venous Line

External Jugular Central Venous Line

Subclavian Central Venous Line

Pulmonary Artery Catheter Placement

Peripheral Intravenous Line

Almost every patient in the intensive care unit needs intravenous access.¹⁻³ If fluids or drugs need to be delivered, if the patient cannot be managed entirely on a PO regimen, if the need to resuscitate may arise, access to the vascular system is required. Most often patients need more invasive access, but peripheral intravenous access still has its utility.

Equipment

The equipment for peripheral venous line placement includes the following: (1) intravenous catheter (always have extras); if volume access is required, a 14-gauge catheter is ideal but often impractical, and a 16-gauge may be a better choice; (2) alcohol wipes; (3) tourniquets; (4) TB or 3-mL syringe with 1% lidocaine plain; (5) 25-gauge needle, preferably a short one; (6) intravenous bag and tubing to connect to catheter, as well as a short section of tubing with flush in it; and (7) steri-drape and tape to secure the line.

Technique

Site of insertion matters, since some places are easier to place lines into than others. The back of the hand is usually handy to review an important point. Look for a Y-shaped vein and aim for the confluence. When you place the line in the hand, think of where the end of the catheter goes. If the end of the catheter is where the wrist bends, you can get a positional line. Antecubital is a favorable site but the patients have to keep their arm straight, so only use this if nothing else looks good. There are big veins in the forearm, but they are mostly L-type veins. Sometimes the anterior aspect of the wrist is the only vein you can see. In obese patients this is sometimes the only option.

Steps for inserting a peripheral intravenous line are shown in [Figure 44-1](#). Always wear gloves. Place the tourniquet, but do not tie it in a knot. Get the vein to pop up by asking the patient to pump the fist, lightly tapping the vein, or hanging the arm down. Other ways to get the vein to stick up include putting warm blankets on the arm or using the blood pressure cuff: inflate the cuff above systolic pressure; wait a minute, then let the cuff down between systolic and diastolic so the blood can go in but can't get out.

Look for a vein that has an inverted Y and aim for the middle of the Y. Apply a little bit of local anesthetic. (Local anesthesia is not

necessary if the first attempt at placing the line is successful, but it is very helpful in cases of repeated attempts.) Use the non-dominant hand to pull the skin taut as a drum. Use the dominant hand to stick the catheter through the skin and into the vein. When the first flash of blood appears in the hub of the needle, advance another millimeter or two to get the catheter into a vein, not just the tip of the needle. Without letting go of the skin, use the dominant hand to advance the catheter all the way into the vein. Keep the needle in. With the non-dominant hand, compress the vein just above the catheter. With the dominant hand, undo the tourniquet. With the dominant hand, pull out the needle and discard it. Connect the intravenous tubing and secure it to the catheter. Place a steri-drape and ensure the line stays in place. Open the line and make sure it runs. Watch for infiltration. If everything works well, remember to slow down the IV.

Clinical Pearls

Most resistance to flow occurs in the long tubing line. A 16-gauge runs as well as a 14-gauge. If there is any doubt about the vein, it is better to use the 16-gauge. The veins that look like an L rather than a Y are harder to hold down and will more likely "roll" away from you. If peripheral veins look impossible, put in a central line. It is a lot less painful than multiple peripheral attempts, after which one may end up placing a central line anyway. Some patients are difficult to get lines into, such as chemotherapy patients, intravenous drug abusers, morbidly obese patients, and those with a history of difficult lines. Only experienced staff should be inserting those lines, and adequate time should be allowed for line placement. A common mistake is to stop when you get a flash of blood in the hub; you might only have the tip of the needle in the vein. The catheter itself is a few millimeters away and you have to insert the catheter into the vein too. If you let go of the skin once you get the blood flash, the skin retracts back, and the underlying vein also pops back, and then the catheter tip is no longer in the vein. Always secure the IV right away as the patient will move later. Intravenous lines tend to infiltrate, especially when they are covered up by sheets or blankets, so they must be inspected frequently.

Complications

Some of the known complications of intravenous line placement are phlebitis, infection, and extravasation. Contributing factors for phlebitis are size of the catheter itself, site of insertion and

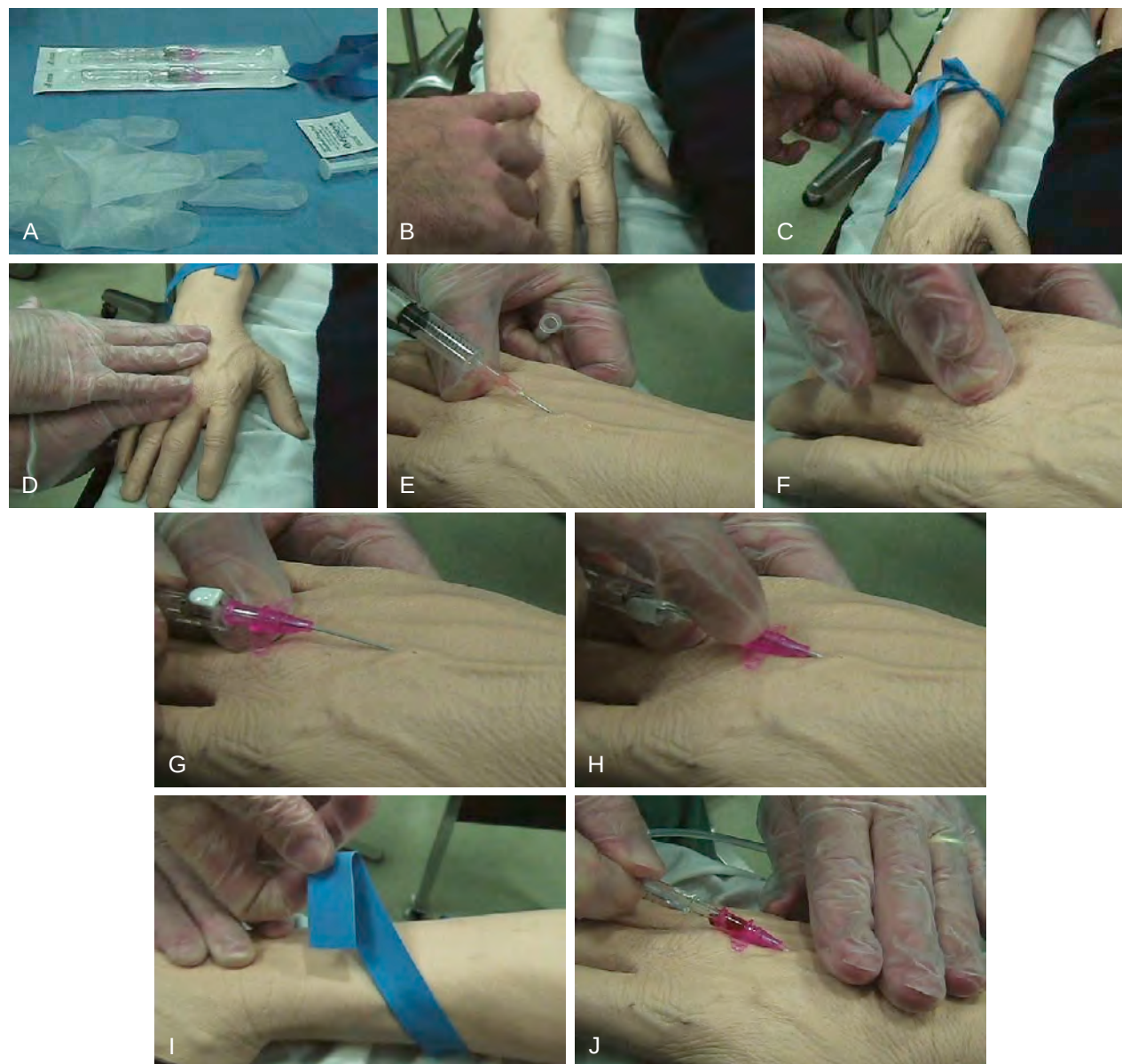


Figure 44-1. Peripheral intravenous line placement. **A**, Lay out all the equipment in an organized way. **B**, Look for a good vein, ideally one shaped like an inverted Y. **C**, Make sure the tourniquet can be undone with one hand. **D**, Try to get the vein to stand out. **E**, Apply alcohol wipe and administer lidocaine. **F**, Pull the skin taut and keep it taut. **G**, Approach at a shallow angle to get the needle and catheter tip in. **H**, Without letting go of the taut skin, advance the catheter. **I**, Undo the tourniquet. **J**, Hold down above the catheter.

skill of the practitioner, and duration. Infection may be aggravated by contaminated infusions, poor technique, and inadequate preparation of the skin. Age, duration, site of insertion, and type of cannula may make patients susceptible to extravasation.

Radial Arterial Line

Indications and Contraindications

The radial artery is the most common location for placing an arterial line.⁴⁻⁸ It is indicated for close blood pressure measurement, where small changes in blood pressure will make a big difference, as well as frequent blood gas sampling. Radial arterial line is contraindicated in patients who underwent radial artery harvesting for a bypass, arterial insufficiency of the hand, and infection at the site. Interestingly, Raynaud's

phenomenon is not a contraindication for placement of a radial arterial line.

Equipment

The equipment for radial arterial line placement includes the following: (1) a board to hold the wrist in extension; (2) tape; (3) 1% lidocaine in a small syringe with a small (25-gauge) needle; (4) cannula (either specially designed Arrow 20-gauge cannula, or a regular cannula) and (5) transducer and pressure tubing.

Technique

Steps for inserting a radial arterial line are shown in [Figure 44-2](#). First, explain the procedure and obtain consent. Set up the equipment so there is pressure tubing ready to connect

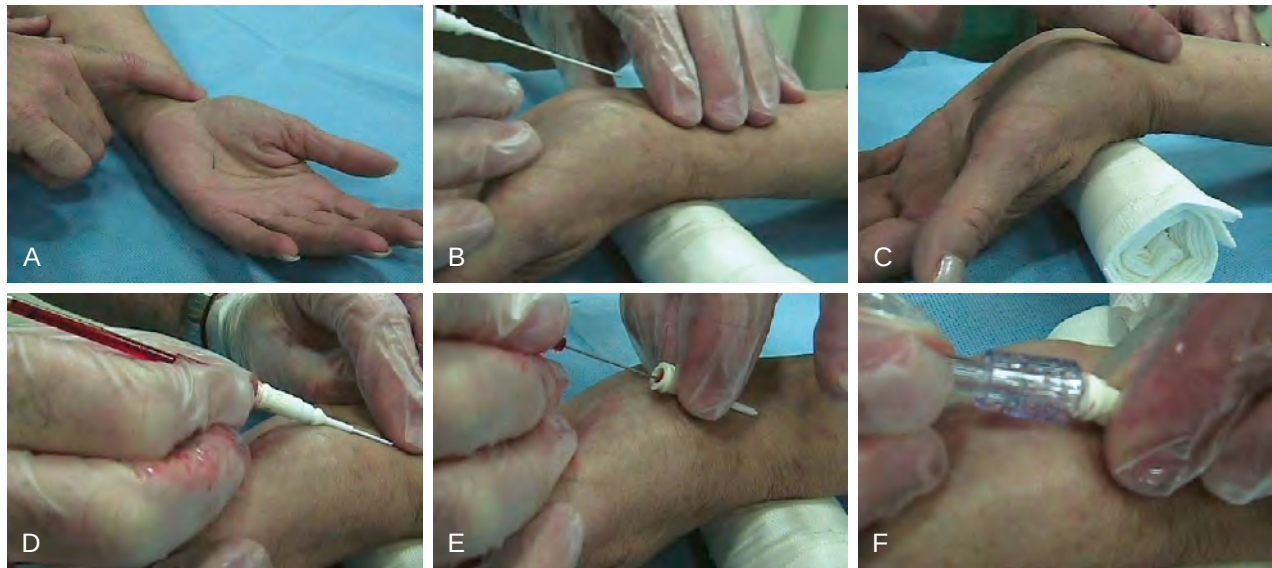


Figure 44-2. Radial arterial line placement. **A**, To approach the radial artery one needs to go over the thenar eminence. **B**, Extending the wrist allows a straight shot to the radial artery. **C**, Approach at a shallow angle to get the needle in, then slide up a little more to get the catheter in as well. **D**, Make sure the blood keeps flowing as you advance. **E**, Slide the catheter in, then hold down above the line so the blood does not squirt out. **F**, It is recommended to use the Luer-Lok to avoid disconnecting the line.

as soon as the line is in, as the blood will be pumping out at arterial pressure. Zero the transducer and make sure the pressure tubing is pressurized. Using the patient's non-dominant hand, extend the wrist and flatten out the hypothenar eminence so there is a straight shot into the radial artery. Going up and over the thenar eminence is much more difficult. Prep and apply a little local anesthetic. In the through-and-through technique, poke all the way into and through the artery, then pull back until the blood flows (signifying the catheter's re-entry into the artery) and then advance the catheter up into the artery. A variant of this technique involves a wire: go through the artery, pull the needle out, then pull back until there is pulsatile flow, slide a wire in, then advance the catheter over the wire. In the go-in-the-first-time technique, do not go all the way through. When blood flow is seen, advance a little (making sure the catheter is in the artery, not just the needle tip), then advance the catheter. There are proponents and detractors of both techniques, so use the one that works best for you. Keep in mind that the blood should keep flowing and the catheter should slide easily with either technique. Hold the artery to keep the blood from spilling when you pull out the needle. Connect the pressure tubing to the catheter via Luer Lok (a non-Luer may fall out). Check the tracing to ensure that there is an arterial waveform. Once the line is in, do not keep the wrist in extreme extension to avoid stretching the median nerve.

If the first attempt is missed, apply pressure and try another spot. Avoid working through a hematoma. Infection is less likely in the high flow of an arterial system than a low-flow venous system, but it can still happen. Ischemia is one of the most feared complications, but it is an unusual event. Allen's test is not a good screening test. Be careful of pushing air into the arterial circulation to avoid embolization. When flushing the line, flush for just a second, wait, then flush again. A prolonged flush can push air all the way into the cerebral circulation.

Clinical Pearls

The radial artery is very skinny and placing a line in it requires extremely fine motor control of the muscles of the hand. Standing and bending over while performing the procedure decreases the success rate; sitting down will increase the success rate. It is best to come at the artery in a shallow angle, along the same axis that the artery is describing. If the trace looks damped, there might be a loose connection or an air bubble in the system. After placing the line, if the hand looks ischemic, call a vascular specialist and make sure one is available in case surgical intervention is needed. You may opt to inject nitroglycerin or papaverin down the line, then pull the line out; as you pull, aspirate in case there is a clot on the end.

Complications

One of the complications that may occur with radial arterial line placement is arterial occlusion. The frequency of this complication correlates with the type and size of cannula, with 20-gauge Teflon having the lowest complication rate. Post-cannulation aneurysms are rare and related to abnormal state of the vessel wall, multiple attempts at cannulation, and hematoma or infection at the cannulation site. Other complications include infection (rare), hematoma, and sclerosis (narrowing of the artery with repeated punctures).

Brachial Arterial Line

Indications and Contraindications

The indications for placing a brachial arterial line^{9,10} are the same as for other arterial lines, i.e., when close blood pressure monitoring and frequent blood gases are needed. In reality, most often a brachial line is chosen after the femoral artery is not an option due to aorto-occlusive disease or history of femoral vascular surgery. Contraindications for placing a brachial arterial line include vascular disease in the arm and infection at the intended site.

Equipment

The equipment for brachial arterial line placement includes the following: (1) a 20-gauge, 12-cm line kit (it is not recommended to place a short line in the brachial artery, because it can come out as the patient moves around); (2) sterile prep, drapes, and gloves; (3) an arm board.

Technique

Steps for inserting a brachial arterial line are shown in [Figure 44-3](#). Explain the procedure and get consent. Position the patient's arm flat on the arm board. Palpate the brachial artery, just medial to the midline in the antecubital fossa. Make a mark on the skin with a marker. Prep, drape, and administer local anesthetic. We recommend the Seldinger technique for line placement. Use the hollow needle to nick the vessel. Disconnect, observe for good blood flow, and then advance wire up the hollow needle. Remove the needle, advance the catheter up the wire, remove the wire, hook up and sew in the line. Ensure all the connections are tight, the trace is good, and that one can draw back easily.

Complications

Complications of brachial arterial line placement include local damage to the artery itself, arterial spasms, as well as accidental intra-arterial injection of drugs. As with any other invasive lines,

chances of infections exist but are rare for arterial lines and will be minimized by using strict aseptic technique. Daily risk of infection for a peripheral arterial catheter is 1.9% per day compared to 3.3% per day for central lines. Arterial sclerosis is also a potential complication, as repeated punctures at the same site may scar the artery and lead to lumen narrowing. This can be overcome by choosing another site of the same artery or choosing a different artery.

Femoral Arterial Line

Indications and Contraindications

Similar to radial arterial line, femoral arterial line¹¹⁻¹³ is indicated for close blood pressure measurement, where small changes in blood pressure can make a big difference, as well as frequent blood gas sampling. Also, in some cases one can anticipate the need for an intra-aortic balloon pump later on, so having a line already in the femoral artery will allow quick access. Femoral arterial line is contraindicated in patients with recent femoral surgery (aorto-iliac procedure, femoral-femoral or femoral-popliteal bypass), infection at the site, those who already have a venous line in the femoral region (can get an arteriovenous malformation), and patients with an occluded aorta (the blood pressure measurement will not be accurate).

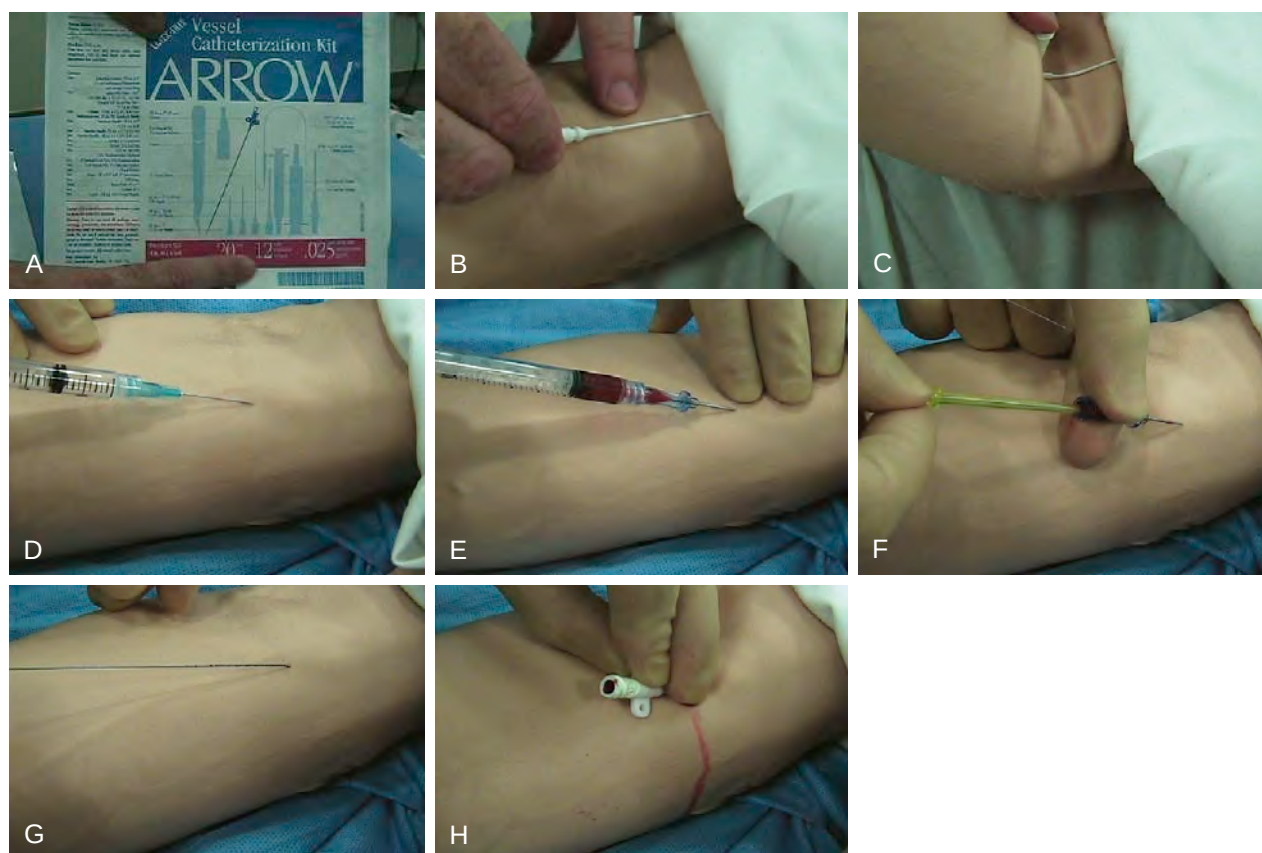


Figure 44-3. Brachial arterial line placement. **A**, Equipment kit for brachial arterial line placement. **B**, Never put a short line in the brachial artery as it will kink when the arm bends. **C**, Feel the brachial pulse just medially to the biceps tendon. **D**, Administer local anesthesia. **E**, Use the standard Seldinger technique to arrive at the artery. **F**, Advance the wire, making sure it progresses easily. **G**, The wire is in place. **H**, Slide the catheter up, check the location again, connect the tubing, and sew in place.

Equipment

The equipment for femoral arterial line placement includes the following: (1) as for any arterial line, have pressurized tubing ready to connect, as well as a monitor to look at the arterial trace; (2) a long catheter with a soft tip (rather than a sharp tip that could erode through the back of the femoral artery and cause a retroperitoneal bleed); (3) a 16-gauge 16-cm single-lumen central line kit (anything smaller or shorter tends to kink); (4) sterile prep and gloves; (5) if the patient is obese, it is very helpful to have someone assist in pulling back the pannus to facilitate access to the artery.

Technique

Steps for inserting a femoral arterial line are shown in [Figure 44-4](#). Explain the procedure and obtain consent. If the operator is right-handed, the right femoral artery is easier to approach. The left femoral artery is easier to approach for a left-handed person. Prep and drape in sterile fashion and have an assistant nearby. Apply local anesthetic liberally as the femoral artery is very deep and it can be uncomfortable. The mnemonic NAVEL is useful to remember for anatomic structures from lateral to medial (Nerve, Artery, Vein, Empty space, Lymphatics). It is recommended to use a

long needle without a finder. Stick below the inguinal crease and go for the pulse. Use ultrasound guidance to find the vessel if it is available. When blood flow is seen, ensure it is arterial and not venous. Pass the wire through the needle without forcing it; it should pass easily. When the wire is in, remove it. Make a small nick in the skin, pass the catheter, again check that there is good flow, sew in place, and put a good dressing on.

Clinical Pearls

Ultrasound guidance offers great help in placing femoral arterial lines. Inexperienced operators as well as anyone with ready access to it should use it. The femoral pulse can seem very wide and seem easy to hit. In reality what one is feeling is a transmitted pulse. If there is pulsatile blood and it is dark, make sure the patient is well oxygenated. The vessel can be quite deep so at first you may have to go straight in; once in, try to flatten the approach a bit so the wire can be passed. Putting a pillow under the patient's knees can alter the plane of the vessels and make it easier. The femoral artery is deep and one can get frustrated during repeated tries. A missed attempt should never lead to mangling. If it looks like a struggle, always stop and ask for help or get an ultrasound.

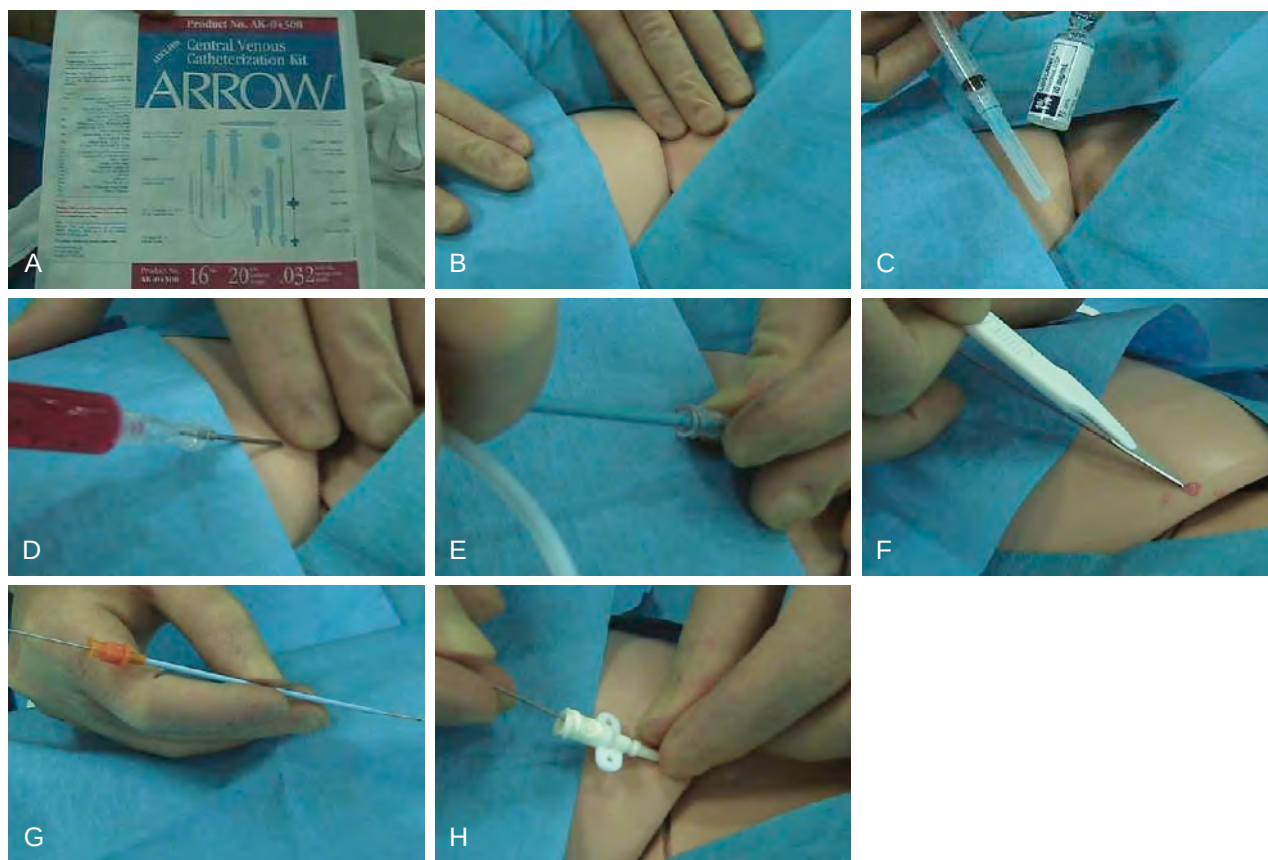


Figure 44-4. Femoral arterial line placement. **A**, Shown is a good kit for femoral arterial line. The needle is soft-tipped so it does not erode and cause retroperitoneal bleeding. **B**, Palpate the femoral pulse and remember the mnemonic NAVEL for anatomic structures going lateral-to-medial (Nerve, Artery, Vein, Empty space, Lymphatics). **C**, Apply local anesthetic generously. **D**, Using the big hollow needle, advance until bright blood is observed. **E**, Once the needle is in, proceed with the Seldinger technique, making sure the wire goes in easily. **F**, A small nick is enough for the 16-gauge catheter to go in easily. **G**, Dilate with caution to avoid a major bleed. **H**, Slide the catheter up, check the location again, connect the tubing, sew in place, and apply dressing.

Complications

Hemorrhage can happen if there is a disconnect (Luer Loks are less likely to disconnect than other types). A hole in the back of the femoral artery can cause a retroperitoneal bleed, so if any unexplained hypotension, tachycardia, or a hematocrit drop is seen, this complication should be suspected. The femoral area may be more prone to infections compared to radial artery area; however, as long as strict aseptic technique is used during insertion and during maintenance, infection should not be a problem.

Nerve damage is another potential complication due to the proximity of the femoral nerve just lateral to the femoral artery. One must always be careful not to damage the nerve, especially in repeated attempts.

One should always watch for signs of vascular insufficiency or emboli. A healthy femoral artery in a young person is extremely unlikely to develop insufficiency from a femoral line, but most femoral arterial lines are not placed in young, healthy people. Sclerosis is rare for large arteries such as the femoral. Other obvious complications include hematoma and local damage to the artery.

Femoral Central Venous Line

Volume access on the venous side usually makes us think of a neck or subclavian line. One should not forget the femoral vein, however, as it is big, relatively easy to hit, does not get infected any more than the central lines in the upper body, and this approach makes one of the ultimate complications, pneumothorax, extremely unlikely.

Indications and Contraindications

Femoral central venous line¹⁴⁻¹⁶ is indicated in patients who need volume access (emergent or otherwise), inotropic access, CVP monitoring, pulmonary artery catheter monitoring, hypertonic fluids, if access from above is interrupted (such as in superior vena cava syndrome), transvenous pacing (in the catheterization laboratory the pacing wire is often passed from below), and temporary hemodialysis. Also, a need for a regular intravenous line can be served by a femoral line. Femoral central venous line is contraindicated in patients who already have a femoral arterial line on the same side (it can later lead to an arteriovenous malformation), infected site, penetrating abdominal trauma, and those in whom access from below is blocked (such as tumor in the inferior vena cava from a renal cell carcinoma). Prior groin surgery is a relative contraindication.

Equipment

The equipment for femoral central venous line placement includes the following: (1) central line kit; (2) an introducer (if big volume or a Swan placement is needed later); (3) sterile prep and drape equipment; and (4) an assistant to pull the abdomen back in case of pannus that needs to be pulled out of the way.

Technique

Steps for inserting a femoral central venous line are shown in Figure 44-5. Explain the procedure and obtain consent. Prep, drape, and set up the kit where it can be reached easily. Never place it on the patient. Pull any pannus back to allow a straight shot into the vessel. The anatomic landmarks can be recalled by using the mnemonic NAVEL (Nerve, Artery, Vein, Empty space, Lymphatics), so one should go in just medial to the artery. Use of

ultrasound is absolutely recommended if there is ready access to it. Apply local anesthetic generously. Use the long hollow needle in the kit without the finder. Once blood flow is observed, make sure it is venous rather than arterial. Advance the wire through the needle, remove the needle, nick the skin, dilate, then advance the catheter. If an introducer is being used, make sure the nick is big enough to slide the catheter in. Make sure you can aspirate easily, then flush and secure the line.

Clinical Pearls

The femoral artery is very deep, so it is important to realize when to use ultrasound guidance or ask for help. A right-handed operator should aim for the right femoral vein due to the easier mechanics.

Internal Jugular Central Venous Line

Indications and Contraindications

Internal jugular central venous line¹⁷⁻²⁷ is the most common central line placed in the ICU. It is indicated in the following situations: (1) same as any venous line, this central line can be “just an IV” when peripheral access is difficult; (2) same as any central line, this can be a mainstay of support; (3) volume access; (4) monitoring central pressures; (5) providing access for cardiosupportive drugs; (6) hypertonic solutions such as TPN; (7) transvenous pacemaking; (8) if a central line is needed but the subclavian line is not the preferred option (the risk of a bleed from a subclavian line and the risk of pneumothorax are higher with subclavian lines); (9) for the easiest approach to floating a pulmonary artery catheter; (10) temporary hemodialysis.

Contraindications for placement of the internal jugular central line are as follows: (1) previous carotid surgery; (2) carotid occlusive disease; (3) superior vena cava syndrome; (4) neck trauma; (5) coagulopathy. As is the case with a lot of other lines, it often happens that the very patient who most needs the line in is the very patient who has a relative contraindication. For example, the person who needs a big volume line in is the very person with a coagulopathy, so one needs to carefully weigh the risks versus. benefits.

Clinically Relevant Anatomy

The internal jugular vein originates at the jugular foramen and ends up behind the sternoclavicular joint where it joins the subclavian vein. It lies right alongside the carotid artery and the vagus nerve within the carotid sheath. The vein is initially posterior to, then lateral and then anterolateral to the carotid artery during its descent in the neck (it literally wraps around the carotid artery). It is the most superficial in the upper part of the neck. At the level of the thyroid cartilage the vein lies deep to the sternocleidomastoid muscle. As it passes toward the thorax, it emerges from behind the muscle and comes to lie at the apex of the triangle between the sternal and clavicular insertions of the muscle.

At the inferior portion of the vein there is a bicuspid valve that directs flow toward the heart. On the left side of the neck the internal jugular vein lies anterior to the thoracic duct. Because of this, the right side is preferred to avoid the risk of thoracic duct injury. On the right side, the vein is typically straight all the way. On the left, in contrast, the vessel takes a right turn once in the thorax; thus, the dilator can tear through the vessel and cause a hemothorax, which is yet another reason to choose the right side.

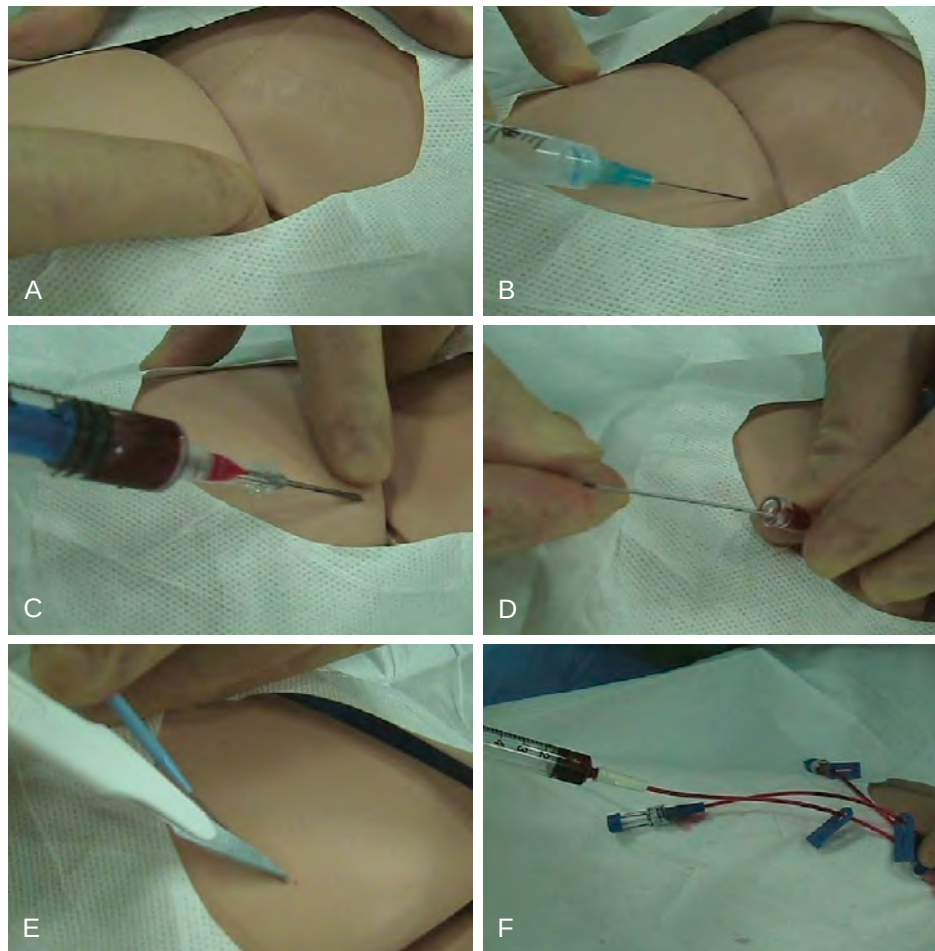


Figure 44-5. Femoral central venous line placement. **A**, The mnemonic NAVEL is very useful for reviewing the anatomic landmarks (Nerve, Artery, Vein, Empty space, Lymphatics). **B**, Apply local anesthesia generously. **C**, Using the hollow needle, advance until dark venous blood is observed. **D**, Hold the needle steady, wire it up, and proceed using the standard Seldinger technique. **E**, Nick the skin, dilate, and pass the line. **F**, Aspirate, flush, sew in place, and apply dressing.

Technique

Steps for internal jugular central venous line placement are shown in [Figure 44-6](#). Obtain consent and explain procedure. Review the history and physical examination to make sure there are no contraindications (such as infection at the site). It is important to make the first attempt the best attempt, e.g., by using ultrasound before the start. Put the patient in Trendelenburg position and administer fluids (if the patient can tolerate them) to make the vein as prominent as possible. Turn the patient's head about 45 degrees. Turning the neck all the way over will compress and flatten the vessel. It is useful to mark the landmarks on the skin before starting the procedure. If the patient can tolerate it, provide sedation. Use strictly aseptic technique. Palpate the carotid and go right next to it. Do not press down on the carotid as it will flatten the internal jugular vein. Also, pressing hard on the carotid artery may cause a vagal reaction. In case of doubt or difficulty, use ultrasound guidance. Administer 1% plain lidocaine. Use a finder, such as a 22-gauge needle on a 3-mL syringe. Go at an angle of 30 degrees to the skin. Insert at the medial border of the sternocleidomastoid between the 2 heads of the muscle toward the ipsilateral nipple. After the internal jugular vein is located, the finder needle is kept in place,

and a larger 18-gauge short bevel needle mounted on a 5-mL syringe is applied just adjacent to the needle finder, with gentle aspiration in the same needle finder track. Go right next to the finder and have the needle entering at the same angle to the skin. With gentle negative pressure advance slowly until dark venous blood appears. Hold the hub firmly as you detach the 18 g from the syringe and observe venous blood flow. Advance the wire into the hollow needle. Slide the 18 g catheter over the wire, remove the wire, and either transduce or hook up a small length of intravenous tubing; observe the blood flow again to ensure that the location is the vein and not the carotid artery. Replace the wire through the catheter, make a nick in the skin, and advance the line over the wire. Watch for dysrhythmias at all times as the wire may “tickle” the heart. If a dysrhythmia occurs, the wire should be pulled back. Make sure the depth is right: 16 cm to the atriocaval junction from the right side, and 19 cm to the atriocaval junction from the left side. Flush all the ports, secure the catheter in place with sutures, apply a sterile dressing, and obtain a chest x-ray to make sure the line is in the right place and there is no pneumothorax. The catheter should lie in the superior vena cava, at the level of T4-T5 below the clavicle.



Figure 44-6. Internal jugular central venous line placement. **A**, Get lined up and then palpate the sternal notch (lower finger) and mastoid process (upper finger) to identify the sternocleidomastoid muscle. **B**, Without any imaging guidance, go in at about the halfway point. **C**, Palpate the carotid artery but do not press down on it to avoid compressing and flattening the internal jugular vein, making it hard to hit. **D**, Use local anesthetic judiciously. **E**, It is crucial to be close to the carotid artery but aiming away from it (at the ipsilateral nipple). If this is performed under ultrasound guidance, carotid artery and internal jugular vein are adjacent to each other. **F**, Proceed until dark venous blood is observed, usually 1-2 cm deep. **G**, Once the finder is in, place the needle right on top of the finder to exactly reproduce the approach angle. **H**, If the blood is bright and squirts out in pulsatile fashion, the attempt has missed and hit the artery. **I**, Assuming that did not happen, advance the wire, keeping an eye out for ectopy. **J**, Once the wire is in, again check that it is in the right place. Slide the 18-gauge catheter down the wire, pull the wire out, and connect the catheter to the extension tubing. **K**, Hold the tubing up, make sure that the blood goes up to CVP height and not to arterial height (it would climb all the way to the top and squirt out). This is a quick and effective way of ensuring the correct location. Proceed with the standard Seldinger technique. **L**, Nick, dilate, flush, sew, and dress. **M**, If a cordis is being placed, the dilator and cordis should be placed as a unit. **N**, Aspirate and flush, without leaving anything open to air, which could lead to an air embolus.

Clinical Pearls

There are several different approaches described (posterior, anterior), but the most important landmark is the carotid artery. The internal jugular vein lies next to it, so feel the carotid artery and go a little off to the side of it. Stay high enough to avoid a pneumothorax. Before starting the procedure always be familiar with central venous catheter types, gauges, length and number of lumens. Make sure you open the right kit. Take the time to set up a good working environment. If you miss, be methodical. Pull straight back, change direction a little, and try again. Don't get fixated on one place. If you just cannot get it, go to the other side.

If the first attempt is unsuccessful, use ultrasound guidance. It is beneficial as it requires fewer needle passes, there are fewer arterial punctures, and fewer failures. On ultrasound, the jugular vein is easily compressed with the Doppler probe; it exhibits the lack of pulsation and enlargement with a Valsalva maneuver.

Complications

It is important to know how to manage pitfalls and complications associated with internal jugular central venous line placement. The most critical complications can arise from inadvertently sticking the carotid artery. Major bleeds can lead to hematoma in the neck and airway compromise. This can also lead to cerebrovascular insufficiency or pseudoaneurysm formation. In case of a carotid artery stick, leave the catheter in place and consult a vascular surgeon. If the patient is at risk of a big bleed, consider intubating to protect the airway prior to removing the sheath. If you remove directly (after having consulted the surgeon and having airway equipment/expertise nearby), apply firm pressure for at least 15 minutes, all the time monitoring for neurologic, airway, or hemodynamic problems.

Other misses can involve the vertebral artery, or even the lung if one goes too deep and inferior, causing a pneumothorax. If the catheter or needle are left in place and open to air, the patient can get a venous air embolism. The pitfalls can involve any of a number of nerves in the neck—vagus, phrenic, hypoglossal, stellate ganglion. Advancing the wire can sometimes cause dysrhythmias. Left bundle branch block can convert to complete heart block as the wire “shorts out” the right bundle branch. In the intubated patient, going too medially can hit the trachea and pop the endotracheal tube cuff. Hitting the thoracic duct can cause a chylothorax. Also, there are the generic complications associated with any line placement, such as infection or misplacement.

External Jugular Central Venous Line

Indications and Contraindications

The external jugular central venous line is included here for complete coverage, but it is rarely performed because it is not an effective procedure. If you choose to place a line in the neck, internal jugular vein is the preferred approach. The indications and contraindications are the same as for other central lines, so we will focus on the technique itself.

Technique

Steps for external jugular central venous line placement (Fig. 44-7) are the same as those shown in Figure 44-6. Place the patient in Trendelenburg position, which reduces the incidence of venous air embolism and makes the external jugular vein more engorged with blood. Turn the patient's head away from



Figure 44-7. External jugular central venous line placement. Steps are equivalent to those described in Figure 44-6.

the site of insertion. Prep the area with chlorhexidine and set up a sterile work environment including gown, gloves, mask, and cap. Administer 1% lidocaine. Too much lidocaine can compress the vessel. With one hand, pull the skin taut and poke through it quickly. The external jugular vein, even when large and prominent, tends to slide away. Stick the catheter through the skin and insert it into the vein. If the flash of blood in the hub can't be seen, connect the catheter to a 3-mL syringe and aspirate as you go (you may be in and not get flow back unless you pull back on the plunger). If the line is intended to be used as a regular IV, keep in mind that it can come out easily when the patient turns the head. If it is intended to be a true central line, it may be difficult to get past the clavicle. It sometimes helps to bend the catheter a little (exaggerated in the figure) to slide into the external jugular vein.

Complications

Complications of this technique are the same as for other central lines. There is decreased success with obesity, short neck, and placements of triple-lumen catheter and pulmonary artery lines.

Subclavian Central Venous Line

Indications and Contraindications

Subclavian central venous line²⁸⁻³⁰ can be useful for the following reasons: (1) the only anatomical landmark is the clavicle—there is no need to palpate the carotid pulse, which can sometimes be difficult (short neck, obese patient, subcutaneous emphysema, neck collar); (2) it does not require turning the neck, which in some patients can be dangerous (C-spine injury) or impossible (severe arthritis); (3) patients tend to tolerate subclavian lines better than internal jugular lines.

Subclavian central venous line is not recommended in the following situations: (1) superior vena cava syndrome/thrombosis; (2) infection at the site of entry; (3) injury to the clavicle that might distort anatomy; (4) coagulopathy; (5) COPD—there is a higher risk of pneumothorax with a subclavian line versus an internal jugular line; and (6) high PEEP.

Technique

Steps for subclavian central venous line placement are shown in Figure 44-8. If the goal is to place a PA catheter or pacing wires, the left subclavian vein is preferable to the right because it is

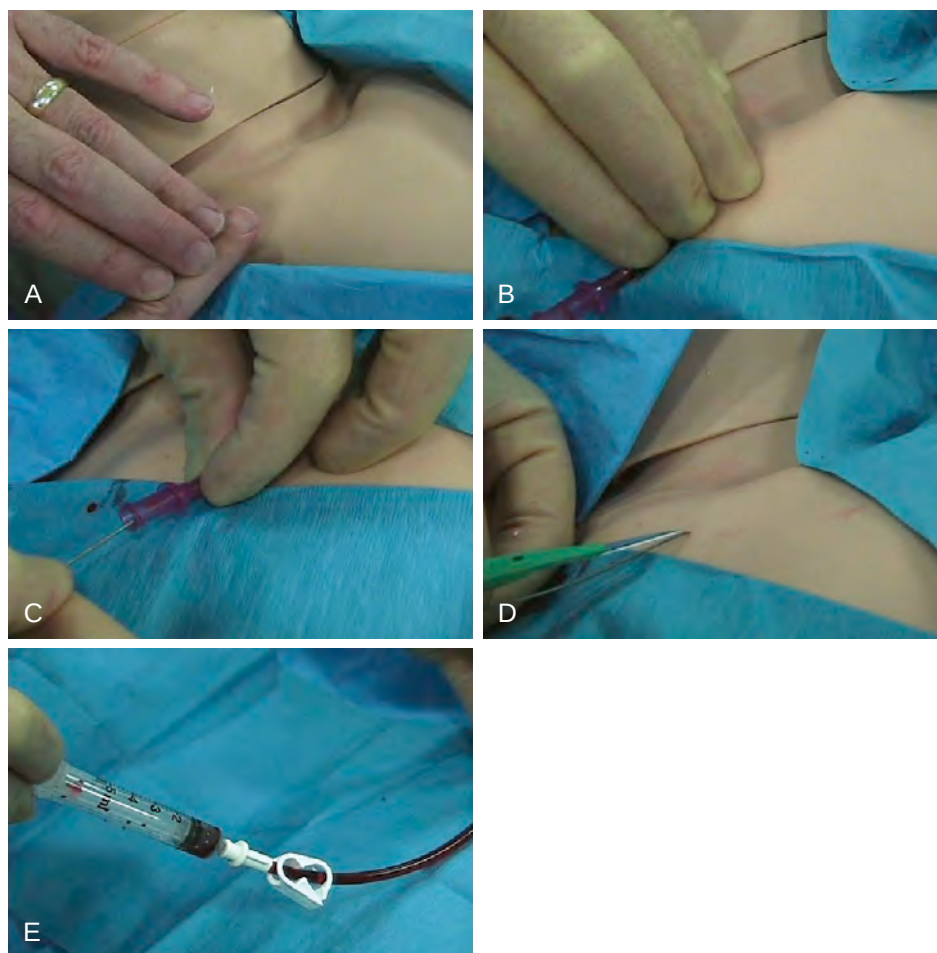


Figure 44-8. Subclavian central venous line placement. **A**, The needle should target the sternal notch, but always angle away from the lungs. If the needle needs to be depressed, press down on top with three fingers so the whole needle goes down flat as a single unit rather than just pointing the tip down. **B**, The needle is in the clavicle and the upper fingers are pressing the needle down as a unit so it goes down but is still inclined away from the lung. **C**, Once the needle is in, the subclavian area has a distinct advantage over the internal jugular vein area, as the needle is held between the clavicle and the first rib and is better secured. **D**, Wire, nick, dilator, and flush. Do not go too medially to avoid getting stuck between the first rib and the clavicle. **E**, Aspirate, flush, sew, and dress.

a more natural angle for placing the PA catheter. If a chest tube is already in, the subclavian line should be placed on the same side. Because the first rib is very close to the clavicle, going too medially might get the wire in, but the line will not be able to pass between the first rib and the clavicle.

Set up the work space including good lighting, a dedicated table for the kit, and a bed that can get into the Trendelenburg position. Set up a sterile work environment, including prep and drape, gown, mask, and hat. Take care of patient explanation and consent. Put a roll down the middle of the patient's back to throw the shoulders back and get a straight shot into the subclavian vein rather than going up and over the shoulder, because lines are not good at turning corners. Ventilated patients should be put on 100% oxygen, lower tidal volumes, and decreased PEEP (if feasible) to make a pneumothorax less likely. Have an assistant pull the shoulder down (5 cm caudal from the neutral position) and put the patient in Trendelenburg position. Make sure the vein is as prominent as possible. Inject 1% lidocaine plain to form a little wheal at the injection site. Using the long hollow needle in the kit, go about 1 cm

below the mid-clavicular point of the lower border of the clavicle. Ultrasound guidance is difficult due to the proximity of the lungs and the bones. Aim for the suprasternal notch and pass below the clavicle. If the clavicle is touched, “walk” off it by pushing down on the needle with your fingers. Stay parallel to the plane of the ground in order to keep the needle directed away from the lungs at all times. Usually the vein is found beneath the inner third of the clavicle, near the clavicular head of the sternocleidomastoid. Sometimes it will be missed going in but found coming back, thus both going in and coming out should be done slowly. Always check to make sure the blood being aspirated is venous. Disconnect the needle from the hub of the syringe and make sure there are no arterial pulsations. Place the wire through the needle, then withdraw the needle while keeping an eye out for ectopy. Nick the skin and advance the dilator over the guidewire using the Seldinger technique. The dilator can get caught between the first rib and clavicle and cause problems. Place the line, flush the lines, sew in place, check the chest x-ray for misplacement or pneumothorax, and place a dressing.

Complications

The biggest concern is hitting the subclavian artery and not being able to stop the bleeding. This may require emergent surgery and is not an easy repair. To avoid pneumothorax, the needle should be kept inclined up and away from the lung at all times. If the lung is dropped and there is not enough time for a chest tube, place a 14-gauge catheter in the second intercostal space on the affected side to achieve emergent decompression of a tension pneumothorax. Infection rates for subclavian central lines are lower compared to those of internal jugular lines and patient comfort is also better with subclavian lines if they are awake and alert.

Pulmonary Artery Catheter Placement

Indications and Contraindications

There is an ongoing debate about the utility of the flow-directed pulmonary artery catheter. The following section reviews how to float such a catheter once venous access is obtained.

Pulmonary artery catheter³¹⁻³⁴ can be useful for the following reasons: (1) obtaining a host of filling pressures (central venous pressure from the proximal port; pulmonary artery systolic and diastolic pressures from the distal port; pulmonary capillary wedge pressure from the distal port); (2) obtaining a host of additional hemodynamic values (cardiac output; continuous cardiac output if the catheter is so equipped; mixed venous oxygenation, either by drawing a sample from the distal port, or by direct measurement in a catheter so equipped; continuous mixed venous oxygenation in a catheter with this function built in; from these measurements, deriving systemic vascular resistance); (3) drawing blood samples from different areas (an unexplained “step up” in oxygenation could indicate the presence of an intracardiac shunt); (4) monitoring the effect of inotropic support by following the trends of pressures, cardiac output, systemic vascular resistance; (5) monitoring volume status in patients in whom central venous pressure alone is not sufficient; (6) management of the critically ill patient, especially one whose urine output defies traditional remedies or one whose hemodynamics defy routine maneuvers; and (7) temporary pacing (some pulmonary artery catheters have built-in pacing capability, while the Paceport Swan catheter allows passing a wire into the right ventricle for temporary pacing).

Pulmonary artery catheter is not recommended in the following situations: (1) post-pneumonectomy patients (due to the risk of occlusion of the one remaining pulmonary artery); (2) clots or infected masses in the right heart (as they may get dislodged); (3) pulmonary hypertension (this situation presents the classic dilemma: one could argue we need this information in this critically ill patient, but the very presence of pulmonary hypertension means this patient is at higher risk for a pulmonary artery rupture); (4) left bundle branch block (due to the risk of blocking the right bundle and converting this to a complete block); (5) superior vena cava syndrome.

Equipment

The equipment for pulmonary artery catheter placement consists of the following: (1) introducer in place (most often the introducer will be in the right internal jugular vein; the pulmonary artery catheter can be floated from any other location since it is flow-directed); (2) pulmonary artery catheter sleeve to keep the catheter from getting contaminated; (3) pulmonary artery

catheter, which comes in different types (continuous mixed venous oxygen saturation, continuous cardiac output, pacing catheters, paceport catheters); (4) transducers connected to the catheter (two transducers are needed to see the distal and proximal ports); (5) sterile set-up; (6) EKG monitor and someone watching, as dysrhythmias are common as the catheter traverses the heart; (7) fluoroscopy may be needed on rare occasions to help pass the catheter; and (8) pacing capability (e.g., external Zoll pads) if the patient has a left bundle branch block.

Technique

Steps for pulmonary artery catheter placement are shown in [Figure 44-9](#). First, clear the area to avoid contaminating the catheter. Pre-flush the catheter so there is no air in the lines. Take care of patient explanation and consent. Prepare a sterile field, gown, hat, and mask. Ensure that transducers are zeroed and leveled. Pull the catheter through the sheath, making sure the sheath is oriented in the correct direction with the locking mechanism toward the patient. Once the catheter is through the diaphragm of the sheath, check the balloon and make sure that it didn't rupture. Put the catheter into the introducer and advance it to 20 cm to put the balloon-tipped end out of the introducer and near or in the right atrium. Watch the monitor for a CVP trace. Inflate the balloon with the special syringe from the catheter kit (do not use more than 1.5 mL) and maintain constant communication with the person inflating and deflating the balloon. When the trace goes from central venous to right ventricular, there will be a change in the waveform. Continue advancing the catheter. If another change in the trace is seen, the catheter should be in the pulmonary artery. Advance until a wedge trace is seen. If the catheter is advanced to 50 cm and there is no wedge trace but there is a good pulmonary artery trace, stop there. Overzealous pursuit of a wedge trace may lead to pulmonary artery rupture. Let the balloon down. If there is a wedge trace, once the balloon is let down the trace should revert to a pulmonary artery trace. If it does not, the catheter is too far out and should be pulled back a few centimeters. If the catheter is pulled too far back, the trace will revert to a right ventricle trace. In this case, the catheter will need to be re-advanced until it is in the pulmonary artery again. Slide the sheath over the catheter and click it in place.

Complications

Pulmonary artery rupture is the ultimate complication and manifests as massive bleeding of bright red arterial blood into the trachea. If that happens, get a thoracic surgeon right away, isolate the lung if possible, and keep the balloon up to try to tamponade the bleeding. If the catheter is tied in a knot, send the patient to special procedures so they can remove it out under fluoroscopic guidance. In cases of ectopy with dangerous runs of ventricular tachycardia, it is recommended to forego the pulmonary artery catheter.

Clinical Pearls

If the catheter does not go into the pulmonary artery, reposition the patient head up and tilted to the right. That favors a balloon floating up and out the pulmonary artery outflow tract. If the patient is on a ventilator, consider turning off the ventilator for a short while to increase venous return and favor forward flow. Inspect the catheter by pulling it out and making sure the balloon still inflates and the catheter is curling the right way (sometimes it points around the wrong way and goes down the arm).



Figure 44-9. Pulmonary artery catheter placement. **A**, Exercise caution when taking the catheter out of the kit to avoid contaminating it. **B**, Put the sheath on. **C**, Make sure the balloon inflates correctly. It can rip as it goes through the sheath. **D**, Advance to 20 cm, then inflate the balloon and advance. Maintain communication with the person inflating the balloon at all times. **E**, Once it is in the right place, snap on the sheath.

Open the IVs to fill up the heart a little more. Try to advance the catheter very slowly, as this allows the catheter to “catch a wave”. If all else fails get a new catheter; a new, stiffer catheter may float out more easily. Alternatively, try advancing the catheter using fluoroscopic or TEE guidance.

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Invasive Hemodynamic Monitoring in the Cardiac Intensive Care Unit

Robin Mathews, David L. Brown

CHAPTER 45

Systemic Arterial Blood Pressure Cardiac Output and Mixed Venous O₂ Consumption

Indications for Pulmonary Artery Catheterization

HEMODYNAMICS is derived hydrodynamics, the physics of the motion and action of water. The dimensions of hydrodynamics include: flow, pressure, static resistance, dynamic impedance, reflectance and compliance, branching effects, viscosity, fluid friction, turbulence, and other physical characteristics.¹ The goals of hemodynamic assessment and manipulation in the critically ill patient are to ensure adequate organ blood flow and oxygen supply.² Noninvasive parameters to measure organ perfusion include systolic and diastolic blood pressure, body temperature, heart rate, and respiratory frequency.³ Though established clinical signs of organ perfusion should be used for monitoring, these sometimes have limited value as accurate indicators of cardiovascular function.⁴ Important pathophysiology may remain obscured if judged solely on clinical signs.² The evolution of modern technology has allowed for quantitative biologic measurements. The principles of hemodynamic monitoring have allowed basic physiologic measurement to be applied in a meaningful manner in the management of cardiovascular aspects of critical illness.⁵ The development of bedside intravascular catheterization procedures has permitted extension of the application of the physiologic principles established early in the century to the population of critically ill patients.⁵

Systemic Arterial Blood Pressure

The continuous measurement of arterial pressure is essential in hemodynamic monitoring. Arterial pressure is the input pressure for organ perfusion.⁶ It is usually monitored noninvasively with a sphygmomanometer. In the Cardiac Intensive Care Unit (CICU), however, a more invasive technique with insertion of an indwelling arterial catheter into either the arm (brachial or radial sites) or groin (femoral arterial site) is often used to provide more precise monitoring. The advantages of arterial catheterization over noninvasive means are continuous monitoring of arterial pressure and its waveform, and serving as a site for repetitive blood sampling.⁶

The arterial pressure is a function of both vasomotor tone and cardiac output. Local metabolic demands determine local vasomotor tone that in turn determines blood flow distribution.⁶ The perfusion pressure and local vascular resistance determine organ perfusion of all capillary beds. Flow is proportional to local metabolic demand if there is no hemodynamic instability to cause increased sympathetic tone.⁶ Cardiac output primarily determines arterial pressure in the setting of varying degrees of

local blood flow and because it is proportional to local metabolic demand, there is no normal value in an unstable, metabolically active patient.⁶ The literature currently suggests maintaining previously nonhypertensive patients at a mean arterial blood pressure (MAP) of 65 mm Hg.^{6,7} Based upon a clinical trial that examined the effects of resuscitative efforts with fluid and vasopressors in circulatory shock patients to varying MAP targets ranging from 60 to 90 mm Hg. No increased organ blood flow could be determined above a MAP of 65 mm Hg.⁸ Thus, there is no proven benefit in forcing either cardiac output or arterial tone to higher levels above this threshold.

Table 45-1 displays indications for arterial catheterization. The transducers used for blood pressure measurement are connected to the circulation via fluid-filled tubing. The accuracy of the system is optimized when the catheters and tubing are stiff, the total length of tubing is not excessive, the number of stopcocks is limited, and residual air bubbles are eliminated.² The “zeroing” of the transducer at the appropriate level in relation to the patient (i.e., midthorax) must be correct to prevent errors caused by hydrostatic pressure of the fluid column.^{2,9} In most cases, the choice of location for insertion of the catheter is the radial artery because the femoral artery approach is more often associated with displacement during patient movement and hemorrhage that is more difficult to control.¹ Although arterial catheterization is an invasive procedure with inherent risks, most complications are not severe (temporary vascular occlusion 20% and hematoma 14%) with permanent ischemic damage, sepsis, and pseudoaneurysm formation occurring in less than 1% of cases.¹⁰

Right Heart and Pulmonary Artery Catheterization: A Historical Perspective

The data that is the basis of our current understanding of cardiac function was obtained nearly 100 years ago. Claude Bernard performed the initial cardiac catheterization in 1844 entering both the right and left ventricles of a horse.⁹ The physiologic and anatomic data obtained over the ensuing years lead to the development of important concepts, such as pressure manometry and cardiac output measurement. In 1929, Werner Forssmann successfully performed a right heart catheterization on himself. In 1947 Lewis Dexter passed a catheter to the distal pulmonary artery and measured pulmonary capillary wedge pressure and oxygen saturation for the first time. Subsequent work from his laboratory noted pulmonary capillary wedge pressure to be a

reliable estimate of left atrial pressure.¹¹ In 1956 Dickinson Richards and Andre Cournard along with Forssmann were awarded the Nobel Prize in Medicine for their work describing cardiovascular physiology using the pulmonary artery catheter (PAC).⁹

Right heart catheterization permitted measurements of cardiac output and right heart and pulmonary pressures that make it possible to calculate other derived hemodynamic parameters, such as cardiac work indices and systemic and pulmonary vascular resistance.² Initially, the procedure was exclusively performed in the cardiac catheterization laboratory primarily to diagnose congenital and valvular heart lesions.¹² However, the increasing numbers of admissions to CICUs for hemodynamic instability as a result of ischemic heart disease prompted an expanded role for invasive hemodynamic monitoring. The 1960s ushered in the establishment of Coronary Care Units (CCU) to manage cardiac arrhythmias in the setting of acute myocardial infarction.^{1,13} It was noted that profound hemodynamic changes might be the primary factor in arrhythmic deaths.¹ However, practical limitations in transporting critically ill patients to a cardiac catheterization suite and the increased risk of induction of cardiac arrhythmias limited the application of invasive hemodynamic monitoring.¹

In 1970, motivated by a lack of understanding of the disease process in those patients admitted with ischemia, Swan developed a balloon-tipped, flow-guided catheter that for the first time established a reliable way to perform bedside catheterization in

specialized cardiac care units.¹⁴ The initial catheter was a double lumen extruded polyvinylchloride catheter with an outside diameter of 1.6 mm and a length of 110 cm.⁵ There was a minor lumen of 0.4 mm in diameter and a major lumen of 1 mm in diameter. The minor lumen was used to inflate the balloon to a volume of about 0.8 mL. Their initial study involved 100 patients in whom successful bedside hemodynamic monitoring was performed.¹⁴ They concluded it was possible to safely catheterize the pulmonary artery (PA) at the bedside without fluoroscopy in a high proportion of patients. The information gained proved to be important in understanding the altered pathophysiology of a given illness and thereby altered management in these patients.⁵

It is following this landmark report that widespread use of PACs began. The relative ease in hemodynamic monitoring transformed the care of cardiac pump failure in the CCU. It allowed recognition of hemodynamic subsets in myocardial infarction, such as right ventricular infarction, and provided additional prognostic insight and allowed for the selection and monitoring of pharmacologic therapy.¹⁵

As stated earlier, the PAC allows for determination of various fundamental hemodynamic parameters, including measurement of cardiac output by the thermodilution (TD) right atrial (RA), right ventricular (RV), PA, and pulmonary capillary pressures; and sampling of blood from the PA, the RV, and RA. Pulmonary vascular and systemic resistance and right and left ventricular stroke work could then be derived. Further developments include continuous measurement of PA blood oxygen saturation¹⁶ and near continuous or instantaneous cardiac output.¹⁷

The Catheter

The catheter most commonly used is a 7.5 French thermodilution catheter. It is a 3-lumen radiopaque catheter, 110 cm long and made of polyvinylchloride. The outside is marked with black rings every 10 cm from the tip that allow determination without fluoroscopy of the appropriate catheter length at which to inflate the distal balloon. The distal lumen terminates at the tip of the catheter, whereas the RA lumen terminates 30 cm proximal to the tip. There is a venous infusion lumen 1 cm proximal to the RA lumen. A thermistor bead located 3 to 5 cm from the tip is connected to an external thermistor connector by a wire. The external thermistor is in turn linked to a computer that allows for determination of cardiac output by the thermodilution method.^{14,15,18} A latex balloon with a maximum inflating capacity of 1.0 to 1.5 mL is positioned at the tip. Upon inflation, the balloon engulfs the catheter tip reducing the transmitted force and hence limiting irritation and injury of endocardium and reducing the frequency of arrhythmia.¹⁴ The inflated balloon facilitates flow-directed advancement of the catheter through the right heart into the pulmonary artery. Once inflated in a distal branch of the pulmonary artery, the balloon occludes the vessel and allows for measurement of pulmonary capillary pressure. Most catheters are heparin-coated to reduce thrombogenicity. In addition, electrodes implanted in some catheters allow for pacing and electrocardiographic recording. The inclusion of fiberoptics allows measurement of oxygen saturation in the PA. The catheter can serve multiple functions including: measurement of CO by TD, PA temperature, intracardiac pressures (RA, RV, PA, PCW), and PA occluded pressure. Blood sampling can be done through the active lumens of the catheter.

Table 45–1. Arterial Catheterization*

Indications for arterial catheterization

As a guide to synchronization of intra-aortic balloon counter pulsation

Probable indications for arterial catheterization

Guide to management of potent vasodilator drug infusions to prevent systemic hypotension

Guide to management of potent vasopressor drug infusions to maintain a target MAP

As a port for the rapid and repetitive sampling of arterial blood in patients in whom multiple arterial blood samples are indicated

As a monitor of cardiovascular deterioration in patients at risk for cardiovascular instability

Useful applications of arterial pressure monitoring in the diagnosis of cardiovascular insufficiency

Differentiating cardiac tamponade (pulsus paradoxus) from respiration-induced swings in systolic arterial pressure; tamponade reduces the pulse pressure but keeps diastolic pressure constant. Respiration reduces systolic and diastolic pressure equally, such that pulse pressure is constant.

Differentiating hypovolemia from cardiac dysfunction as the cause of hemodynamic instability. Systolic arterial pressure decreases more following a positive pressure breath as compared with an apneic baseline during hypovolemia. Systolic arterial pressure increases more during positive pressure inspiration when LV contractility is reduced.

*Adapted from Polanco PM, Pinsky MR: Practical issues of hemodynamic monitoring at the bedside. Surg Clin North Am 2006;86(6):1431-1456.

Equipment and Signal Calibration

Properly functioning electronic monitoring equipment is essential. The fluid-filled PAC is connected via a semirigid pressure tubing to pressure transducers. These transducers consist of a fluid-filled dome, a diaphragm, and a strain gauge Wheatstone bridge arrangement.¹⁸ An electric current directly proportional to the fluid motion is amplified and transmitted to the oscilloscope equipment for display. Other factors that influence accurate reproduction of a biologic signal include frequency response, natural frequency, damping, and catheter whip artifact.

The system must have a frequency response of flat to 15 to 20 Hz to be adequate for human studies. Pressure waveforms are not reliable in patients with excessively rapid heart rates of greater than 180 beats/min. The length of the pressure tubing determines the natural frequency of fluid-filled systems. Excessively long tubing will drop the natural frequency to below physiologic range, causing an overamplification of signal resulting in falsely elevating pressure readings. The recommended length of pressure tubing is 3 to 4 feet.¹⁸ Damping is the opposite effect with a loss of physiologic signal, which most often

results from air trapped in the circuit. Because air, unlike fluid, is compressible, less motion is transmitted to the diaphragm per unit of pressure. Damping of the PA pressure signal may make it difficult to discern from the wedge pressure. Catheter whip artifact results from motion imparted to the catheter with each cardiac contraction. High-frequency filters can eliminate this artifact.¹⁸

Accurately measuring pressure signals requires proper calibration of the monitoring system. With a patient supine, the pressure transducer is aligned with the fourth intercostal space midway between the front and the back of the chest.¹⁸ This site serves as the standard zero reference point. The calibration of the monitor involves the introduction of a known pressure signal. This can be done either internally or externally. Zero reference and calibration should be checked each day of hemodynamic monitoring.¹⁸ Table 45-2 lists the required equipment for PAC insertion. Prepackaged kits with the above materials are available.

Catheter Insertion

Catheter equipment should be inspected and calibrated. All lumens should be flushed with normal saline and be free of air. Insertion site selection can vary between internal jugular, subclavian, and femoral veins (Table 45-3). Although the site of insertion is at the discretion of the operator, the right internal jugular vein is preferable because of the straight course to the superior vena cava. Meticulous preparation of the chosen site with aseptic technique is crucial. The operator and any assistants should be in sterile gown, gloves, facemasks and caps. Any other personnel in the room should also have masks and caps.

The patient should be properly prepped, draped, and in the Trendelenburg position. The site is then accessed percutaneously through a modified Seldinger technique. After local anesthesia, an 18-gauge, 7.6-cm Cook needle with attached syringe is inserted bevel up at approximately 45 degrees between the heads of the sternocleidomastoid muscles toward the ipsilateral nipple, while palpating the ipsilateral carotid artery. After free flowing venous blood is obtained, the syringe is disconnected from the needle and a 40 cm long J-tipped guide wire is inserted into the needle and passed gently into the vein. The guide wire should pass without any resistance. The guide wire should never be advanced if any resistance is encountered. The needle is then removed and the skin puncture is enlarged with a scalpel blade. The dilator sheath system is then advanced over the guide wire into the vein with a gentle rotating movement. Once the sheath is properly positioned, the wire and dilator should be removed and the sheath sutured in place.

Table 45-2. Equipment Required for Swan-Ganz Catheter Insertion

Appropriate Swan-Ganz catheter
Dilator-sheath-side arm assembly
Three-way stopcocks
Pressure tubing
Transducers
18-gauge, thin-walled Cook needle
Sterile gowns, drapes, gloves
1% lidocaine
Heparinized saline
J-tipped guidewire
Towel clips, syringes, suture material
Electrocardiography and pressure-monitoring equipment
Intravenous line
Atropine
Defibrillator unit

Table 45-3. Comparison of Venous Access Routes

Vein	Advantages	Disadvantages
Internal jugular	Rapidly accessible Does not interfere with CPR Provides a straight route to the heart Less restrictive to patient movement	Air embolism, carotid artery puncture, and tracheal injury may occur Pneumothorax (more common in the left than the right internal jugular vein) Thoracic duct injury (left internal jugular vein only)
Subclavian	Rapidly accessible Allows free neck and arm movement Easier to keep sterile	Air embolism, more frequent pneumothorax and hemothorax; subclavian artery puncture; injury to nerve bundle may occur
Femoral	Rapidly accessible Does not interfere with CPR	Sepsis, in situ thrombosis, and pulmonary embolism may occur usually requires fluoroscopy

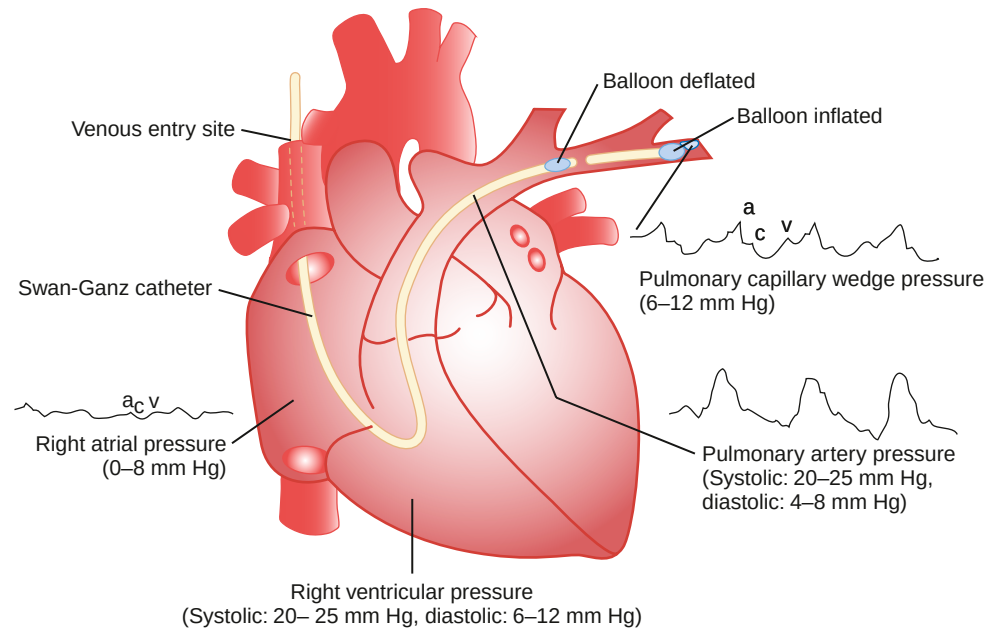


Figure 45-1. Normal hemodynamic pressures. (Adapted from Swan HC: *The pulmonary artery catheter*. *Dis Mon* 1991;37:518.)

The PAC should be inspected for bends and kinks and the balloon tested with air inflation underwater to evaluate for leaks. The catheter should then be connected with pressure tubing to calibrated pressure transducers. Finally, a plastic sleeve is placed over the catheter to preserve the sterile length of the catheter outside of the body for possible future manipulation.

The catheter is then inserted and advanced approximately 10 cm before the balloon is inflated with 1 to 1.5 mL of air. In most patients the catheter will reach the RA within 10 to 15 cm from the internal jugular or subclavian vein. Once in the RA, the catheter should be quickly advanced under continuous pressure and electrographic monitoring across the tricuspid valve, through the RV, PA, and into the pulmonary wedge position. The catheter should reach the PA approximately 50 to 55 cm from the internal jugular vein. One should suspect catheter coiling if significantly greater lengths are required. Figure 45-1 illustrates typical pressure waveforms.

The deflated catheter should recoil slightly into the proximal PA. With inflation, the catheter should then float to a wedge position. The goal is passive occlusion of a distal vessel impeding blood flow to that area. The balloon should be slowly inflated while pulmonary artery pressure is continuously monitored. Wedge tracings obtained at substantially less than the full inflation volume indicates distal migration of the catheter. With the balloon deflated, it should be repositioned with slow withdrawal of 1 to 2 cm at a time. Poor wedging can be due to patient movement, mechanical ventilation, positive end-expiratory pressure (PEEP), and eccentric balloon inflation.¹⁸ Catheter position should be checked routinely by overpenetrated chest x-rays.¹⁸ To minimize the risk of endothelial damage to the PA, PA rupture, or pulmonary infarction, wedge time should be kept to a maximum of about 8 to 15 seconds.¹⁸ End-expiration diastolic pulmonary pressures should approximate mean wedge pressure in the absence of increased pulmonary arteriolar resistance, such as with pulmonary hypertension or pulmonary embolus.¹⁸

The pressure recorded through a wedged end-hole catheter is that of the next vascular system, which in most circumstances reflects the left atrium (LA) or left ventricular (LV) end-diastolic

pressure. This assumes that the vascular system distal to the catheter tip provides a direct connection to the LA without any anatomic or functional interruption. The ideal placement of the catheter is the lower lung zone. In zone 3, the most dependent portion, both pulmonary artery and venous pressures exceed alveolar pressure thereby maintaining an open vascular system from the catheter tip to the LA.¹⁸ In the upper lung, or zone 1, alveolar pressure exceeds pulmonary artery and venous pressures, keeping the capillaries closed and therefore disrupting the system preventing accurate measurement of LA pressures. The arterial pressures in the central lung, or zone 2, should exceed alveolar pressure, but low pulmonary venous pressure may prevent retrograde transmission of pressures to assessment of the LA. Fortunately, most of the lung in the supine position is in zone 3 and flow-guided catheters will usually enter this zone. A lateral chest x-ray can confirm position of the catheter tip below the LA.

Pulmonary Artery Occluded and Wedge Pressure

Pulmonary capillary pressure is a phase-delayed, amplitude-damped version of LA pressure. During diastole with a nonstenotic mitral valve, the pulmonary venous system, LA, and LV is a continuous circuit and the pulmonary capillary pressure is then reflective of the LV diastolic pressure.¹⁵ The level of pulmonary capillary wedge pressure is important for two reasons. First it provides the measure of hydrostatic pressure that is responsible for forcing fluid out of the pulmonary vascular space. Additionally, the capillary pressure is directly related to diastolic fiber stretch according to Starling's principle, which states that the strength of contraction is proportional to myocardial fiber length/left ventricular volume.¹⁵ When applied to construct a cardiac function curve, it is often termed left ventricular filling pressure.

The pulmonary artery occluded pressure (PAOP) is obtained after inflating the distal balloon of the PAC in a large branch of the PA (about 10 mm in size). A static column of fluid is created between the site of occlusion and where the venous flow resumes as other venous branches connect down stream.⁷

As downstream pulmonary flow decreases, the PA pressure decreases to a minimal value reflecting that pressure.⁶ The compliance of the vasculature relative to the catheter causes a slight dampening of the pressure signal. Therefore PAOP pressures are lower than PA diastolic pressure with dampened waveforms.⁶ The wedge pressure is obtained when a catheter tip engages a small PA vessel (less than 2 mm) as opposed to an occlusion pressure obtained from balloon inflation in a medium to large vessel. The anatomic territory affected by the wedge is smaller than that affected by the occlusion pressure therefore subjecting each to varying forces that generate a pressure. The term occluded pressure is preferred to wedge.¹

The natural oscillation in intrathoracic pressure associated with respiration directly affects intraluminal pulmonary vascular pressure. During spontaneous breathing, end-expiration occurs at the highest vascular pressure values. This is the opposite of mechanical positive pressure ventilation where end-expiration occurs at the lowest pulmonary vascular pressures.⁶ To minimize this artifact, recorded pressures should be made at end-expiration. Even in the setting of end-expiration, with a direct intact fluid column from the catheter tip to the venous system, PAOP measures can still be overestimated if pleural pressures are elevated at end-expiration. Factors such as hyperinflation, air trapping, and PEEP in relation to lung and chest wall compliance increases pleural pressure to varying degrees.⁶ Normal pulmonary vascular resistance (PVR) ranges from 150 to 250 sec/cm⁵. If pulmonary hypertension is associated with increased PVR, then causes are primarily within the lung, such as pulmonary embolism, pulmonary fibrosis, essential pulmonary hypertension, and pulmonary veno-occlusive disease. Normal PVR in the setting of pulmonary hypertension is more indicative of LV failure.

Cardiac Output and Mixed Venous O₂ Consumption

Though cardiac output (CO) can be measured by several techniques, the two most commonly used are the indicator thermodilution technique and the Fick oxygen technique. Both are based on the theoretical principle devised by Adolf Fick in 1870, which states that the total uptake or release of any substance by an organ is the product of blood flow to the organ and the arterio-venous (AV) concentration difference of the substance.²⁰ The clinical marker commonly used is oxygen and the difference between arterial and venous oxygen content is the uptake of oxygen as it flows through the lungs.²⁰

The Indicator Dilution Method

Stewart was the first to use this method to determine cardiac output in 1897.²¹ There have been a number of indicators used in the past, but the most commonly used today is the “cold” indicator in the thermodilution (TD) method. This technique applies this principle to the change in the temperature of blood caused by introduction of a known quantity of heat upstream from a point of temperature measurement.²⁰ Typically cold saline is injected into the right atrium. This results in cooling of the blood that is measured downstream by a thermistor to produce a thermodilution curve. The area under the curve represents the integral of the instantaneous mixing temperature at the sensing point²⁰ (Fig. 45-2). Cardiac output is automatically computed from these measurements using a small microprocessor device.

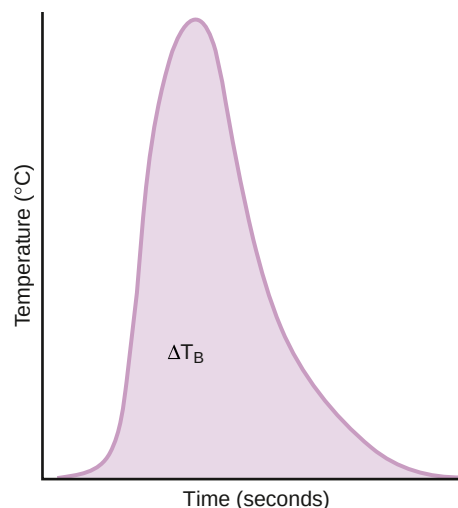


Figure 45-2. Sample thermodilution curve shows the change in instantaneous mixed temperature at the sensing point (thermistor) versus time. (Adapted from Ehlers KC, Mylrea KC, Waterston CK, et al: *Cardiac output measurements: a review of current techniques and research.* *Ann Biomed Eng* 1986;14:219-239.)

Accurate calculation of CO by TD assumes that the injectate mixes completely with the blood and its concentration can be measured correctly. Though Felger described the TD method in 1954, it gained wide clinical use only after Swan and Ganz developed a multilumen PAC with a distal thermistor.²⁰

The validity of results depends on the precision of the technique. The injection technique should be smooth and rapid to avoid dispersion of the injectate. Multiple measures should be taken and averaged to avoid ventilatory cycle specific patterns.⁶ The presence of significant tricuspid regurgitation can introduce error into the calculation and overestimate the cardiac output. In a patient with a left-to-right intracardiac shunt, measurement of the right ventricular CO would not reflect LV function. CO measurements via the TD method show good correlation with the Fick method for CO in the range of 3 to 6 L/min.^{22,23} In the case of low flow states, loss of indicator may occur because of warming of the blood by the walls of cardiac chambers. Grondelle and colleagues noted TD measurement overestimated CO consistently in patients with CO less than 3.5 L/min (with the greatest discrepancy in patients with CO <2.5 L/min).^{22,24} A modification of the standard TD method now allows for continuous CO monitoring. The flow-guided catheter was modified with placement of a blood-warming filament on the catheter at the region of the catheter injectate port. The catheter filament delivers heat to the flowing blood with a random on/off sequence that is continuously repeated with approximate total heating time of about 50%. Cardiac output is derived from the reconstructed washout curve using an equation analogous to the Stewart-Hamilton equation used for solution-based flow measurements.¹⁷ This advancement simplifies the assessment of CO at the bedside, eliminating the need for accurate repeated injection of solution.

Fick Method

In the Fick method of CO measurement, pulmonary blood flow is determined by measuring the AV difference of oxygen across the lungs and the rate of uptake by blood across the lungs.

If there are no intracardiac shunts, pulmonary and systemic blood flow should be equal and the CO equals oxygen consumption divided by AV oxygen difference.⁹

$$\text{CO (vol/time)} = \frac{\text{O}_2 \text{ consumption (mass/time)}}{[\text{arterial} - \text{venous O}_2 \text{ content}] (\text{mass/vol})}$$

The oxygen consumption $\dot{V}\text{O}_2$ can be either directly measured or calculated. Direct measurement is preformed with exhaled breath analysis using a spirometer, such as the metabolic rate meter (MRM) or the Deltatrac II.⁹ In a steady state, oxygen consumption can be determined by having the patient breathe pure O₂ from the spirometer with a CO₂ absorber and measuring O₂ uptake directly by the net gas flux.²⁰ Normal oxygen consumption in a resting individual is approximately 250 mL O₂/min. Calculation of the $\dot{V}\text{O}_2$ can be done with rearranging the Fick equation:

$\dot{V}\text{O}_2$ (mL O₂/min) = CO × (Cao₂ – CVO₂), where Cao₂ is the arterial oxygen content and CVO₂ is the mixed venous blood content. Normal Cao₂ and CVO₂ are 20 mL O₂/dL and 15 mL O₂/dL, respectively.

Oxygen consumption can also be estimated using from a nomogram based on age, sex, height, and weight. The AV difference is calculated by obtaining blood from a peripheral artery and the pulmonary artery for a mixed venous sample. The oxygen saturation is then multiplied by theoretical oxygen carrying capacity to yield the oxygen content of the sample (Fig. 45-3).

Mixed venous oxygen saturation (SVO₂) reflects the relationship between oxygen consumption ($\dot{V}\text{O}_2$) and oxygen delivery (DO₂).

$$\text{SVO}_2 = \frac{\text{oxygen delivered (SaO}_2 \times \text{Hb} \times \text{CO})}{\text{oxygen consumed } (\dot{V}\text{O}_2)}$$

It should be measured from blood drawn from the distal tip of the PAC to allow for adequate mixing of superior vena cava, inferior vena cava, and coronary sinus samples. The normal range of SVO₂ is 60% to 80%. If the SVO₂ is normal, one can assume that tissue perfusion is adequate, whereas high or

low values reflect an imbalance between oxygen supply and demand. A low SVO₂ reflects either decreased oxygen delivery (i.e., decreased Hb, SaO₂, or cardiac output) or increased oxygen demand. Conversely, high SVO₂ reflects increased oxygen delivery or decreased oxygen demand such as in the case of sepsis.

Complications

As with any invasive procedure, complications are an inherent risk of pulmonary artery catheterization. Multiple observational and randomized studies have investigated the incidence and significance of adverse events related to PAC use. Complications have been associated with catheter insertion (pneumothorax, arrhythmia, atrioventricular block) and those associated with the catheter once in place (pulmonary infarction, local thrombosis, pulmonary artery rupture, catheter-related infection).

Arrhythmias and Atrioventricular Block

Though ventricular and atrial ectopy is not uncommon, sustained ventricular arrhythmia is rare. Ventricular tachycardia has been reported in 12% to 68% of patients undergoing PA catheterization.^{25,26} Most episodes resolve with catheter movement and seldom require treatment. PAC-related arrhythmia does not appear to influence patient outcome.

In patients with pre-existing left bundle branch block (LBBB), the insertion of a PA catheter may be associated with the development of concomitant right bundle branch block (RBBB), thereby resulting in complete heart block. However, Sprung and co-workers studied 293 patients undergoing 307 PAC insertions and found a 3% incidence of new RBBB. They found no difference in the incidence of complete heart block in patients with pre-existing LBBB and development of RBBB in those with no underlying conduction disease.²⁷ Though prophylactic pacemaker placement is not indicated, the use of catheters that provide for ventricular pacing is advisable in patients with pre-existing LBBB.

Pulmonary Vascular Damage

Pulmonary artery infarctions appear to range in incidence in earlier studies from 7.2%²⁸ to 1.3% in later studies.^{29,30} These may occur as a result of either damage to the pulmonary endothelium, emboli originating from the catheter shaft, or placement of the catheter in the distal PA. Infarct can be avoided by minimizing the time the catheter is in the distal PA and by preventing migration of the tip into the distal pulmonary vessel.¹ These small, segmental infarcts usually resolve within 48 hours and though undesirable, appear to be of limited clinical significance.

PA rupture, though rare, is the most serious complication associated with PA catheter use. Pulmonary artery rupture has been reported in up to 0.2% of patients undergoing catheter insertion.^{29,31-33} In a retrospective chart review of more than 32,000 patients with PA catheters in a single institution over 17 years, Kearney reported 10 patients with PA rupture (Rate: 0.031%) with 70% mortality. All 10 patients developed hemoptysis and 5 had pulmonary hypertension.³² Risk factors for PA rupture include advanced age, pulmonary hypertension, and cardiopulmonary bypass surgery.^{1,34} Inflation of the balloon in a peripheral diseased pulmonary vessel may produce the force necessary to cause rupture; however, even a deflated catheter tip in the wedge position can cause arterial erosions.¹ The clinician must be careful to limit the length of time the catheter is in a peripheral artery, inflate the balloon only when the catheter

Step 1. Theoretic oxygen-carrying capacity: Hemoglobin (g/dL) × 1.36 (ml of O ₂ /g of Hb) × 10 = _____ ml O ₂ /L blood		
Step 2. Saturation of arterial (BA, PA, Ao) blood = _____ %		
Step 3. Oxygen content of arterial blood: Theoretic capacity × % saturation = _____ mL/L (step 1) (step 2)		
Step 4. Saturation mixed venous (PA) blood = _____ %		
Step 5. Oxygen content of mixed venous blood: Theoretic capacity × % saturation = _____ mL/L (step 1) (step 4)		
Step 6. AV O ₂ difference: Arterial O ₂ content venous O ₂ content = _____ mL/L (step 3) (step 5)		

Figure 45-3. Calculation of oxygen content and arteriovenous (AV) oxygen difference when using the reflectance oximetry method.

Ao, aorta; BA, brachial artery; PA, pulmonary artery. (Adapted from Baim DS [ed]: *Grossman's Cardiac Catheterization, Angiography, and Intervention*, 7th ed. Philadelphia, Lippincott Williams & Wilkins, 2006, p 154.)

position is known, and to confirm a safe “parking spot” of the deflated catheter in the main PA or proximally in the right or left branches.¹ A PA catheter that allows for surveillance of appropriate position by monitoring RV pressure via a middle lumen located 10 cm from the distal tip is available.³⁵ Recording a ventricular pressure tracing from this lumen ensures that the catheter is in the appropriate position.

Infection

Strict sterile technique is paramount with any invasive procedure. The incidence of catheter-related infection ranges from 0.5% to 2%.^{29,36} A recent randomized control study on PAC use in 433 patients found catheter-related infection to be the most common adverse outcome with a incidence of 1.9%.³⁷ Mermel and colleagues prospectively examined 297 PAC cases for infection and found a 22% incidence of local infection of the introducer sheath with only a 0.7% incidence of bacteremia.³⁸ The patient's skin was noted to be the single most important source for infection. Most investigators agree that the risk of catheter-related sepsis increases when a catheter is left in place for greater than 72 hours.^{29,36,38}

Thrombosis

A thin fibrin coating will usually envelope PA catheters within 24 hours of insertion.¹ In an autopsy series of 32 patients with PAC, thrombosis was identified in 53% and intimal fibrin deposition was identified in 66% of patients along the entire length of the PA catheter.³⁹ The incidence of thrombosis was significantly higher in cases where the catheter was left in place for more than 36 hours. A review by Ducatman found no difference in the incidence of pulmonary emboli in those with and without thrombi.⁴⁰ Though these thrombi can possibly embolize or become infected, the incidence and clinical significance appears to be low.

PAC use in the CICU and its complication profile is similar to the procedure performed at other locations; however, there are some important caveats. For instance, the use of anticoagulation such as antiplatelet and antithrombin therapy in the setting of acute coronary syndromes increases the propensity for bleeding and hematoma formation. In addition, the majority of these patients are already at increased risk for morbidity and mortality due to their underlying conditions. The overall morbidity of PAC use should not exceed 2% to 5%. Swan estimated the added mortality risk in the CICU environment to be less than 0.25%.¹

Indications for Pulmonary Artery Catheterization

Hemodynamic data derived from PACs may aid in diagnosis and guide management. The clinical use of invasive hemodynamic monitoring has changed and defined the modern practice of critical cardiac care. Despite the widespread use of PACs the effect on patient outcome remains controversial. The accepted indications for PA catheterization have been based largely on expert opinion.⁴¹ The decision to place a PAC should be based on a clinical question regarding a patient's hemodynamic status that cannot be answered with noninvasive assessment. There needs to be the intent to act on the information gathered by invasive hemodynamic monitoring to justify PAC placement.

In general, patients requiring invasive monitoring include those with homodynamic compromise, including circulatory collapse, cardiogenic shock, and severe heart failure. Right ventricular infarct, ventricular septal rupture, and cardiac tamponade are currently more appropriately diagnosed with echocardiography.

Table 45–4. When Hemodynamic Monitoring May Be Used

In patients with myocardial infarction complicated by:
Severe heart failure
Low output syndrome
Shock
Mechanical lesions
Mitral regurgitation
Ventricular septal rupture
Subacute cardiac rupture with tamponade
Recurrent, severe postinfarction ischemia
In critically ill patients with multiorgan dysfunction such as:
Severe respiratory dysfunction
Severe renal dysfunction
Extensive burns
Extensive trauma
Severe sepsis
Massive pulmonary embolism
Suspected cardiac tamponade
Persistent low cardiac output syndrome
Shock
Cardiogenic or noncardiogenic pulmonary edema
Gastrointestinal hemorrhage
Pancreatitis
Drug overdose
Adult respiratory distress syndrome
In high-risk cardiac patients before, during, and after any surgical procedure
In high-risk obstetric patients who have
Known cardiac disease
Toxemia
Suspected abruptio placenta
In patients with unstable angina, left ventricular dysfunction, or hemodynamic instability if intravenous nitroglycerin or other vasoactive drugs are required
In patients with chronic heart failure to:
Assess ventricular function at rest, during exercise, and in response to therapeutic intervention
Distinguish a specific cause of heart failure, such as constrictive pericarditis
Restrictive cardiomyopathy
Precapillary pulmonary hypertension
A research tool for clinical investigation

Table 45-4 outlines potential indications for invasive hemodynamic monitoring with PA catheterization.

Clinical Applications

Pulmonary Edema

At times, diagnosis of the etiology of pulmonary edema through radiographic and clinical means may be difficult.⁴² Often these patients are critically ill, have severe blood gas abnormalities, and have radiographic evidence of generalized interstitial and alveolar infiltrates. In noncardiogenic pulmonary edema, the PCWP would be normal. This distinction is critical for the appropriate choice of therapy (i.e., diuretics and vasodilators in cardiogenic pulmonary edema versus supportive care in the case of adult respiratory distress syndrome). Often for patients in shock, a therapeutic trial of volume expansion may be indicated. PAC is indicated in these patients when these initial strategies may be contraindicated, have failed, or when there are coexisting features of cardiac and noncardiac etiologies making therapeutic decision making difficult. Following the diagnosis, PA catheterization may be helpful in effectively titrating doses of diuretics, vasodilators, inotropes, and vasopressors.

Pericardial Tamponade

Pericardial tamponade is a clinical diagnosis (distant heart sounds, pulsus paradoxus, and hypotension) best made by echocardiography. When echocardiography is unavailable or technically suboptimal, PAC can provide support for the diagnosis.

The low ventricular volume during systole creates a dominant x descent on the RA tracing. The y descent is attenuated or absent. During inspiration, the mean RA pressure declines allowing one to distinguish tamponade from constriction and right ventricular (RV) infarction where there is equalization of RA and wedge pressure⁴³ (Fig. 45-4). Therapeutic intervention should never be delayed in unstable patients to await a right heart catheterization.

Severe Heart Failure

Invasive hemodynamic measurements may be useful for effectively treating some episodes of severe acute decompensation of chronic heart failure by allowing more precise adjustments of therapy, including diuretics, vasopressors, vasodilators, and inotropes⁴⁴ based upon real time assessment of hemodynamics. Stevenson and colleagues outlined a concept of "tailored therapy" for advanced heart failure in 152 patients awaiting heart transplant that included use of nitroprusside, furosemide, and oral vasodilators with target PAOP and SVR. They demonstrated a correlation between mortality and failure to improve PAOP during therapy.⁴⁵

Acute Myocardial Infarction

The routine use of a PAC in the setting of uncomplicated acute myocardial infarction has never been the practice. A prospective study by Gore observed PAC use in acute MI over the 70s and 80s in hospitals in Worcester, Mass. More than 96% of the instances of PAC use were in the setting of congestive heart



Figure 45-4. Right atrial (RA) and aortic pressure tracings from a patient with pericardial tamponade. Aortic pressure declines by 20 mm Hg during inspiration (pulsus paradoxus). RA pressure declines normally during inspiration. A dominant x descent can be seen. (Adapted from Sharkey SW: *Beyond the wedge: clinical physiology and the Swan-Ganz catheter*. *Am J Med* 1987;83:118.)

failure (CHF), hypotension, and cardiogenic shock.⁴⁶ A retrospective analysis of two large randomized acute coronary syndrome trials looking at PAC use found an overall use of 2.8%. Those undergoing PAC insertion were more likely to have ST elevation MI and advanced Killip classification (III and IV).⁴⁷ As per the current American College of Cardiology/American Heart Association (ACC/AHA) guidelines, indications for PAC are related to specific complications of myocardial infarction including (1) hypotension, low cardiac output, and cardiogenic shock due to LV failure; (2) acute mechanical complications (MR from papillary muscle rupture/ischemia, ventricular septal defect (VSD), or ventricular free wall rupture; (3) complicated right ventricular infarction; and (4) heart failure or pulmonary edema refractory to usual management.⁴¹

Shock/Low Cardiac Output

Diminished cardiac output is typically the result of several mechanisms but most often due to decreased contractility as a result of infarct, ischemia, or arrhythmia. Mechanical causes such as mitral insufficiency and ventricular septal defect, though less frequent, are not uncommon causes of low cardiac output states.¹⁵ PAC is recommended in the setting of shock to confirm hemodynamic criteria and assess filling pressures to distinguish cardiogenic from other causes of shock including hypovolemia. Patients that exhibit progressive hemodynamic deterioration with cardiac indices less than 1.8 L/min/m², elevated PA pressure, and PCWP above 25 mm Hg, may require mechanical ventilation, afterload reduction, heart rate control, and various vasoactive medications and devices. CO measurements can be followed to assess the response to therapy.¹ An analysis of the The SHould we emergently revascularize Occluded Coronaries for cardiogenic shock (SHOCK) registry of patients with acute myocardial infarction complicated by cardiogenic shock found overall use of PA catheters in 66% of patients. However, there

was a significant decrease in use from the early to late 1990s.⁴⁸ Though there is no data that proves a survival benefit in cardiogenic shock patients associated with the use of PAC, most studies have been limited by selection bias that precludes clear conclusions.^{46,49}

Mitral Regurgitation Due to Papillary Muscle Rupture

Though acute mitral regurgitation (MR) can be accurately diagnosed by echocardiography, severe mitral regurgitation associated with papillary muscle rupture is an indication for prompt right and left heart catheterization and Cardiac surgery evaluation for possible valve replacement. The ejection of blood into a normal-sized, noncompliant left atrium causes a giant *v* wave on the wedge pressure tracing. The giant V wave is transmitted to the PA tracing yielding a bifid PA waveform composed of a pulmonary systolic wave and V wave⁴³ (Fig. 45-5). Inflation of the balloon obliterates the systolic wave as the catheter is wedged but the V wave remains. Careful attention needs to be paid to avoid mistaking the wedge and PA tracing in these patients. The systolic wave in the PA tracing occurs earlier in QRS cycle than does the V wave. Prominent V waves are not specific to acute MR but can also be seen with dilated or ischemic heart disease where a noncompliant LA experiences increased blood flow such as in acute ventricular septal rupture. Bedside PAC may help guide vasodilator and inotropic therapy in acute MR.

Ventricular Septal Defect

Echocardiography is highly sensitive and specific for the diagnosis of ventricular septal defect and can provide quantitative measures regarding the magnitude of the shunt, pulmonary artery pressures, and right ventricular function.⁴¹ Though not typically required, PAC can be helpful if echocardiography is unavailable or suboptimal in evaluating the magnitude of the shunt. Clinical differentiation of acute MR and VSD can be difficult. PAC would be

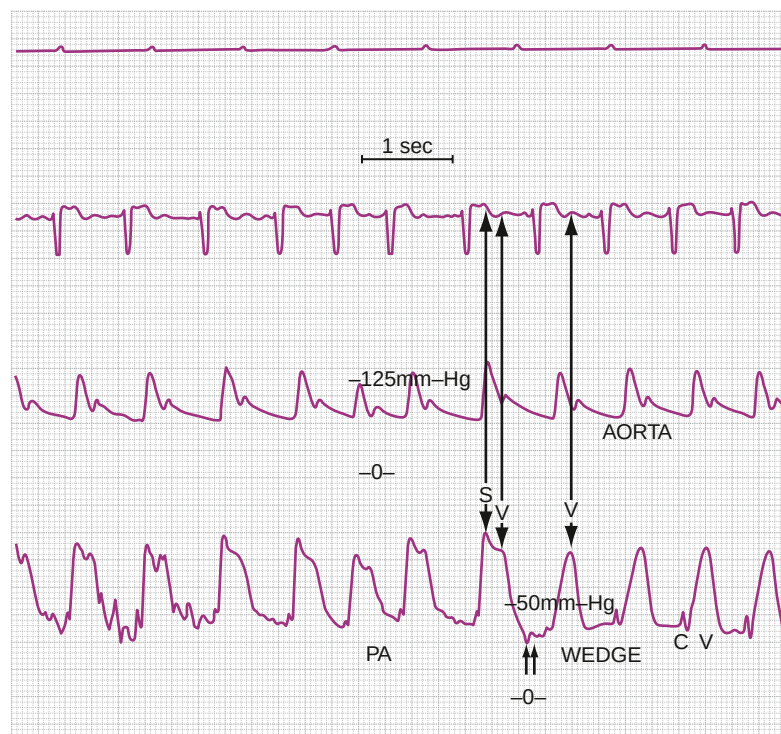


Figure 45-5. Arterial, pulmonary artery (PA), and wedge pressure waveforms in a patient with acute mitral regurgitation. A prominent V wave is present in pulmonary artery and wedge tracings. The bifid PA waveform reflects the systolic (S) and V wave. The double arrow denotes inflation of the balloon and wedging, which obliterates the S wave. (Adapted from Sharkey SW: *Beyond the wedge: clinical physiology and the Swan-Ganz catheter*. *Am J Med* 1987;83:115.)

helpful in distinguishing VSD from acute MR if echocardiography is unavailable. Rupture of the septum causes acute volume overload into the right ventricle with increased pulmonary to systemic blood flow ratio greater than 2:1.⁴³ The diagnosis is confirmed with the presence of a step up in oxygen saturation of greater than 10% between the right atrium and pulmonary artery.⁹

Right Ventricular Infarction

Right ventricular infarction complicates acute inferior wall MI in up to 30% of cases.⁴³ The characteristic hemodynamic profile of acute RV dysfunction includes RA pressure disproportionately increased relative to wedge pressure; a steep y descent and RV pressure tracing that may show a diastolic dip and plateau referred to as the square root sign¹⁸ (Fig. 45-6). Though a prominent x and y descent are typical, the y descent may exceed the x descent because of the presence of a dilated noncompliant RV that is confined by the pericardium.⁴³ During inspiration, the RA pressure may increase response known as Kussmaul's sign.⁴³ Tricuspid insufficiency due to papillary muscle dysfunction and RV dilation may complicate RV infarction.⁴³ These findings may be detected in only about 50% of patients with acute RV dysfunction. Volume loading may be necessary to unmask these hemodynamic abnormalities.¹⁸

Constrictive Pericarditis

As in tamponade, constrictive pericarditis produces diastolic pressure equalization with elevated right- and left-sided filling pressures. However, unlike tamponade, constriction displays an early diastolic dip followed by a pressure plateau in both right and left ventricular pressure tracings.¹⁸ The RA tracing displays the characteristic M or W shape with a preserved x descent and a prominent early y descent (Fig. 45-7).

Restrictive Cardiomyopathy

The hemodynamic profiles of restrictive and constrictive pericarditis do mirror each other. Though both display the characteristic M or W shaped RA pressure tracing and diastolic dip and plateau, a differentiation of these two can be made. The left-sided filling pressure tends to be higher than the right-sided pressures in patients with restriction. Also the diastolic pressure plateau is usually less than one third the RV systolic pressure in restrictive cardiomyopathy.¹⁸

Controversies

The PAC has become a widely used monitoring device in critically ill patients since its introduction in 1971. Its initial use, however, was not supported by clinical trials, but instead benefit was assumed. Retrospective analyses from the 1980s^{46,49} studying PAC use in acute myocardial infarction, found no difference in mortality after adjusting for severity of illness. This prompted more interest in the potential benefit or harm of PAC use. In 1996, a retrospective observational study of more than 5500 cardiac and noncardiac critically ill patients concluded that, after adjustment for treatment selection bias, the PAC was associated with increased mortality and increased length of stay.⁵⁰ An accompanying editorial proposed a moratorium on RHC use.⁵¹ This prompted a response by multiple organizations including the ACC/AHA who issued a consensus statement. The ACC concluded that, despite attempts to account for selection bias by the authors, flaws existed. Patients with lack of response to initial therapy were more likely to undergo PAC placement. In addition patients with PACs in place were more likely to enter the study with multiorgan failure, respiratory failure, and congestive heart failure—all factors associated with higher mortality. These criticisms did not discount the possibility that PAC use may be associated with detrimental outcomes, but instead highlighted the need for further trials, randomized if possible. However, the consensus committee also cautioned that even data from randomized trials may not resolve the issue because of the difficulty in controlling for the effects of therapies administered and to accommodate the large numbers of patients necessary to be enrolled.⁴¹

In 2005, two large multicenter randomized trials were published examining the effectiveness of PAC in management of critically ill patients. The first reported on more than 1000 critically ill patients enrolled between 2001 and 2004. Patients were randomized to PAC insertion or no PAC use. The authors found no statistical difference in hospital mortality between the groups (68% versus 66%, $p = 0.39$, adjusted hazard ratio 1.09 (0.94–1.27)).⁵² It also found that the less than 10% complication rate did not directly lead to any increase in mortality. Later that year, the second trial was published. Patients admitted with severe symptomatic and recurrent heart failure from 2000 to 2003 were randomized to PAC or no PAC insertion. The authors found that therapy in both groups lead to substantial reduction in

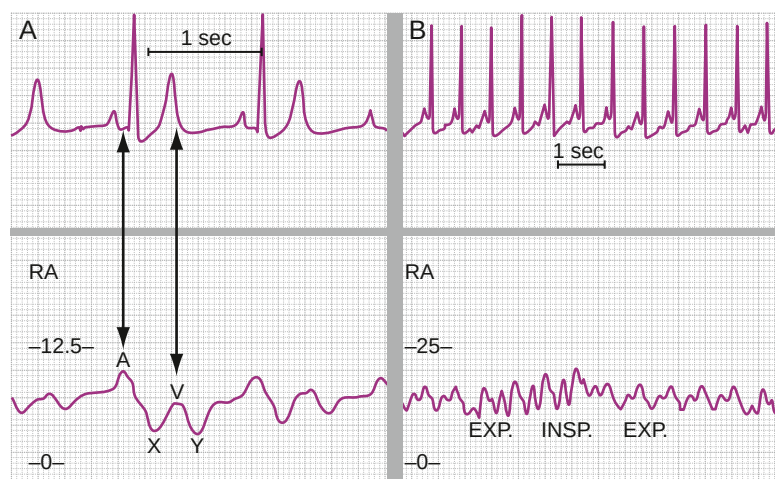


Figure 45-6. **A**, Right atrial (RA) pressure waveform in a patient with right ventricular infarction. Note the steep x and y descents. **B**, The inspiratory increase of RA pressure in right ventricular infarction is known as Kussmaul sign. (Adapted from Sharkey SW: *Beyond the wedge: clinical physiology and the Swan-Ganz catheter*. *Am J Med* 1987;83:116.)

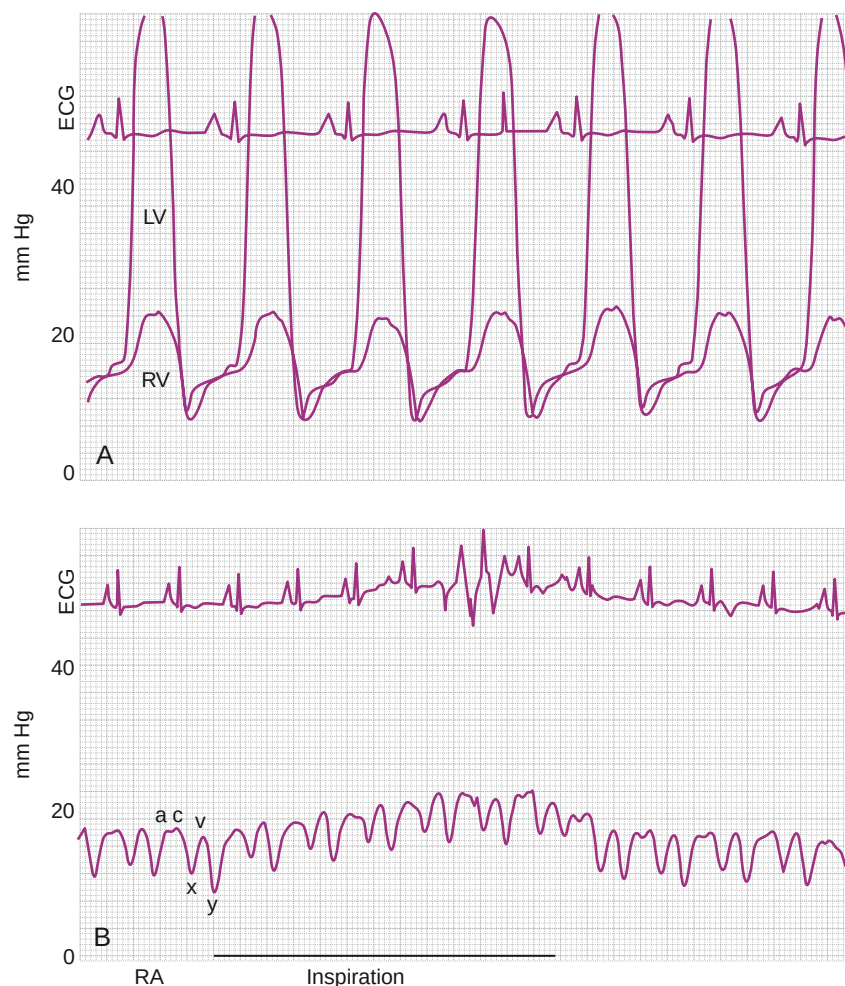


Figure 45-7. **A**, Simultaneous right ventricular (RV) and left ventricular (LV) tracings show equalization of end-diastolic pressures along with the “square root sign” (i.e., early diastolic dip and late diastolic plateau). **B**, Kussmaul sign—the inspiratory increase in right atrial pressure.

symptoms, jugular venous pressure, and edema. The use of PAC did not significantly affect the primary end point of 6-month mortality.³⁷ Therefore basing the decision to administer vasodilator and diuretic therapy on PAC data plus clinical judgment was not superior to decisions based on clinical judgment alone.³⁷ The authors did note there was a trend toward better outcomes using PAC-guided therapy in centers with large numbers of patients. Ultimately the data from both trials found PAC use to be safe and did not substantiate previous retrospective reports of excessive mortality associated with PAC use.

Safe and effective PAC use should be predicated on careful catheter placement, attention to measurement techniques, and thoughtful interpretation of data. Iberti and colleagues published a multicenter evaluation of physician knowledge of PAC use in 1990.⁵³ The authors used a 31-question multiple-choice examination of 496 physicians to assess physician understanding of PAC use. They found a mean test score of 67% correct with a standard deviation 5.4. Mean scores varied independently by training and with the frequency and use of PAC in clinical practice.

Every physician who performs hemodynamic monitoring should understand the indication for the procedure, be technically competent with insertion techniques, and have the ability to interpret data obtained⁵⁴ (see [Table 45-5](#)).

Table 45-5. Technical Skills Needed to Perform Hemodynamic Monitoring*

1. Ability to perform venous access from two (or multiple) sites with the percutaneous technique. Ability to do cutdowns is also desirable.
2. Ability to perform arterial access (primarily radial artery puncture), although the ability to do arterial cutdown is desirable.
3. Ability to operate all instrumentation involved in hemodynamic monitoring, including catheters, introducers, strain gauges and recorders and to perform calibration, balancing, and zeroing techniques
4. Knowledge and ability to correct (“trouble shoot”) common artifacts and technical problems with recording instrumentation and catheter/tubings

*Adapted from Friesinger G, Williams S: Clinical competence in hemodynamic monitoring. A statement for physicians from the ACP/ACC/AHA task force on clinical privileges in cardiology. *J Am Coll Cardiol* 1990;15(7):1460-1464.

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Intra-Aortic Balloon Pump Counterpulsation

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CHAPTER 46

Physiologic Principles
Monitoring of IABP Counterpulsation
Contraindications to the Use of IABP Counterpulsation
Insertion, Removal, Maintenance, and Complications

Cardiogenic Shock
High-Risk Percutaneous Coronary Intervention
Cardiac Surgery
Transplantation and Dysrhythmias
Conclusion

INTRA-AORTIC BALLOON PUMP (IABP) counterpulsation has emerged as one of the most effective and most frequently employed methods of mechanical circulatory support. Specifically, it relies on the twin concept of diastolic augmentation and afterload reduction to facilitate the functioning of an ischemic and failing myocardium. This concept was originally proposed by Mouloupoulos and associates in 1962; subsequently, they documented improvement in hemodynamic parameters in experimental animal models.¹ The first clinical report of human use by Adrian Kantrowitz appeared 6 years later.² During the last 4 decades, IABP has experienced a technological evolution. With the advent of a percutaneous approach to insertion, the device has been used in an expanding array of clinical settings: managing cardiogenic shock; treating persistent and intractable angina; during weaning from cardiopulmonary bypass; during thrombolytic therapy in patients at high risk for occlusive rethrombosis; during complex and high-risk coronary angioplasty; and in the setting of severe stenosis of the left main coronary arterial trunk or critical aortic stenosis before surgical intervention.³ Due to its widespread usage, practitioners in the critical care setting need to be familiar with the fundamental principles of IABP counterpulsation therapy to effectively manage cardiac patients. As evidence of its prevalent usage, one report estimates that more than 70,000 IABP devices are annually placed in the United States.⁴

Physiologic Principles

The IABP has two main hemodynamic effects: during the diastolic phase of the cardiac cycle, a volume of blood is displaced to the proximal aorta following inflation; during the systolic phase, a vacuum effect is created in the proximal aorta following rapid deflation, thereby reducing the afterload experienced by the contracting left ventricle. To optimize these two hemodynamic effects, the IABP must inflate and deflate in synchrony to a patient's cardiac cycle. Since 1970, observations have revealed that the single most important determinant of effective balloon-assisted circulation is the balloon pump's timing to the cardiac cycle.⁵ Once proper timing has been established, an IABP will achieve three goals: an improvement in myocardial oxygen delivery via an increase in coronary perfusion pressure;

a reduction in cardiac work by a decrease in systolic blood pressure (afterload); finally, an improvement in forward blood flow in patients with impaired cardiac contractile function.⁶ Following technological advancements during the past three decades, modern intra-aortic balloon pumps now use a closed-loop control system to automatically optimize pump timing.⁷⁻¹¹

The principal objective of balloon counterpulsation is to enhance the balance between myocardial oxygen consumption and supply. Several factors affect the achievement of a favorable balance: the volume of the balloon; its position in the aorta; the underlying heart rate and rhythm; the compliance of the aorta; lastly, the systemic vascular resistance.¹² For instance, an increase in arterial elastance (a property which is affected by compliance) is associated with a greater degree of hemodynamic improvement from an IABP.¹³ Despite the presence of multiple factors that can cause variability in the effects of an IABP, a majority of patients do exhibit a specific hemodynamic profile in the setting of cardiogenic shock (Table 46-1).

Table 46-1. Effect of Intra-aortic Counterpulsation on Hemodynamic Parameters

Hemodynamic Parameter	Effect
Aortic systolic pressure	Decrease
Aortic diastolic pressure	Increase
Mean aortic pressure	Increase
Left ventricular afterload	Decrease
Mean pulmonary capillary wedge pressure	Decrease
Cardiac output	Increase
Left ventricular ejection fraction	Increase
Diastolic pressure-time index (DPTI)	Increase
Tension-time index (TTI)	Decrease
Endocardial viability ratio (DPTI/TTI)	Increase

Data abstracted from Scheidt S, Wilner G, Mueller H, et al: Intraaortic balloon counterpulsation in cardiogenic shock. *N Engl J Med* 1973;288:979.

This profile includes the following parameters: a decrease in systolic pressure by 20%; an increase in diastolic pressure by 30%, which may subsequently enhance coronary blood flow to a territory perfused by an artery with a critical stenosis; a reduction of heart rate by less than 20%; a decrease in the mean pulmonary capillary wedge pressure by 20%; and an elevation in the cardiac output by 20%.¹⁴ The reduction in aortic pressure, which is caused by the rapid deflation of the balloon, effectively decreases left ventricular afterload, and consequently diminishes myocardial workload.⁶ Afterload (pressure work) is significantly more costly in terms of myocardial oxygen consumption than cardiac output (volume work).¹⁵ In fact, many authorities in this field maintain that afterload reduction is the most beneficial aspect of balloon counterpulsation on a failing left ventricle.^{16,17} Two indices that are measured during IABP counterpulsation include the tension-time index (TTI), which is the time integral of left ventricular pressures during systole, and the diastolic pressure-time index (DPTI), which is the time integral of the proximal aortic pressures during diastole. Proper balloon inflation augments diastolic pressure (i.e., increases DPTI) whereas rapid balloon deflation decreases left ventricular afterload (i.e., decreases TTI). A ratio can be constructed from these two indices (DPTI:TTI ratio); this ratio has been termed the endocardial-viability ratio and illustrates the relationship between myocardial oxygen supply and demand. With IABP counterpulsation optimally synchronized to a patient's cardiac cycle, the endocardial-viability ratio will be increased.^{6,18}

Monitoring of IABP Counterpulsation

The appropriate timing of balloon counterpulsation to the mechanical events of the cardiac cycle is crucial to deriving optimal hemodynamic benefits (Fig. 46-1). To maximize diastolic augmentation, the balloon should inflate at end-systole, immediately after closure of the aortic valve. Balloon inflation augments coronary perfusion pressure, thereby providing greater myocardial oxygen delivery. Mean diastolic pressure (MDP) correlates well with coronary perfusion and hence oxygen delivery.⁶ Smith and colleagues confirmed the proposal that maximal coronary perfusion occurs when balloon inflation coincides with end-systole.^{9,19} The timing of balloon deflation, which best decreases left ventricular oxygen consumption, is less well defined. Deflation before the ventricular ejection of blood unequivocally creates a vacuum effect in the proximal aorta, which in turn reduces afterload and peak systolic pressure. The resultant net decrease in oxygen consumption is difficult to quantitate. However, peak systolic pressure is directly related to ventricular wall stress; a decrease in the latter parameter is associated with a reduction in myocardial oxygen consumption.⁶

The triggering of balloon counterpulsation requires the existence of a predictable, reproducible, and reliable event. The trigger marks a time point in which balloon inflation and deflation are planned. In most cases, the R wave of the surface ECG serves as the triggering event. The more sophisticated IABP systems do offer other triggering capabilities, such as arterial pressure waveforms, and ventricular or atrioventricular pacer spikes. The IABP can also function in an asynchronous pumping mode with a trigger rate set by the operator. Such a mode can be employed during cardiopulmonary resuscitation.⁶

Loss of optimal hemodynamic effect occurs when balloon counterpulsation is not appropriately timed to the mechanical

events of a patient's cardiac cycle. Mahaffey and colleagues have provided lucid descriptions of four different scenarios involving faulty coupling of balloon counterpulsation with the cardiac cycle.²⁰

During late inflation, the dirotic notch on the aortic pressure waveform is clearly visualized. The balloon inflates well beyond closure of the aortic valve. In this scenario, diastolic augmentation of central aortic pressure is decreased, whereas ventricular afterload is minimally affected. The classic morphologic finding on the central aortic pressure tracing is the presence of a distinct dirotic notch with the augmented diastolic pressure wave occurring well afterward. To correct late inflation of the intra-aortic balloon pump, the timing interval should be gradually decreased until the onset of inflation coincides with the dirotic notch on the arterial pressure waveform.

During early inflation, the balloon inflates before closure of the aortic valve. Pressure augmentation is thus superimposed upon the systolic aortic pressure tracing thereby leading to the following hemodynamic effects: a decrease in left ventricular emptying (a decrease in stroke volume); a decrease in cardiac output; an increase in left ventricular afterload; an overall increase in myocardial oxygen consumption. In this scenario, there is loss of the distinct systolic peak of the central aortic pressure waveform and loss of the dicrotic notch. To correct early inflation, the timing interval should be slowly increased until the onset of inflation occurs at the dicrotic notch.

The two previously described scenarios dealt with inappropriate timing of balloon inflation. However, the following two scenarios involve faulty timing of balloon deflation.²⁰

During late deflation, the balloon is deflated after the onset of systole and the opening of the aortic valve. The resultant hemodynamic profile is similar to the one observed with early inflation: afterload is increased, thereby leading to increased left ventricular work and myocardial oxygen consumption along

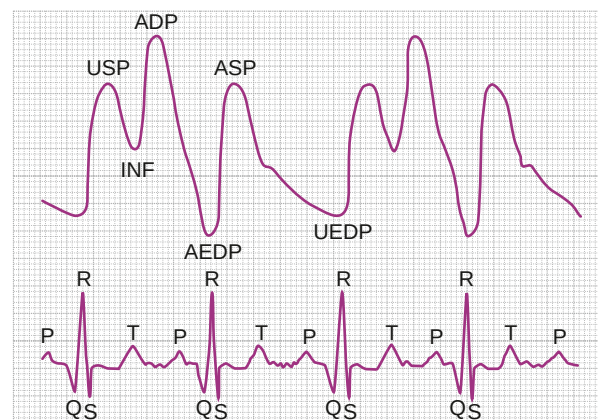


Figure 46-1. Optimal timing of an intra-aortic balloon pump. Arterial pressure tracing from a patient with an intra-aortic balloon pump. The balloon was set at 2:1 to evaluate timing. Inflation (INF) was timed to the dicrotic notch to follow aortic valve closure. There is augmentation of diastolic pressure (ADP) and reduction of the end-diastolic pressure with augmented beats (AEDP) compared with the unaugmented end-diastolic pressure (UEDP). The augmented systolic pressure (ASP) is often lower than the unaugmented systolic pressure (USP) as well. (*Adapted from Holleney S, Saltzberg M, Soble J, Parrillo J. Heart Failure and Cardiomyopathy. In Crawford MH, Dimarco JP, Paulus WJ (eds): Cardiology. London, Mosby, 2001.*)

with reduced stroke volume and cardiac output. Analysis of the arterial pressure tracing usually reveals the loss of a distinct valley representing the end-diastolic pressure before the central aortic systolic wave. To correct late deflation, the timing interval should be decreased gradually until the balloon deflates before the onset of cardiac systole.

During early deflation, the balloon deflates prematurely and consequently the benefits of diastolic augmentation disappear. Analysis of the arterial pressure tracing reveals the presence of a peaked diastolic augmentation wave along with a broad U-shaped wave preceding the onset of cardiac systole. Early deflation is not as detrimental as the other counterpulsation timing abnormalities. However, the potential benefits of diastolic augmentation are not optimized in this scenario. To correct early deflation, the timing interval should be increased until the augmented diastolic wave becomes appropriate.

Contraindications to the Use of IABP Counterpulsation

When intra-aortic counterpulsation therapy is being considered, the risks and benefits of this modality must be individually assessed for each patient (Table 46-2).

Absolute Contraindications. These include the following situations: distal aortic occlusion or severe stenosis, suspected aortic dissection, documented abdominal or thoracic aortic aneurysm, and severe aortic regurgitation.²¹

Relative Contraindications. They are more frequent and must be taken into account when deciding to use intra-aortic counterpulsation therapy. These include the following scenarios: severe peripheral vascular disease (PVD), aortic or iliofemoral arterial grafts, a contraindication to the usage of heparin or other parenteral anticoagulation, moderate aortic regurgitation, and uncontrolled sustained tachyarrhythmias (heart rate exceeding 160 beats/min).²¹ Patients with vascular abnormalities such as distal aortic stenosis, aortic dissection, or aortic aneurysm have a significantly increased risk of catastrophic vascular complications. The presence of PVD or iliofemoral grafts

increases the risk of complications associated with balloon insertion and removal. Aortic regurgitation can potentially lead to further cardiac decompensation. During balloon inflation, an increased regurgitant volume may be generated across the incompetent aortic valve, thereby resulting in increased left ventricular volumes. Data from animal studies have demonstrated increased regurgitant flow but also enhanced left ventricular stroke volumes, despite the increased diastolic volumes.²² Therefore, although patients with severe aortic valvular insufficiency should be excluded from IABP counterpulsation therapy, patients with lesser degrees of aortic regurgitation should be considered but with close monitoring during the initial phase of the therapy. Sustained tachyarrhythmias with heart rates exceeding 160 beats/min hamper the ability of the balloon drive system to accurately track the mechanical events of the cardiac cycle and provide hemodynamic support. A cardiac electrophysiologic evaluation can be considered before implementation of intra-aortic counterpulsation therapy in such patients.²⁰

Insertion, Removal, Maintenance, and Complications

Placement of the IABP Is the First Step for Counterpulsation Therapy

The percutaneous route via cannulation of the femoral artery is most often employed. Once it is concluded that the patient no longer requires circulatory support, the removal of the IABP is also a straightforward process. Mahaffey and colleagues have devised a simple stepwise approach to device insertion and removal (see Appendix A).²⁰

A thorough vascular physical examination should precede the insertion of the IABP. This examination should include palpation of all lower extremity pulses along with auscultation of the lower half of the abdomen and of the femoral arteries. The femoral artery with the best palpable pulsation should be selected to minimize any vascular complications.³ Early single-lumen balloons were inserted via a femoral artery cutdown or a large (11F) sheath. Newly available balloons (7.5F) are inserted percutaneously over a guidewire using a smaller sheath (8F to 9F) or sheathless. The downsizing of IABP catheters and sheathless insertion has significantly reduced the incidence of ischemic peripheral vascular complications, especially in patients with small or atherosclerotic arteries. In patients with severe peripheral atherosclerosis or distal abdominal aortic aneurysms, the IABP can be inserted through the axillary or the brachial arteries.

Following insertion of the device, fluoroscopy can be used to ensure that the device has been placed in the descending thoracic aorta distal to the origin of the left subclavian artery. Intra-aortic counterpulsation can begin thereafter with augmentation in one inflation for each cardiac cycle (1:1 ratio) being ideal for optimal hemodynamic support. However, adjusting counterpulsation timing is best done with the console set at 1:2 pumping so that the pressure tracings with and without counterpulsation can be compared. Daily chest films and continuous monitoring of hemodynamic parameters ensures good placement and appropriate timing of the device.

No conclusive data support the need for intravenous anticoagulation in the setting of IABP use. A trial involving 153 patients found no difference in vascular complications or laboratory end points in patients undergoing intra-aortic counterpulsation

Table 46-2. Contraindications to Intra-aortic Balloon Pump Counterpulsation Therapy

Absolute Contraindications	Relative Contraindications
Occlusion or severe stenosis of distal aorta	Severe peripheral vascular disease
Aortic aneurysm	Aortic or iliofemoral bypass grafts
Aortic dissection	Contraindication to intravenous anticoagulation
Severe aortic regurgitation	Moderate aortic regurgitation Sustained tachyarrhythmias (with ventricular rate >160 beats/min)

Data from Mahaffey KW, Kruse KR, Ohman EM: Perspective on the use of intra-aortic balloon counterpulsation in the 1990s. In Topol EJ (ed): Textbook of Interventional Cardiology, Update Series, No. 21. Philadelphia, WB Saunders, 1996, pp 303-320.

therapy, with and without continuous heparin anticoagulation.²³ Industry guidelines do not require continuous anticoagulation therapy, especially when the device is set in a 1:1 assist ratio. Currently, it is reasonable to use intravenous heparin with the goal of maintaining an aPTT of 60 to 75 seconds in a patient without contraindications to anticoagulation and when IABP counterpulsation therapy is planned for greater than 24 hours or at lesser assist ratios.³

Although no conclusive data exist in the literature, some authorities recommend gradual weaning of the balloon pump before it is finally removed. Typically, a gradual reduction in the assist ratio from 1:1 to 1:2 and then to 1:3 over several hours is done. If hemodynamic stability is demonstrated at lesser assist ratios, the device can be safely removed. Another weaning protocol involves the gradual reduction of the balloon volume over the course of an hour. This latter method may provide a more gradual resumption of the demands of intrinsic hemodynamic support on the heart.²⁰

Complications. Complications arising from IABP counterpulsation therapy can be categorized into vascular and non-vascular events. In the Benchmark Registry, which included almost 17,000 patients who had an IABP inserted between 1996 and 2000, major complications (defined as major limb ischemia, severe bleeding, balloon leak, and death related directly to device insertion or to device failure) occurred in 2.6% of the patients.²⁴ In this registry, the overall in-hospital mortality rate was 21%, one half of which occurred while the IABP was in place. However, mortality directly stemming from usage of the IABP was only 0.5%.²⁵

The true incidence of complications associated with placement of an IABP is difficult to determine because of differing definitions. However, the frequency of complications is most likely decreasing as techniques, equipment, and experience with the device improve.³ Studies citing complication rates are diverse in terms of the indications for intra-aortic counterpulsation therapy, the insertion technique (surgical or percutaneous), the duration of use, and the specific definitions of a complication.^{24,26-30} The most common reported complications are bleeding and arterial trauma.³

Vascular complications occur in 6% to 25% of cases. The most common types of vascular complications include limb ischemia; vascular laceration necessitating surgical repair; and major hemorrhage.^{25,31-33} Arterial obstruction and limb ischemia can occur when the IABP is inadvertently placed into either the superficial or profunda femoral artery, instead of the common femoral artery. The superficial and the profunda femoral arteries are usually too small to accommodate the IABP without compromising blood flow to the limb. In this scenario, prompt removal of the device and contralateral insertion (with avoidance of an excessively low needle puncture) is the best solution. Arterial dissection can occur with improper advancement of a guidewire with subsequent insertion of the IABP into a false lumen. Vascular complications of lesser frequency include spinal cord ischemia along with visceral organ ischemia. Less frequent but nevertheless feared complications of IABP counterpulsation include cholesterol embolization, stroke, sepsis, and balloon rupture.²⁵ Balloon rupture is uncommon, but because helium is insoluble in blood, helium embolization can cause prolonged ischemia or stroke. These patients can be treated with hyperbaric oxygen to maintain tissue viability. Various multivariate regression analyses have been performed in an effort to identify clinical variables

Table 46–3. ACC/AHA Practice Guidelines: Indications for IABP Counterpulsation Therapy

Clinical Scenario	ACC/AHA Recommendation	Level of Evidence
Severe or refractory unstable angina	Class IIa	C
Refractory decompensated heart failure	Class IIb	C
Cardiogenic shock	Class I	B
Refractory polymorphic ventricular tachycardia	Class IIa	B

Data from Antman EM, Anbe DT, Armstrong PW, et al: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction. *J Am Coll Cardiol* 2004;44:671-719.

that predispose to a higher rate of complications. The presence of peripheral arterial disease (including a history of limb claudication, femoral arterial bruit, or absent pulsations) has been the most consistent and reproducible clinical predictor of subsequent complications.^{3,24,34-36}

Clinical Efficacy and Indications

Counterpulsation therapy with IABP improves the hemodynamic and metabolic derangements that are associated with circulatory collapse.²¹ Historically, this modality has been mainly used in the setting of acute ischemic syndromes associated with hemodynamic decompensation. In the decades since its introduction, more data have accumulated supporting the use of intra-aortic counterpulsation therapy in a variety of clinical scenarios (Table 46-3).²⁴ Santa-Cruz and colleagues have recently performed a comprehensive survey of the literature and have formulated an outline of the current evidence-based indications for IABP counterpulsation therapy.³

Unstable Angina. Data are sparse regarding the use of IABP counterpulsation in patients having unstable angina. These data are mostly confined to small observational retrospective studies. Gold and colleagues studied 11 patients experiencing persistent angina despite aggressive medical therapy after an acute myocardial infarction (AMI); 9 of these patients exhibited symptomatic improvement following placement of an IABP.³⁷ Fuchs and colleagues examined 7 patients who had proximal LAD arterial stenoses exceeding 90% along with unstable angina.³⁸ The use of intra-aortic counterpulsation before intervention improved symptoms and enhanced coronary arterial blood flow (as assessed with a Doppler flow wire).³⁸ Despite the small sample sizes, these trials support the use of the IABP in patients with refractory angina until definitive therapy can be instituted. The ACC/AHA practice guidelines give a Class IIa indication for intra-aortic counterpulsation therapy in unstable angina patients, before or after cardiac catheterization, whose ischemic symptoms are not alleviated by aggressive medical therapy.³

Acute Myocardial Infarction. The use of IABP counterpulsation as an adjunct therapy and support device has been tested in the setting of thrombolytic therapy, primary percutaneous coronary intervention (PCI), and rescue PCI in patients having acute myocardial infarction (AMI). The benefits of the IABP in these settings are postulated to result from a multitude of factors: increased recovery of ischemic myocardium; decreased arterial

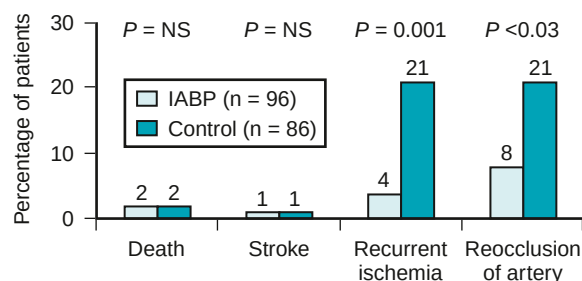


Figure 46-2. Clinical outcomes of patients with acute myocardial infarction randomly assigned to intra-aortic balloon pump (IABP) after percutaneous revascularization. (Data from Ohman EM, George BS, White CJ, et al; Randomized IABP Study Group: Use of aortic counterpulsation to improve sustained coronary artery patency during acute myocardial infarction: results of a randomized trial. *Circulation* 1994;90:792-799.)

reocclusion; enhanced lysis of thrombus within the coronary arterial lumen; and higher flow within the coronary arterial vasculature.^{39,40,41}

Two randomized trials have studied the clinical and hemodynamic effects stemming from intra-aortic counterpulsation therapy in the setting of AMI and PCI. Van't Hof and colleagues enrolled 284 high-risk AMI patients following the completion of primary PCI to either intra-aortic counterpulsation or to standard medical therapy. No difference was detected between the two treatment groups with respect to the primary end point of death, nonfatal MI, stroke, and LVEF. However, a weakness of this trial was the occurrence of a significant treatment arm crossover (25%).⁴² Ohman and colleagues conducted another randomized controlled trial in which 182 patients with AMI and subsequent emergent PCI (<24 hours) were divided into two treatment arms: prophylactic intra-aortic counterpulsation therapy for 48 hours versus standard medical therapy. Patients randomized to the counterpulsation therapy arm experienced less recurrent ischemia, fewer repeat emergency PCI procedures, and a significantly lesser rate of reocclusion of the infarct-related artery (8% versus 21%, $P < 0.03$) at median follow-up angiography 5 days afterward (Fig. 46-2). The composite end point of death, stroke, reinfarction, need for emergent revascularization, or recurrent ischemia was significantly lower in patients randomized to IABP (24% versus 13%, $P < 0.04$). Although there was a trend toward increased hemorrhagic complications, the overall bleeding complication rate in the intra-aortic counterpulsation therapy arm was still low (2%).⁴³

The TAMI trials prospectively evaluated a variety of therapeutic strategies following fibrinolytic therapy for AMI.³⁹ Multivariate analysis revealed that the primary predictors of infarct artery reocclusion were Thrombolysis In Myocardial Infarction (TIMI) flow grade, treatment with tPA, heart rate, and the anatomic location of the infarct.⁴⁴ The addition of IABP counterpulsation therapy to the multivariate logistic regression model indicated that this therapeutic strategy was associated with a significant decrement in arterial reocclusion ($P < 0.0003$).⁴⁵ However, use of the IABP was associated with significantly higher rates of bleeding and vascular complications.

The PAMI-2 trial data extend the benefit and safety of intra-aortic counterpulsation therapy to patients with AMI who underwent PCI.^{46,47} In this trial, 904 patients who were going to undergo PCI were classified into high- and low-risk cohorts.

This risk-stratification scheme was constructed using clinical and angiographic features. The high-risk cohort included patients with the following characteristics: age older than 70 years; LVEF less than 45%; presence of three-vessel coronary artery disease; suboptimal PCI result; vein graft occlusion; and occurrence of dysrhythmia. Patients in this high-risk cohort were then randomized to PCI with either IABP therapy or to standard medical therapy. The use of IABP was associated with fewer ischemic events, repeat interventions, reinfarctions, and a lesser number of episodes of decompensated heart failure. The vascular complication rates between the intra-aortic counterpulsation and standard medical therapy groups were 2.2% and 4.7%, respectively. The use of intra-aortic counterpulsation did not confer any observable benefit in the patients from the low-risk AMI cohort who received PCI.

A registry of 1490 patients with AMI who were then treated by primary PCI was analyzed by Brodie and colleagues.⁴⁸ In this observational study, a total of 105 patients had an IABP placed before PCI, whereas 108 patients had an IABP inserted following the completion of PCI. Although the former cohort of patients exhibited a higher prevalence of cardiogenic shock and multivessel CAD, they still had substantially higher procedural success and less adverse events (e.g., dysrhythmias and shock) during the PCI. In this observational study, the initiation of IABP counterpulsation therapy before PCI was an independent predictor of lower periprocedural complications.

The Benchmark Registry was the first large database to be formulated on patients receiving intra-aortic counterpulsation.³⁰ Of the 22,663 patients who were registered into this computerized database, 5495 (24%) had a diagnosis of AMI. An IABP was placed for the following indications: cardiogenic shock (27%), support of high-risk PCI (27%), preoperative support for high-risk cardiac surgery (11%), and refractory post-MI unstable angina (11%). Intra-aortic counterpulsation was associated with an average increase in mean arterial pressure postinsertion (87 mm Hg versus 82 mm Hg, $P < 0.001$), whereas no significant difference was observed with the heart rate (90 beats/min versus 89 beats/min, $P = 0.59$). Patients treated with an IABP in this registry constituted a high-risk population. The overall in-hospital mortality rate was 20%. However, the complication rate directly stemming from IABP placement was low; specifically, only three patients (0.05%) died from complications of device placement. Other complications cited in the Benchmark Registry included severe bleeding at the vascular access site (1.4%), major limb ischemia (0.5%), and limb amputation (0.1%).

Another analysis of the Benchmark Registry performed by Urban and colleagues revealed that patients who received IABP counterpulsation therapy in conjunction with surgical (19.2%) or percutaneous (18.8%) revascularization had a lower in-hospital mortality rate when compared with patients treated medically (32.5%).²⁶ Obviously, it is difficult to precisely quantitate how much of the mortality benefit in this analysis stemmed exclusively from intra-aortic counterpulsation therapy and not from the revascularization strategy. The primary reason for IABP insertion in these patients was cardiogenic shock. Moreover, the highest mortality was clustered in the first 3 days of hospitalization. Urban and colleagues recommend rapid risk-stratification and early use of IABP counterpulsation therapy in such patients.

Although only a few randomized trials exist; review of the previously cited studies consistently indicates that intra-aortic counterpulsation in the setting of AMI as an adjunctive measure

to percutaneous revascularization is associated with a decreased incidence of ischemic events along with vascular and hemorrhagic complications. The current ACC/AHA guidelines state a Class I indication for IABP counterpulsation therapy in the setting of AMI associated with the following sequelae: recurrent postinfarction angina, reinfarction, and the mechanical complications of AMI (specifically, interventricular septal rupture and acute mitral valvular insufficiency due to papillary muscle dysfunction or rupture).

Cardiogenic Shock

Cardiogenic shock occurs in 5% to 10% of patients who have AMI and is still associated with high mortality rates despite the availability of more aggressive interventional strategies.^{49,50} The 30-day mortality rate for the 0.8% of GUSTO I trial patients with cardiogenic shock treated with thrombolytic therapy was 58%.⁵¹ In the interventional era, the mortality rate of cardiogenic shock still remains substantially high with estimates ranging from 50% to 80%.^{52,53} Before the advent of the thrombolytic era, two small randomized trials of intra-aortic counterpulsation showed no benefit in the setting of cardiogenic shock.^{54,55} Since the advent of thrombolytic therapy, several observational series have supported the potential benefits of IABP counterpulsation therapy in the setting of AMI complicated by cardiogenic shock.⁵⁶⁻⁵⁸

In the Duke Cardiovascular Databank, 200 patients who had AMI complicated by cardiogenic shock were managed by an early aggressive strategy.⁵⁰ The in-hospital mortality of this cohort was 53%. Infarct-related artery patency, cardiac index, and peak creatine kinase enzyme levels were the most important variables in predicting in-hospital mortality. An IABP was placed in 99 patients within this cohort. The patients receiving intra-aortic counterpulsation had an in-hospital mortality rate of 48% whereas the patients not receiving an IABP had a mortality rate of 57% ($P = 0.23$). Based on subgroup analysis, a decrement in mortality rate was conferred when IABP counterpulsation therapy was used in conjunction with PCI compared with when intra-aortic counterpulsation was used alone (38% versus 63%, $P = 0.01$).

In the SHOCK trial, 302 patients having cardiogenic shock were randomized to receive initial emergent revascularization versus medical management. An IABP was placed in 86% of these patients. At a 6-month interval, the patients who had been randomized to the early intervention treatment arm exhibited a lower mortality rate when compared with those patients who were managed medically (50.3% versus 63.1%, $P = 0.027$). When compared to data from historical controls, both treatment arms in the SHOCK trial still exhibited lower overall mortality rates. This discrepancy may have arisen from intensive medical management and the increased usage of IABP counterpulsation therapy.⁵⁹ A retrospective analysis of the SHOCK trial revealed a trend toward a decreased mortality rate in the medical stabilization arm when patients were treated with fibrinolytic therapy and intra-aortic counterpulsation (41% versus 64%, $P = 0.07$).⁶⁰ Although intra-aortic counterpulsation does not substantially enhance blood flow distal to a critical coronary arterial stenosis, it does increase total blood flow to coronary vascular beds that are maximally dilated by ischemia; as a result, there is increased delivery of the fibrinolytic agent to the region of occlusive thrombus, thereby enhancing the overall thrombolytic effect.^{14,61-64}

In the GUSTO I trial, 7% of the patients ($n = 2972$) developed cardiogenic shock in the setting of ST segment elevation myocardial infarction. Intra-aortic counterpulsation was used in 734 of these patients and eventually showed a trend toward decreased mortality at a 30-day interval when the IABP was placed before or at the time of PCI versus when the device was placed late or not at all (47% versus 60%, $P = 0.06$).⁵¹

The International Shock Registry, the SHOCK Trial Registry, and the National Registry of Myocardial Infarction-2 (NRM-2) provide the largest and most contemporary clinical experience with patients in cardiogenic shock.³ In the International Shock Registry, 251 patients having cardiogenic shock were enrolled. The unadjusted mortality was lower in the 173 patients who received an IABP compared with those without this device (57% versus 72%, $P = 0.039$).⁵² In NRM-2, the largest registry to enroll patients with AMI ($n = 23,180$), 31% of the patients in cardiogenic shock received an IABP. When IABP usage was combined with a reperfusion strategy, especially thrombolytic therapy, a substantial mortality benefit was observed (49% versus 67%). However, when primary PCI was the sole reperfusion strategy, the overall mortality rate was lower and was not influenced by the use of intra-aortic counterpulsation (45% versus 47%). During a subgroup analysis of 12,730 patients from the NRM-2 registry, hospitals with a higher frequency of IABP usage showed a lower cardiogenic shock mortality rate when compared with hospitals with a lower frequency of device usage (50.6% versus 65.4%, $P < 0.001$). This finding was independent of other factors such as baseline patient characteristics, treatment strategy, and procedures performed (including PCI).⁶⁵ The hospitals with a higher volume of IABP usage may have had more expertise with the device, which eventually translated into better outcomes among the patients having cardiogenic shock.³

High-Risk Percutaneous Coronary Intervention

Patients with significant comorbidities and higher cardiac risk (poor LVEF, multivessel coronary artery disease, left main stenosis, hemodynamic instability) are also treated with percutaneous interventions in the current era as a result of refinements in catheterization technology and techniques.⁶⁶⁻⁶⁸ In this subset of patients, placement of an IABP before the intervention may be beneficial because of enhancement of coronary perfusion pressure and stabilization of hemodynamic parameters.

Small retrospective studies have reported the use of elective IABP counterpulsation support before high-risk PCI and have found good results with no major adverse events transpiring within 72 hours of the intervention.^{61,70,71} Briguori and colleagues reported on 133 consecutive patients who were undergoing high-risk PCI. The patients were divided between two groups: those with an elective preprocedural placement of an IABP and those with provisional (i.e., standby) usage of an IABP. Among patients with a low LVEF, the rate of major adverse cardiac events (acute myocardial infarction, shock, stroke, emergent CABG, or death) was 17% in the standby IABP group versus 0% in the group that received an elective preprocedural IABP ($P = 0.001$).⁷²

There is also evidence that supports the use of intra-aortic counterpulsation therapy before emergent CABG after coronary angiography. In these patients, the IABP improves

hemodynamic parameters and also contributes to resolution of ECG changes.^{73,74} One small study examined 32 patients who required emergent CABG following a failed PCI attempt. Preoperative ST segment elevation was observed in 21 patients; 15 of these patients were managed with intra-aortic counterpulsation. Although a statistically significant difference was not seen, a lower rate of postoperative myocardial infarction was observed in those managed with an IABP before CABG (20% versus 33%). Because of the absence of solid, incontrovertible evidence, the decision to use intra-aortic counterpulsation therapy preceding high-risk PCI should be based on a case by case evaluation by the clinician.^{3,37}

Cardiac Surgery

Intra-aortic counterpulsation therapy is recommended in the setting of left main disease detected after coronary angiography. However, the indication for its usage is less clear in patients with significant left main disease but with minimal or no symptomatology.⁷⁵ Increasing evidence corroborates the placement of a prophylactic IABP before CABG in patients possessing certain high-risk features: critical coronary arterial anatomy (including presence of left main disease), severe left ventricular dysfunction, or unstable angina.⁷⁶⁻⁷⁸

In a small prospective study, Christenson and colleagues randomized 60 consecutive high-risk patients who were going to receive CABG to either conservative management or to preoperative intra-aortic counterpulsation commencing 2, 12, or 24 hours before surgery. Most of these patients had left ventricular dysfunction, unstable angina, and/or left main stenosis. Although no mortality benefit was ultimately observed, patients who were randomized to preoperative intra-aortic counterpulsation of any duration did have significantly higher cardiac output levels, shorter intervals on mechanical ventilation, and shorter lengths of hospitalization.⁷⁷

Off-pump coronary arterial bypass grafting is another setting where IABP counterpulsation may be a valuable modality.^{3,79} In a retrospective study, Suzuki and colleagues examined 32 high-risk patients with preoperative intra-aortic counterpulsation compared with 101 moderate- to low-risk patients without intra-aortic counterpulsation scheduled for off-pump bypass surgery. Although patients treated with preoperative intra-aortic counterpulsation had substantially higher frequencies of left main trunk disease and emergent surgeries, outcomes were similar in both groups. The authors surmised that the insertion of the IABP had improved the intraoperative hemodynamic state of the patients, thereby stabilizing their postoperative course. In the end, the high-risk patients experienced a similar mortality rate when compared with the low- to moderate-risk cohort.⁸⁰

Transplantation and Dysrhythmias

In patients with severe end-stage cardiomyopathy who are being prepared for cardiac allograft transplantation, intra-aortic counterpulsation can be used as a bridging modality. Some case series have reported successful bridging via intra-aortic counterpulsation in both the critical care and the ambulatory settings.⁸¹ However, some of the pretransplant patients are now more successfully bridged via left ventricular assist devices. Hemodynamic support following transplant rejection could be accomplished via intra-aortic counterpulsation therapy.

Arafa and colleagues reviewed a series of patients experiencing postcardiac transplant allograft rejection requiring mechanical circulatory support. An IABP was inserted in five patients who exhibited predominantly right ventricular failure. After 12 hours, significant improvements in pulmonary vascular resistance (4.6 wood units versus 1.8 Wood units, $P < 0.05$), mean arterial pressure (53 mm Hg versus 74 mm Hg, $P < 0.05$), and a trend toward enhanced cardiac output were demonstrated. The use of intra-aortic counterpulsation to unload the left ventricle and to increase perfusion of the right ventricle could possibly improve outcomes in such patients.^{3,82}

Severe malignant ventricular tachyarrhythmias can be associated with an uncorrected ischemic substrate. In the literature, several anecdotal reports have described cessation of ventricular tachycardia and fibrillation following the initiation of intra-aortic counterpulsation therapy.²¹ The current ACC/AHA guidelines have given a Class IIa recommendation to the use of IABP counterpulsation therapy for treating malignant dysrhythmias that are perpetuated by underlying myocardial ischemia and are refractory to medical therapy.

Conclusion

IABP has emerged as an effective and widely used mechanical circulatory assist device. Based on the dual physiologic concept of diastolic augmentation and systolic afterload reduction, intra-aortic counterpulsation has become an important strategy to salvage the function of an ischemic and failing left ventricle. The development of a percutaneous approach to insertion has enhanced the speed and the ease with which this device can be placed in patients experiencing hemodynamic decompensation from an acute cardiovascular event. Moreover, refinements in device technology have decreased the complications associated with the IABP. As a result of this improved risk-benefit profile, the IABP has become a prevalent modality in the current cardiac intensive care setting.

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APPENDIX A

Insertion and Removal of the Intra-Aortic Balloon Pump

The following steps are involved during insertion of an IABP:

1. An initial physical examination focusing on peripheral vasculature should be conducted including palpation and demarcation of the femoral, popliteal, dorsalis pedis, and posterior tibial pulses and auscultation for femoral and abdominal bruits.
2. The side with the better arterial pulsations should be selected for insertion.
3. The inguinal region should be inspected for landmarks and the femoral artery should be identified.
4. The inguinal region should be prepared and draped in a sterile fashion.
5. Following administration of a local anesthetic agent, a skin incision is made 2 to 3 cm below the inguinal ligament.
6. Using a modified Seldinger technique, the femoral artery is cannulated with a needle and a J-tipped guidewire is then advanced through the needle after brisk flow of arterial blood is confirmed.
7. The guidewire should be advanced to the level of the descending aorta under fluoroscopic guidance.
8. A dilator is inserted and removed until an arterial sheath can be safely placed.
9. The intra-aortic balloon is passed over the guidewire to a position just distal to the origin of the left subclavian artery.
10. The guidewire is subsequently removed and the catheter lumen is aspirated to remove any residual air or thrombus.
11. The intra-aortic balloon is connected to the drive system console and counterpulsation can subsequently begin.
12. The hemodynamic tracing should be inspected for proper timing.
13. A chest radiograph should be obtained to document correct positioning.
14. The intra-aortic balloon catheter and femoral sheath should be secured with sutures.

Removal of an IABP:

1. Anticoagulation should be stopped; confirm that the activated clotting time (ACT) is less than 180 seconds or the activated partial thromboplastin time (aPTT) is less than 40 seconds.
2. Conscious patients should receive a low dose narcotic and/or analgesic agent.
3. The securing sutures are cut.
4. The drive system console is turned off.
5. The intra-aortic balloon is completely deflated by aspiration with a 20-mL syringe attached to the balloon inflation port.
6. The sheath and intra-aortic balloon catheter are pulled as one unit.
7. Blood is allowed to flow from the arterial access site for a few seconds to remove any thrombi.
8. Manual pressure is applied above the puncture site for 30 minutes or longer if hemostasis is not obtained; a mechanical compression device can also be used to help apply pressure to promote hemostasis.
9. Distal arterial pulsations are palpated.
10. The patient should remain recumbent for a minimum of 6 hours to prevent any subsequent hemorrhage or vascular complications at the arterial access site.

Ventricular Assist Device Therapy in Advanced Heart Failure—State of the Art

Gabriel Sayer, Yoshifumi Naka, Ulrich P. Jorde

CHAPTER 47

Background
LVAD as Bridge to Transplantation
LVADs as Destination Therapy
Axial Flow Pumps

Future Directions
Bridge to Recovery
Conclusion

THE BURDEN of congestive heart failure (CHF) continues to grow, with more than 500,000 new cases annually. Fortunately, increased understanding of the disease process, and advances in pharmacologic and pacemaker-based therapies have led to significant improvements in survival for patients with CHF over the past 2 decades.¹ For example, 1-year mortality in subjects with NYHA class IV CHF participating in clinical trials investigating ACE-inhibitors, β -blockers and aldosterone antagonists has decreased from approximately 50% in 1986 to less than 15% in 2002.²⁻⁴ However, many patients with advanced CHF continue to have significant symptoms despite these interventions. For these patients, prognosis remains very poor with 1-year mortality rates approaching 75%.⁵

When CHF is refractory to medical therapy, and in appropriate candidates, cardiac transplantation is the most effective treatment modality. Refinement in techniques and immunosuppressive regimens has produced 1-year survival rates of approximately 90%.^{6,7} However, the number of transplants performed annually in the United States has plateaued at 2200 because of a limited number of donor organs (Fig. 47-1), and many patients die while waiting for a transplant.⁸

In the last 15 years, left ventricular assist devices (LVADs) have emerged as a method to prolong the survival of these patients as they wait for a suitable donor heart. By mechanically unloading the failing heart and improving systemic end-organ perfusion, LVADs can reverse the systemic abnormalities seen in advanced CHF, improving survival and quality of life. Advances in design and clinical experience have significantly reduced the morbidity and mortality associated with LVADs, and have led to the continual spread of this technology.⁹ Further advances are currently under evaluation and promise to make LVADs available to a greater number of patients. Importantly, use of LVADs is no longer limited to subjects waiting for heart transplants, but is now approved to treat end-stage heart failure refractory to medical therapy in patients not suitable for transplantation because of age and/or comorbidities. This review discusses the evolution of LVAD devices, the current uses of this therapy, and its potential future applications.

Background

Mechanical circulatory support devices were initially developed in the 1960s as a means to assist patients who could not be weaned from cardiopulmonary bypass following cardiac

surgery. Dr. Michael E. DeBakey implanted the first device in 1963 to treat cardiogenic shock following aortic valve surgery. Although the patient did not survive to hospital discharge, this operation proved the feasibility of mechanical circulatory assistance.¹⁰ Through the 1960s and 1970s, researchers developed several devices for investigational use. These “early” LVADs caused significant hemolysis and had high rates of bleeding and infection because of their size and extracorporeal location. Furthermore, patients with otherwise good clinical recovery remained significantly limited in their mobility because of the large power consoles (Fig. 47-2).

Limitations of the early devices, however, provided the impetus for development of an intracorporeal LVAD powered from an external source through a percutaneous driveline. Situating the pump inside the body provided patients with greater independence, allowed discharge from the hospital, and substantially improved quality of life. In addition, outpatient LVAD management led to significant cost savings over prolonged inpatient stays.¹¹ Consequently, the Heartmate 1000 IP (Thoratec Corp., Pleasanton, Calif.) received FDA approval as a bridge-to-transplantation device in 1994. The power console of this pneumatic LVAD was smaller than that of earlier pumps, but its size remained a significant limitation. Further research produced an electric power source connected to a wearable battery pack. An LVAD using this technology, the Heartmate Vented Electric (VE) (Thoratec Corp.), was approved by the FDA in 1998 (Fig. 47-3).

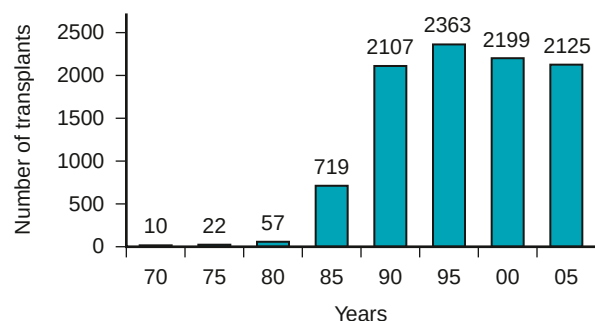


Figure 47-1. Number of heart transplants performed annually in the United States, 1970-2005.

LVAD as Bridge to Transplantation

Currently, there are two LVADs approved for bridge to transplantation: the Heartmate I and the Novacor (World Heart Corp., Ottawa, Ontario, Canada). Both are surgically implanted in a pocket in the abdominal wall (see Fig. 47-3). An inflow conduit is attached to the left ventricular apex and an outflow conduit is anastomosed to the ascending aorta. Bioprosthetic valves ensure unidirectional blood flow. The blood is expelled by electromagnetically powered pusher plates that contract a polyurethane diaphragm and provide pulsatile flow to the aorta. The devices can pump blood at rates up to 10 L/min. Each device is connected to a wearable battery pack through a percutaneous line that also houses the venting system.

In patients refractory to medical therapy, LVAD support leads to improved renal function, right heart function, and overall physical conditioning.^{11,12} Multiple studies have shown that LVADs can be successfully used as a bridge to transplantation,¹³⁻¹⁶ with one prospective series showing an increase in survival to transplant from 33% to 71% with use of the Heartmate LVAD (when compared with historical controls managed

with medical therapy alone).¹⁵ By implanting an LVAD in these patients, surgeons reduce their subsequent operative risk for transplantation, making them better transplant candidates and improving their posttransplant outcomes.^{15,16}

Although most commonly implanted into patients with symptoms of Class IV CHF that are refractory to medical therapy, intracorporeal LVADs have also been used for the treatment of post-cardiotomy shock, myocardial infarction complicated by cardiogenic shock, myocarditis, and primary graft failure following cardiac transplantation.¹⁷⁻²⁰ The following criteria should generally be met before consideration of LVAD implant: clinical evidence of impaired end-organ perfusion with cardiac index less than 2 L/min/m², pulmonary capillary wedge pressure greater than 20 mm Hg, and systolic blood pressure less than 80 mm Hg despite maximal medical support including inotropes and an intra-aortic balloon pump if indicated.²¹ Although it is important to meet these criteria, LVAD implantation needs to be performed before extensive end-organ damage for maximal chance of success.

Adverse Events

Table 47-1 shows the most commonly encountered adverse events in patients who receive LVADs as a bridge to transplant. Different complications are seen in the early period following LVAD implantation and the later period following prolonged use.

The two major *perioperative* complications are bleeding and right ventricular (RV) failure. Bleeding causes significant morbidity and mortality, and often requires exploration of the surgical site. The degree of RV failure is difficult to predict before LVAD implantation, although the presence of elevated central venous pressure (CVP), high pulmonary vascular resistance, and significant RV dilation raise concern that additional RV support may be required postoperatively. The importance of the RV in the management of LVAD patients cannot be underestimated. With a functioning LVAD in place, cardiac output is dependent on the ability of the RV to provide sufficient preload to the left side of the heart. Postsurgical RV dysfunction can compound underlying contractile weakness and cause right heart failure, which is correlated with worse outcomes.²² Treatment consists

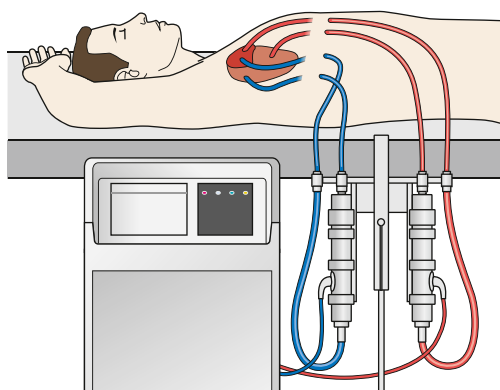


Figure 47-2. ABIOMED BVS 5000 extracorporeal ventricular assist device.

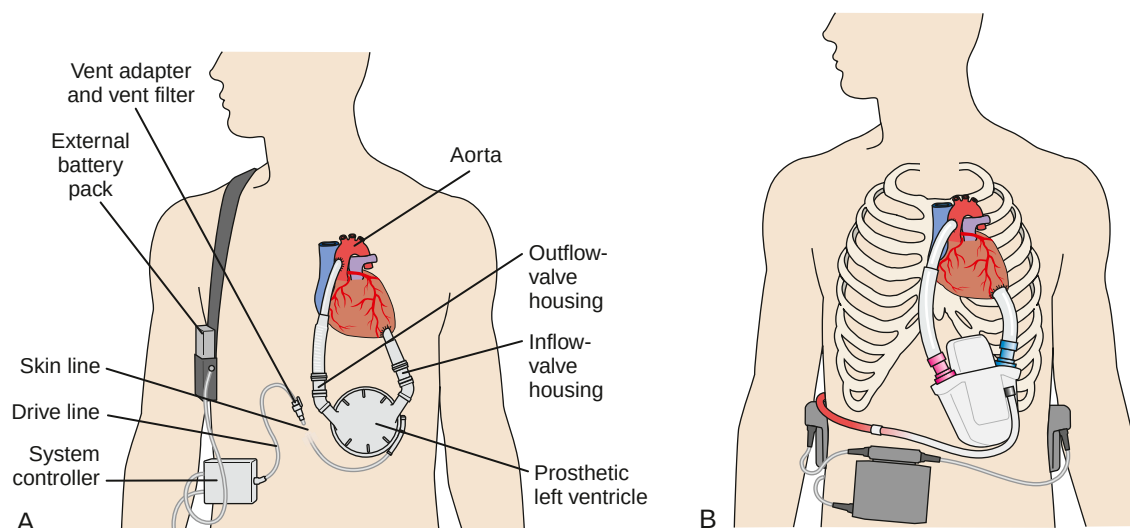


Figure 47-3. Intracorporeal left ventricular assist devices. **A**, Heartmate VE left ventricular assist system. **B**, Novacor left ventricular assist system.

Table 47–1. Adverse Events in Patients with the Heartmate VE When Used as a Bridge-to-Transplantation

Event	Frequency
Bleeding	48%
Infection	48%-55%
Neurologic event	10%-27%
RV failure	7%-11%
Thromboembolism	12%
Device failure	12.8%

Adapted from references 6, 15, and 25.

of pharmacologic augmentation of RV contractility and reduction of pulmonary vascular resistance (see “Management of Acute Complications” later). Occasionally, refractory RV failure dictates placement of a right ventricular assist device (RVAD).

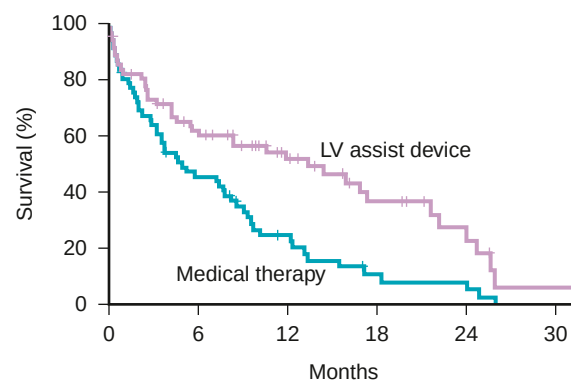
With *intermediate and long-term use*, the most common complication is infection, occurring in up to 55% of patients.²³⁻²⁵ The relative immunosuppression of critical illness and the presence of large amounts of foreign material leaves LVAD patients particularly susceptible to infectious complications. Infections can occur in the device pocket or surrounding surgical area, along the percutaneous drive lines and inside the device itself. Prevention efforts, including enhanced prophylactic antibiotic regimens, new surgical techniques, improved drive line design, and attention to drive line management are critical in reducing the overall infection rate.²⁶

With prolonged use, device failure can occur. Most commonly, this is due to deterioration of the device inflow valves and resultant regurgitation. Bearings attached to the motor are also subject to decay because of the repetitive wearing motion of the pump. Additionally, the electrical system can malfunction, causing abrupt cessation of LVAD function. These complications are medical emergencies, and often necessitate explantation or replacement of the device.

The risk of thromboembolism and neurologic events has been significantly reduced through the introduction of the Heartmate LVAD. The Heartmate I has a unique, textured design that promotes the formation of an endothelial layer on its blood-contacting surfaces. This “natural” surface has low thrombogenicity, and the Heartmate therefore does not require systemic anticoagulation.²⁷ With other devices, thrombotic complications remain prevalent and necessitate anticoagulation.

LVADs as Destination Therapy

As patients with LVADs survived for longer periods of time before transplantation, the concept of using LVADs as “destination therapy” arose. In the late 1990s, researchers conducted the REMATCH study, a randomized, controlled, clinical trial of LVADs compared with optimal medical management.⁵ One hundred and twenty-nine subjects with NYHA Class IV CHF who were not candidates for transplantation were followed for 2 years. The results showed a 48% reduction in the risk of all-cause mortality at 2 years with LVAD therapy. In the LVAD group, the primary causes of mortality were sepsis and device failure, whereas in the medical management cohort, almost all patients died from progressive heart failure. REMATCH must



No. at risk

LV assist device 68 38 22 11 5 1
Medical therapy 61 27 11 4 3 0

Figure 47-4. Kaplan-Meier survival curves from the REMATCH trial with superimposed survival curves for cardiac transplantation. LV, left ventricular.

be considered a seminal study because it conclusively demonstrated that subjects in the most advanced stages of CHF (nearly all of them inotrope-dependent) can survive a major cardiac operation and that the small increase in short-term mortality because of perioperative deaths is significantly outweighed by the long-term benefits of device therapy. Indeed, patients in this cohort who were on inotropic therapy at randomization derived the largest benefit.²⁸ In addition to reduced mortality, patients with LVADs spent fewer days in the hospital and had a higher quality of life. Following the publication of REMATCH, the Heartmate LVAD received FDA approval for use as destination therapy in 2002. As with bridge to transplantation, employment of destination therapy early in the clinical course is recommended as high-risk patients have significantly worse survival than low-risk patients.²⁹

Despite the superiority of LVADs to medical therapy for this group of patients (Fig. 47-4), the absolute mortality rate for LVAD patients in REMATCH was still 48% at 1 year and 75% at 2 years. These statistics indicate the severity of illness in the REMATCH cohort and emphasize the need for further improvements in pump design and management. Since REMATCH, further clinical experience with destination therapy has produced lower complication rates and 2-year mortality in REMATCH type patients has been reduced to 60% at experienced centers.²⁶

Axial Flow Pumps

The LVADs currently in use have several significant drawbacks. Their size is a source of patient discomfort, and implantation requires a large operation, increasing the risk of both bleeding and infection. The pump is noisy and subject to failure because of the presence of wearing mechanical parts. Valves inside the pump decay over time. The percutaneous drive lines remain major sources of infection. Each of these problems has spurred the development of new devices designed to overcome the limitations of the first-generation LVADs. An ideal device would be small, quiet, totally implantable, and durable.

With respect to pump design, it is important to recognize that as blood moves through the systemic circulation, the initial pulsatile flow in the aorta is progressively dampened,

transforming into continuous flow at the level of the capillary (Fig. 47-5). Thus, pulsatile flow may not be necessary for humans. An understanding of this particular aspect of circulatory physiology fueled the development of axial flow pumps.³⁰ These LVADs propel blood forward in a continuous fashion with a rotary impeller (Fig. 47-6). With this design, the device has only one moving part and does not require valves, reducing the long-term risk of mechanical failure. Axial flow pumps are also smaller and lighter than the first-generation LVADs, and they function in virtual silence. Early concerns about the adverse effects of continuous flow on end-organs have been alleviated with successful long-term use of these devices.³¹

Three axial-flow devices are in advanced stages of clinical testing (Fig. 47-7): the Thoratec Heartmate II (Thoratec Corp.), the MicroMed-DeBakey VAD (MicroMed Cardiovascular, Inc., Houston) and the Jarvik 2000 (Jarvik Heart, Inc., New York). Early clinical data suggest that the axial flow devices have comparable success in bridge to transplantation as pulsatile flow devices.³²⁻³⁴ Because of their small size, the axial flow devices have fewer perioperative complications, with less bleeding and a shorter duration of intensive care.^{34,35} By nature of their small size, these devices eliminate the infections associated with a large abdominal pocket and also reduce the incidence of drive line infections.^{35,36} Mechanical failure is less frequent as well.³⁷ On the other hand, thromboembolism has been a significant issue and all axial flow pumps require systemic anticoagulation.^{37,38} An ongoing clinical trial will provide the first head-to-head comparison of pulsatile (Heartmate I) and axial flow (Heartmate II) pumps as destination therapy (see Figs. 47-3 and 47-7).

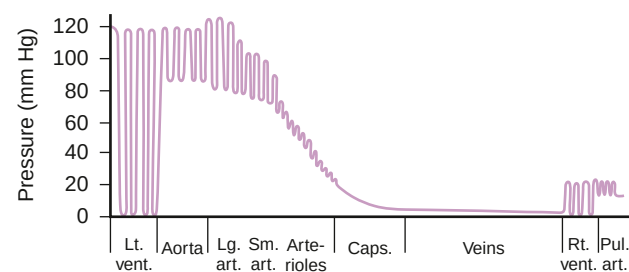


Figure 47-5. Pressure and volume distribution in the systemic circulation.

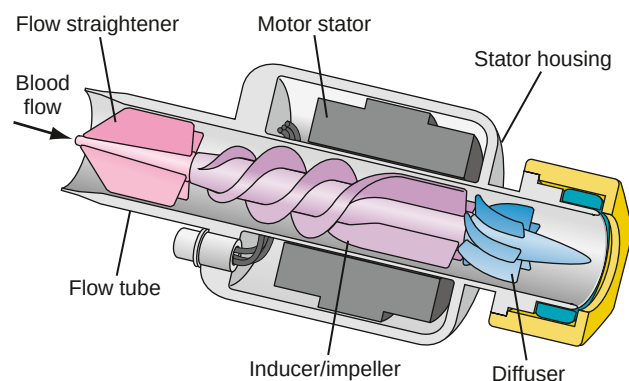


Figure 47-6. Interior of the MicroMed-DeBakey axial flow left ventricular assist device.

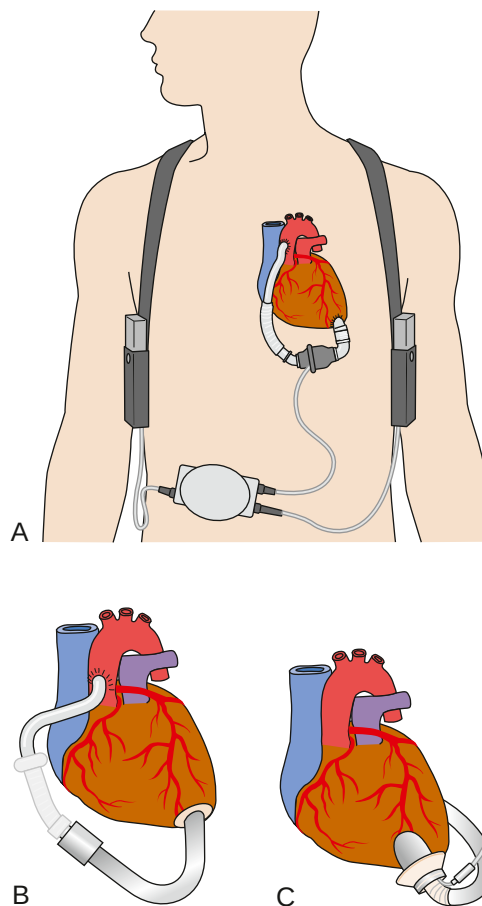


Figure 47-7. Axial flow ventricular assist devices. **A**, Thoratec Heartmate II. **B**, MicroMed-DeBakey ventricular assist device. **C**, Jarvik 2000.

Future Directions

With the advent of the continuous flow pumps and improved operative experience, the risk associated with LVAD implantation has decreased substantially. The Jarvik 2000 allows placement through a lateral thoracotomy rather than the traditional median sternotomy, allowing the surgery to be performed without cardiopulmonary bypass and substantially reducing recovery time. As more advances such as this are incorporated into the design of subsequent devices, we believe that LVAD implantation will increasingly be used earlier in the clinical course, in the same way that valve surgery is most therapeutic when performed at the beginning, not end, of a downward spiral. Further refinements may ultimately allow these devices to be used to improve the quality of life for patients with earlier stages of heart failure.

The two primary obstacles left to conquer are drive line infections and the risk of thromboembolism with the continuous flow pumps. A transcutaneous energy transfer system that would replace the percutaneous drive line is in the early stages of clinical testing. Increasing clinical experience with the anticoagulation regimens needed in continuous flow pump recipients should prove successful at reducing the thromboembolic complications. Finally, third-generation devices are entering the clinical trial phase of development. These pumps feature electromagnetically levitated motors that would eliminate the need for bearings, and thus reduce the risk of device failure.

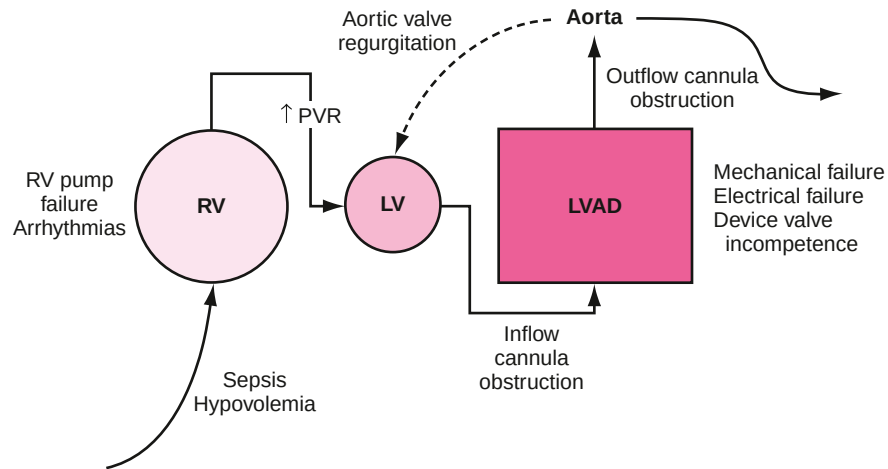


Figure 47-8. Cardiac pathophysiology after left ventricular assist device (LVAD) implantation. Red lettering and lines indicate causes of poor cardiac output and systemic hypoperfusion. LV, left ventricle; PVR, pulmonary vascular resistance; RV, right ventricle.

Management of Acute Complications

Figure 47-8 shows cardiac physiology following LVAD implantation, and identifies causes of decreased cardiac output, which can be divided into three general categories:

1. Decreased pump preload
2. Increased pump afterload
3. Intrinsic pump malfunction

Decreased Preload: Reduced filling of the LVAD chamber can be device-related (inflow cannula obstruction, usually in the early postoperative period and secondary to malpositioning against the ventricular septum) or patient-related. RV failure will be the most common cause of low pump flows. Hypovolemia from any cause also has decreased preload and can worsen underlying RV dysfunction.

Increased Afterload: An inability to fully empty the LVAD chamber can occur with obstruction of the outflow cannula by mechanical kinks and infections. Injection of radio-paque dye may be used to identify the source of the problem, and LVAD replacement is the primary solution to outflow cannula obstruction. Systemic hypertension can also prevent complete emptying of the LVAD chamber and afterload reduction is crucial to maintaining adequate LVAD blood flow.

Pump Malfunction: Disruption of the LVAD's motor or electrical system is usually evident to both the patient and physician. Pulsatile-flow LVADs can be attached to a pneumatic hand pump and manually operated until the source of the problem can be found. This option is not available for axial flow pumps. Replacement of the battery pack is often sufficient to repair electrical failures. Worn bearings or a malfunctioning motor require replacement of the entire LVAD.

Right heart catheterization can differentiate causes of low pump output (Table 47-2). Low central venous pressure (CVP) and low pulmonary capillary wedge pressure (PCWP) indicate hypovolemia. A finding of elevated CVP with a low PCWP is most likely because of RV dysfunction. Elevated CVP and PCWP are seen with inflow cannula obstruction, pump malfunction, and outflow cannula obstruction. Echocardiography can pinpoint the source of the problem.

Hypotension or poor systemic perfusion can also be seen in the setting of normal or elevated pump flows. Vasodilation due to sepsis is the most likely cause in these situations and

Table 47-2. Differentiation of the Etiology of Hypotension in the LVAD Patient Using Intracardiac Pressure Measurements

	CVP	PCWP	LVAD Output	Cardiac Output
Hypovolemia	↓	↓	↓	↓
Sepsis	↓	↓	↑	↑
RV failure	↑	↓	↓	↓
Pump failure or cannula obstruction	↑	↑	↓	↓
Valvular regurgitation	↑	↑	↑	↓

Abbreviations: (CVP), Central venous pressure; (PCWP), pulmonary capillary wedge pressure; (LVAD), Left ventricular assist device; (SG), Swan-Ganz catheter; (RV), Right ventricular.

an infectious source should be sought aggressively. Infections within the pump itself often necessitate explantation of the device. In the absence of infection, the patient with hypoperfusion and preserved device flow should be evaluated for valvular incompetence. If the cardiac output obtained from the Swan-Ganz catheter is low and the cardiac output reported by the pump is high, the most likely cause is regurgitation through either the native aortic valve or one of the valves within the LVAD. Echocardiography can localize the culprit valve.

Bridge to Recovery

The ability of LVADs to support an acutely failing heart while it recovers function is well documented.^{17,18} However, observations have also noted the potential for myocardial recovery in patients with chronic heart failure. In many patients with LVAD support, the size of the left ventricle (LV) decreases,³⁹ the myocardial pressure-volume relationship normalizes,⁴⁰ and the LV function improves.⁴¹ The exercise capacity of patients with LVADs improves dramatically.⁴² At the cellular level, there is a regression of myocyte hypertrophy,⁴³ a downregulation of

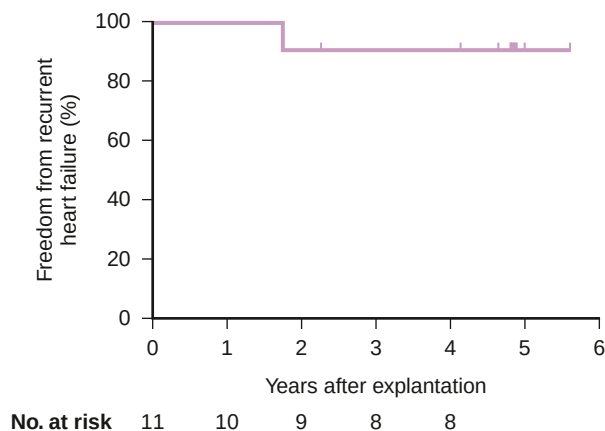


Figure 47-9. Long-term freedom from recurrent heart failure after treatment with the Harefield protocol and left ventricular assist device explantation.

cytokines that are elevated in CHF,⁴⁴ and an upregulation of β -adrenergic receptors.⁴⁵

These findings encouraged the explantation of LVADs in select patients who had demonstrated sufficient recovery of myocardial function. Recovery is less likely in patients with ischemic cardiomyopathy, and most data have shown that few patients achieve enough recovery of function to allow explantation.^{46,47} Recurrence of heart failure is common following removal of the LVAD.⁴⁸ Recently, physicians in Harefield, England have reported provocative findings using high-dose neurohormonal blockade and clenbuterol, a β_2 -adrenergic receptor agonist, to promote myocardial recovery in LVAD patients. With this protocol, 73% of patients were explanted, and 73% of these patients demonstrated sustained recovery over 4 years (Fig. 47-9).⁴⁹ A multicenter trial is ongoing in the United States to confirm these results.

Conclusion

Ventricular assist device therapy has made tremendous progress since the first devices were tested in the 1960s. The success of the LVAD as a bridge to transplantation and as destination therapy provides cardiologists and cardiothoracic surgeons with a new tool for the management of advanced heart failure. The current devices offer significant benefits to patients' quality and quantity of life. With continued device improvement and clinical experience, LVADs may not only become a viable alternative to transplantation, but may be used to improve the quality of life of patients in earlier stages of advanced CHF. The application of the LVAD as a bridge to recovery is an exciting development with significant potential to alter physicians' approach to the management of congestive heart failure.

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Cardiac Transplantation

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CHAPTER 48

Stage D Identification and Candidate Selection Criteria Pretransplant Patient Management

Posttransplantation Management in the Critical Care Setting Future Directions

DESPITE NUMEROUS advances, heart failure remains a leading cause of morbidity and mortality in the United States. Roughly 5 million Americans are presently afflicted with heart failure, and each year approximately 550,000 new cases are identified.¹ Considerable effort, expense, and resources continue to be dedicated to improvements in heart failure prevention and treatment.

Cardiac transplantation remains the most effective treatment for selected patients with end-stage heart failure. Once transplanted, survival is routine, as shown in Figure 48-1.² Most infections and rejection episodes are either preventable or treatable. Furthermore, advances in mechanical circulatory support have expanded the candidate pool, enabling additional critically ill heart failure patients to undergo successful heart transplantation.

In recent years, however, the number of cardiac transplants performed has declined to approximately 2000 per year in the United States and 3000 per year worldwide. Transplant candidates now generally wait longer before transplantation than in earlier eras, in many cases waiting a year or longer. The increased waiting times have precipitated a rise in the number of patients who deteriorate and therefore require hospitalization or mechanical circulatory support before transplantation.² Because heart transplantation depends on a limited supply of donor hearts, individuals listed as candidates for transplantation should be those who are most likely to benefit.

Those involved in cardiac intensive care need a sound understanding of issues surrounding cardiac transplantation. In addition to being expert at managing acute decompensated heart failure, cardiac intensivists must be able to: (1) determine which patients have stage D heart failure; (2) determine which stage D heart failure patients are potentially suitable heart transplant candidates; (3) manage critically ill transplant candidates, escalating therapies from intravenous diuretics, to intravenous inotropes and vasodilators, and finally to mechanical circulatory support, as required; (4) manage or assist in managing recipients immediately following heart transplantation; and (5) evaluate and manage longer-term posttransplant complications that necessitate cardiac intensive care. Moreover, a strong collaborative approach with a transplant cardiologist is vital for overall patient care. Specifically, pretransplant evaluation and care, early identification of patients having posttransplant comorbidities, including hemodynamically compromising cardiac allograft

rejection, atypical infections, immunosuppressive therapy and its potential adverse effects, among others, must be seamlessly coordinated.³

Stage D Identification and Candidate Selection Criteria

Stage D heart failure patients have end-stage disease and a short life expectancy, typically only 50% at 1 to 2 years. Medications that previously were beneficial are no longer well tolerated and hospitalizations are frequent. As shown in Figure 48-2, therapeutic options are limited to end-of-life strategies, transplantation, or support with a left ventricular assist device intended as permanent or “destination” therapy.^{3,4}

Once a stage D heart failure patient is identified, transplant candidacy should be determined. Careful candidate selection

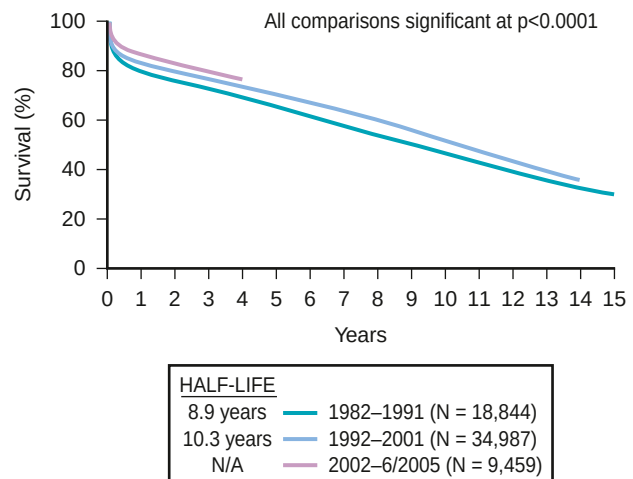


Figure 48-1. Kaplan-Meier survival for adult heart transplants performed between January 1982–June 2005. Recipient survival improves with each successive 5- to 10-year era; however, the major gains in survival are limited to the first 6 to 12 months, with the long-term attrition rate being unchanged. (Adapted from Taylor DO, Edwards LB, Boucek MM, et al: Registry of the International Society for Heart and Lung Transplantation: Twenty-fourth Official Adult Heart Transplant Report—2007. *J Heart Lung Transplant* 2007;26:773.)

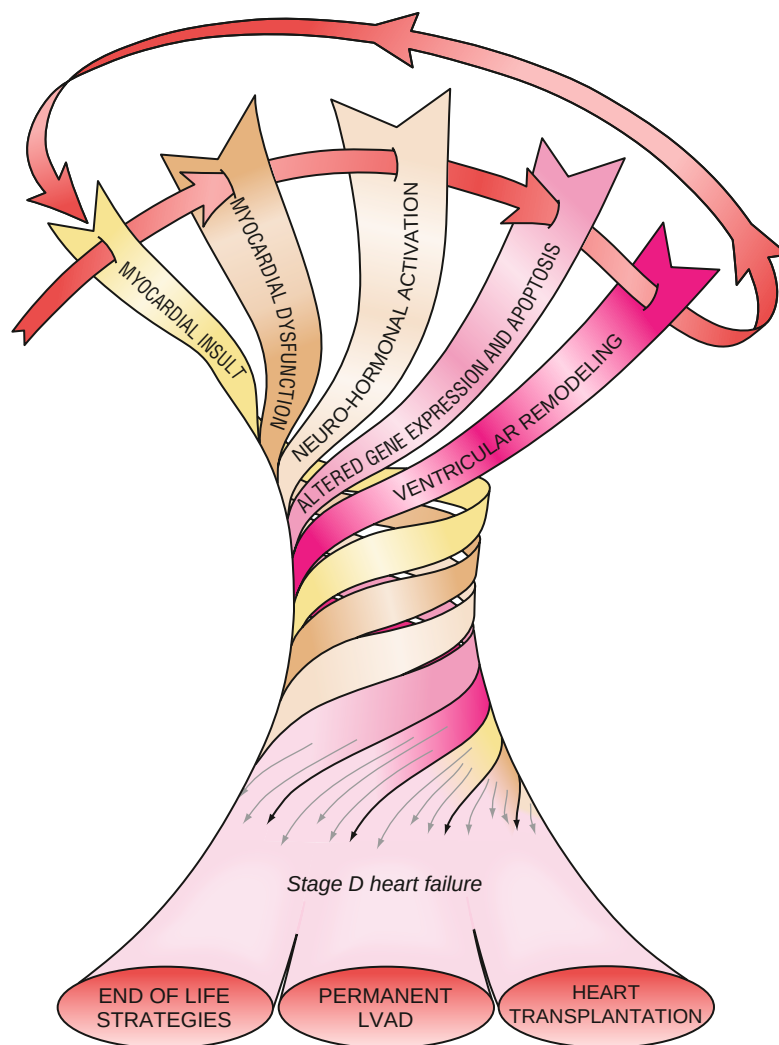


Figure 48-2. Pathophysiologic mechanisms in heart failure and treatment options for end-stage disease. An insult such as a myocardial infarction or a viral infection initiates the decline toward symptomatic heart failure, stage C (current or past symptoms associated with structural heart disease) and stage D (refractory, end-stage disease). Repetitive and iterative pathophysiologic derangements occur, as depicted schematically here. The sequence of events is myocardial insult → myocardial dysfunction → neurohormonal activation → altered gene expression and apoptosis → adverse remodeling → further myocardial dysfunction. Many stage D patients become poorly tolerant of previously beneficial drugs. End-of-life strategies, permanent or destination left ventricular assist device (LVAD) support, or heart transplantation is required.

rations the limited supply of donor hearts to patients most likely to benefit from transplantation. The question, “Is this patient a suitable heart transplant candidate?” must therefore be asked and answered. The evaluation is comprehensive, including the elements outlined in Table 48-1. However, a thorough evaluation is either unnecessary or could be delayed, if indications are not met (Table 48-2) or if risks are inordinately high (Table 48-3). A history of severe heart failure or suboptimally treated heart failure is, per se, an insufficient indication for heart transplantation. These patients may actually still have stage C heart failure.³

Specific selection criteria vary among transplant centers, but several general patient characteristics and factors are common among the majority of programs. Table 48-2 lists the indications generally used when a patient is considered for cardiac transplantation. Left ventricular function parallels the prognosis in severe cardiac failure. Survival dwindles as objective measures of left ventricular function decline. However, a low left ventricular ejection fraction alone is an inadequate indication for heart transplantation. Additional objective evidence of severe cardiac impairment is needed. For example, objective determinations of exercise capacity and oxygen consumption have proven useful in determining the degree of cardiac dysfunction and

prognosis.^{5,6} A peak oxygen consumption ($\dot{V}O_2$) of ≤ 14 mL/min/kg or ≤ 12 mL/min/kg in patients on β -adrenergic receptor antagonists⁷ indicates a degree of cardiac dysfunction sufficient to warrant consideration for transplantation. Alternatively, a peak $\dot{V}O_2$ of less than 50% of predicted for age and gender can prompt consideration for cardiac transplantation evaluation.⁶ Serial measurements provide a way to gauge the effectiveness of current therapies and the progression of disease during the waiting period. It is recommended that peak $\dot{V}O_2$ values be adjusted for patient age, gender, and weight.

Subjective measures also influence the decision to proceed with cardiac transplantation as part of the management of chronic heart failure. An unsatisfactory quality of life and intolerable symptoms of cardiac disease despite maximal medical therapy are key factors to consider. Although refractory heart failure is the principal reason by far for considering cardiac transplantation, numerous other cardiac disease entities also have been proposed as bases for transplantation, as shown in Table 48-2. Whatever the cause underlying the cardiac impairment, a predicted survival of 50% at 1 to 2 years without cardiac transplantation warrants proceeding with transplant evaluation and placement on the waiting list while conventional therapies are continued.

Table 48–1. Evaluation of Potential Cardiac Transplant Candidates

Detailed medical history and thorough physical examination
Laboratory evaluation:
CBC
Renal function tests (BUN/creatinine, creatinine clearance, GFR)
Liver function tests (alkaline phosphatase, bilirubin, albumin, transaminases)
Coagulation (prothrombin time, partial thromboplastin time)
Urinalysis
ABO blood type and antibody screen
Serologies for hepatitis A, B, C; HIV; cytomegalovirus; Epstein-Barr virus; herpes simplex virus I, II; <i>Toxoplasma gondii</i> ; syphilis; skin test for tuberculosis with controls
Right heart catheterization
Left heart catheterization/coronary angiography (if indicated)
Echocardiogram (or other form of ventriculography, if indicated)
ECG and/chest x-ray
Carotid ultrasound (if indicated)
Pulmonary function tests
Exercise testing with measured oxygen consumption $\dot{V}O_2$
Histocompatibility leukocyte antigen (HLA) typing/panel reactive antibody (PRA)
Psychosocial/financial consultation

CBC, complete blood count; BUN, blood urea nitrogen; GFR, glomerular filtration rate; HIV, Human immunodeficiency virus; ECG, electrocardiogram.

Table 48–2. Indications for Heart Transplantation

Heart failure requiring respirator, intra-aortic balloon pump, or ventricular assist device
Heart failure requiring continuous inotropic support
Refractory NYHA Class III or IV symptoms despite maximal medical and surgical therapy
Estimated 1-year survival without transplantation $\leq 50\%$
Peak oxygen consumption $\dot{V}O_2 \leq 12$ -14 mL/kg/min or marked serial decline over time
Hypertrophic or restrictive cardiomyopathy with NYHA Class IIIb-IV symptoms
Refractory angina pectoris despite optimal medical, surgical, and/or interventional therapy
Recurrent life-threatening ventricular arrhythmias despite optimal medical, electrophysiologic, device, and surgical therapy
Cardiac tumors with low likelihood of metastasis
Medically refractory NYHA Class III-IV heart failure due to surgically untreatable complex congenital heart disease
Hypoplastic left heart syndrome

NYHA, New York Heart Association.

Table 48–3. Risk Factors

Age ≥ 65 years
Diabetes mellitus if:
End-organ dysfunction (retinopathy, nephropathy, neuropathy)
Poor glycemic control despite aggressive medical and dietary therapy
Intractable pulmonary hypertension despite maximal vasodilators/inotropes
Transpulmonary gradient ≥ 15 to 20 mm Hg
PVR ≥ 4 -6 Wood units
Extensive peripheral vascular disease
Significant cerebrovascular disease
Marked renal impairment
Serum creatinine >2.5 mg/dL
Creatinine clearance <50 mL/min
Marked hepatic impairment
Serum bilirubin >2.0 mg/dL
Serum transaminases $>$ twice upper limits of normal
Elevated prothrombin time without anticoagulation
Significant pulmonary dysfunction
Active infection
Malignancy/history of malignancy without evidence of cure
Obesity: BMI >40 kg/m ²
Active psychiatric disorders
Inadequate financial resources/social support

PVR, pulmonary vascular resistance; BMI, body mass index.

Once the degree of cardiac impairment meets one of the preceding indications, a comprehensive evaluation is performed to detect conditions that decrease the likelihood of a favorable posttransplant outcome. Table 48-3 delineates many of the risk factors that help determine the safety and appropriateness of transplantation for stage D heart failure. Most of these are no longer viewed as contraindications to cardiac transplantation, but risk factors only. In fact, while not routinely advisable, most have been successfully overcome in carefully selected individual patients.

Age

Most centers set a specific age limit beyond which patients are not considered as potential candidates.^{8,9} Although survival in older patients has modestly improved in recent years, the registry of the International Society for Heart and Lung Transplantation (ISHLT) indicates that older age remains a continuous predictor of 1-year and 5-year mortality following transplantation.² Enthusiasm for transplanting patients older than 65 to 70 years of age is further tempered by the scarcity of donor hearts and the higher prevalence of coexistent medical illnesses in the older patient population. Although not a universally accepted practice, alternate waiting lists have been used for candidates over the age of 70 years. Transplantation then proceeds using donor hearts that otherwise would not have been used.

Diabetes Mellitus

Some patients with diabetes mellitus and no, or minimal end-organ damage have been transplanted with excellent short and intermediate outcomes. Yet diabetes still poses additional challenges posttransplant. Patients with less than optimal glycemic control often worsen considerably with the use of corticosteroids following transplantation. Insulin may be required for a time postoperatively even in those patients previously well controlled with dietary measures or oral hypoglycemic agents. Evidence of end-organ damage before transplantation may identify patients with more advanced diabetes and define a subset of diabetics likely to suffer considerable deterioration of diabetes following the procedure. In general, those patients with manifestations of proliferative retinopathy, nephropathy, neuropathy, or peripheral vascular complications secondary to their diabetes are considered higher-risk candidates for cardiac transplantation. The most recent ISHLT registry indicates a significant 1-year mortality risk in insulin-dependent diabetic recipients.²

Pulmonary Hypertension

Elevated pulmonary arterial pressures and pulmonary vascular resistance are common in patients with the degree of cardiac failure that compels consideration of cardiac transplantation. However, excessive elevations of pulmonary vascular resistance identify patients at high risk following the transplant procedure. Several studies have shown that marked pulmonary hypertension is associated with increased early mortality secondary to right ventricular failure during the perioperative period.^{10,11,12} During the initial evaluation of a patient under consideration, right heart catheterization and direct measurement of the hemodynamic parameters is performed. A pulmonary artery systolic pressure of 50 mm Hg, a transpulmonary gradient of 15 mm Hg, or a pulmonary vascular resistance of 3 Wood units should prompt a challenge with a vasodilator and/or an inotropic agent. If these parameters can be corrected during initial hemodynamic measurement (e.g., with the administration of intravenous nitroprusside or inotropic agent), then it can safely be assumed that these abnormalities are secondary to the marked degree of cardiac dysfunction. Alternatively, patients whose initial hemodynamic status precludes consideration may be re-evaluated after a period of augmented medical therapy, particularly if earlier therapies had not yet been maximized. Patients with persistent pulmonary arterial hypertension despite a trial of different medical therapies may be considered for mechanical circulatory support to decrease left ventricular filling pressures over a period of months and assessing whether pulmonary pressures have become acceptable for heart transplantation. Serial measurements of hemodynamic status are routinely performed during the waiting period, not only to monitor the effectiveness of current medical therapies, but also to allow intervention if worsening pulmonary hypertension and elevated pulmonary vascular resistance are detected. On occasion, it is necessary to hospitalize patients and administer continuous intravenous vasodilators or inotropes to avoid the development of irreversible pulmonary hypertension, which would prohibit cardiac transplantation. In some instances, using a larger donor heart than would normally be required based upon the recipient body surface area may offer increased right ventricular work capacity to overcome the elevated pulmonary vascular resistance. Otherwise, only a combined heart-lung transplantation or heterotopic heart transplantation to surmount excessive pulmonary

hypertension would be feasible.¹³ In this age of increased use and better timing of mechanical circulatory support, these latter options are seldom used.

Peripheral Vascular Disease and Cerebrovascular Disease

Symptomatic peripheral vascular disease and significant cerebrovascular disease pose additional hazards following transplantation. Severe peripheral vascular obstruction can occasionally preclude the use of an intra-aortic balloon pump and may impede the functional capacity of the transplant recipient in the long run. The risk of stroke and lower extremity ischemia following transplantation should be assessed. As part of the routine pretransplant evaluation, carotid Doppler ultrasound should be performed in patients with coronary artery disease or in patients older than 40 to 50 years of age. If significant carotid occlusive disease is identified, surgical correction should be strongly considered before transplantation.¹⁴

Renal and Hepatic Impairment

Abnormal renal and hepatic function are common consequences of poor cardiac performance. Restoration of adequate perfusion following heart transplantation resolves the dysfunction. In cases of irreversible dysfunction of liver or kidneys not due to poor pretransplant perfusion, however, the dysfunction may worsen after transplantation due to the well-described hepatic and renal toxicities of the immunosuppressive agents used to prevent rejection.

Pulmonary Function

Severe chronic lung disease not only carries an increased risk of complications during the perioperative period, but also independently lessens the patient's functional capacity and survival following transplantation. An increased incidence of pulmonary infection has been noted in patient's with pulmonary dysfunction who receive immunosuppressive therapy. As a general rule, a forced expiratory volume in 1 second (FEV₁), a forced vital capacity (FVC), or an FEV₁/FVC ratio of $\leq 60\%$ of predicted despite maximal therapy identifies a serious impediment to a successful transplantation.

Infection

Active infection greatly increases the risk of transplantation as the infection will worsen after immunosuppression is begun. Hospitalized patients awaiting transplantation are at particular risk for exposure to various nosocomial infections. Diligent evaluation of any clinical or laboratory abnormality that suggests the possibility of infection should be undertaken. Any febrile syndrome or leukocytosis must be thoroughly investigated to avert potential disaster once immunocompetence is diminished. Candidacy is deferred until adequate treatment of active infection is assured.

However, a patient who tests positive for cytomegalovirus, *Toxoplasma gondii*, Epstein-Barr virus, or who has a positive tuberculin skin test is not excluded from consideration; rather the patient requires additional care and treatment after immunosuppression is begun. A thorough dental examination, with appropriate treatment, and screening for hepatitis B and C and human immunodeficiency virus (HIV), are warranted. Positive testing for hepatitis B or C does not necessarily preclude transplant consideration but requires additional evaluation.

Furthermore, even a patient who is HIV positive without a history of an AIDS-defining illness may not be excluded from transplant evaluation. These patients should be evaluated on an individual basis.¹⁵

Malignancy

Transplantation of a patient with a malignancy without evidence of cure is extraordinarily risky. Despite some reports indicating moderate short-term success in patients with malignancies undergoing successful transplantation,¹⁶ consideration should be given only to those patients who have a suitable response to medical or surgical therapy, have a low malignancy recurrence rate, and have been disease-free for a sufficient period of time following the initial diagnosis.

Obesity

At most transplant centers, class III or morbid obesity (body mass index [BMI] ≥ 40 kg/m²) has been considered a relative contraindication. This degree of obesity may predispose to poor wound healing, higher infection risk, and worse functional recovery after transplantation. Obesity has also been associated with increased cardiac allograft vasculopathy and worse survival after transplant.^{17,18} In addition, difficulty is encountered identifying a suitable donor heart, which can accommodate the size match required for a morbidly obese transplant candidate.

Psychosocial Issues

Psychiatric illness can impede a patient's ability to understand, consent to, and comply with a complex medical regimen. Simple reactive depression associated with severe cardiac impairment is not unexpected and likely does not preclude cardiac transplantation. A careful and thorough evaluation by qualified professionals, though, is essential for a comprehensive pretransplant examination. In addition to active psychiatric illness, certain behaviors can reduce a patient's suitability for transplant. Active substance abuse, or prior substance abuse without clearly documented abstinence, may profoundly increase the risk of both posttransplant medical noncompliance and substance abuse recidivism. Tobacco use and alcohol abuse should be categorized with illicit drugs in estimating the scope of active or previous substance abuse. Psychosocial concerns must be resolved so that participation in the intricate and continual process of care after transplantation can be assured.

Finances

Most insurers and third-party carriers will cover the expenses incurred in the transplant procedure itself. Some even have allowances for medications and long-term care. However, the costs of future care and the need for psychosocial support must be evaluated and addressed. Undergoing a heart transplant is challenging and when onerous financial issues are added to the complexity, noncompliance, and suboptimal outcomes may result.

Pretransplant Patient Management

To care for a patient with end-stage heart failure awaiting heart transplantation, the physician must determine whether ongoing therapy, be it outpatient, inpatient, or intensive care unit-based, is sufficient. If the care is insufficient, metabolic, cellular, and nutritional health is compromised. Transplantation at a

time when end-organ function is marginal, increases posttransplant morbidity and mortality. Many patients may have a very low functional threshold beyond which additional demands upon their cardiac performance lead to decompensation and end-organ compromise. Frequent and diligent examination of candidates awaiting cardiac transplantation is needed to ensure continued suitability for transplantation. The common symptoms, physical signs, and objective measures of cardiopulmonary status that are regularly assessed are listed in Table 48-4. Evidence of deterioration is often heralded by an increase in the

Table 48-4. Evidence of Instability in Heart Failure

Indications of Intolerance of Current Medical Management

Worsening Cardiovascular Symptoms

- Easy fatigability
- Increasing frequency and severity of angina
- Exertional dyspnea/shortness of breath at rest
- Orthopnea/paroxysmal nocturnal dyspnea
- Dysrhythmia (tachycardia, palpitations)

Worsening Cardiovascular Physical Signs

- Hypotension/low pulse pressure
- Resting tachycardia/frequent ventricular ectopy/atrial fibrillation
- Elevated jugular venous pressure
- Prominent S₃/S₄
- Loud murmur of mitral/tricuspid regurgitation
- Hepatomegaly/ascites/hepatojugular reflux
- Edema/anasarca
- Diminished peripheral perfusion (cyanosis/delayed capillary refill)

Worsening Objective Measures of Cardiac Performance

- Diminished renal perfusion (prerenal azotemia/rising serum creatinine)
- Hepatic congestion (elevated liver function tests)
- Decreased end-organ perfusion (metabolic acidosis/elevated serum lactate)
- Deteriorating left ventricular function by echocardiogram
- Decreased left ventricular ejection fraction by radionuclide ventriculography
- Worsened cardiomegaly/pulmonary edema on chest x-ray
- Diminished maximal oxygen consumption $\dot{V}O_2$ on exercise testing
- Abnormal parameters on right heart catheterization
- Elevated central venous pressure
- Worsening pulmonary arterial hypertension/pulmonary vascular resistance
- Declining cardiac output/cardiac index
- Increasing arteriovenous oxygen difference (A- $\dot{V}O_2$)

frequency and severity of these parameters. Continued decline despite appropriate adjustments to the patient's medical regimen signals a severity of illness beyond the capacity of ongoing therapy and should prompt an escalation in the therapeutic intensity.

Invasive hemodynamic monitoring plays an integral role in the management of any patient awaiting cardiac transplantation. As discussed earlier, it is essential to accurately determine the reversibility of the elevated pulmonary arterial pressures and pulmonary vascular resistance to ensure the highest likelihood of a favorable outcome following transplantation. Furthermore, the determination of cardiac filling pressures is a valuable aid in predicting prognosis during the waiting period. As an adjunct to a detailed history and physical examination, and the laboratory and other studies previously described, periodic hemodynamic evaluation is essential to successful pretransplant patient management.

Medical Therapy in Advanced Cardiac Failure

Effective management of the patient awaiting cardiac transplantation requires an intricate strategy, and no single approach will be equally effective in all patients with severe cardiac dysfunction. Numerous general guidelines do exist. The medical evidence behind current heart failure treatment algorithms is found elsewhere in this textbook. Broadly speaking, there should be a low threshold for hospitalization and more intensive heart failure care for hemodynamic deterioration. Therapy should be escalated as needed from intravenous diuretics to intravenous inotropic agents and from intravenous inotropic agents to intra-aortic balloon pump or mechanical circulatory support. Further, drugs that earlier in the course of heart failure were beneficial and well-tolerated frequently are no longer tolerated at prior doses, if at all. The following list briefly addresses situations encountered in candidates awaiting heart transplantation.¹⁹

Relief of congestion. Effective diuresis can generally be achieved using loop diuretics in high doses or in continuous infusions, in combination with metolazone or intravenous thiazides, or at times with support from inotropic infusions or the administration of nesiritide. Ultrafiltration or even dialysis may occasionally be necessary.^{20,21} Thoracentesis for significant pleural effusions and paracentesis for ascites not resolving with diuresis is occasionally used.

Restoration of normal fluid status markedly enhances the response to vasodilators. Previously ineffective doses now lead to effective or even excessive vasodilation. Careful assessment generally distinguishes between excessive vasodilation and excessive diuresis. Diuretics should not needlessly be withheld.

Many patients effectively treated will have some increase in creatinine and blood urea nitrogen, often by as much as 50%. Slowing the rate of diuresis and avoiding excessive vasodilation will often allow renal function to stabilize.

Intravenous inotropic and vasodilator therapy. All inotropic agents should be used in as low a dose as possible and initially only to achieve a short-term goal, such as promoting effective diuresis or treating hypoperfusion with end-organ dysfunction. Although dobutamine, milrinone, and occasionally dopamine are the agents of choice, epinephrine and rarely isoproterenol can also be considered for very short-term support. Combining phosphodiesterase inhibitors with β -agonists may provide sufficient inotropic response with less than usual quantities of either agent, potentially averting the adverse effects of each when used

at higher doses. Dependence upon continuous intravenous inotropic support is a significant indicator of illness severity in patients awaiting cardiac transplantation. Those who require this mode of therapy to maintain hemodynamic stability are afforded a higher priority on the transplant waiting list.

Although intravenous inotropic agents are effective in improving cardiac hemodynamics acutely, they are unsafe for intermediate or chronic use. Administration should be limited to severely decompensated heart failure patients or patients who repeatedly demonstrate an inability to be weaned. Attempts to discontinue intravenous inotropes should be made. This requires careful titration of vasodilators and volume status. Some patients will have symptomatic hypotension on a dose of an angiotensin-converting enzyme (ACE) inhibitor that was tolerated during the inotrope infusion. Lower ACE inhibitor doses or other vasodilators should be attempted. One of the most common reasons patients do not tolerate the addition of ACE inhibitors during the weaning and discontinuation of intravenous inotropes is over-vasodilation and intravascular volume depletion. This is often indicated by a low systemic vascular resistance (SVR), which can be derived from Swan-Ganz catheter measurements. Furthermore, a rise in serum creatinine may also be observed given the concomitant renal vascular vasodilation. Modest adjustments in oral vasodilators to maintain appropriate SVR and cardiac output are essential before discontinuation of inotropic therapy. If repeated weaning attempts are unsuccessful, chronic inotropic therapy may be necessitated. If used in outpatients awaiting a suitable cardiac donor, an implantable cardioverter-defibrillator is warranted (ICD).

In some patients with marked systemic vasoconstriction, nitroprusside or nitroglycerin may provide similar acute hemodynamic benefits as inotropic therapy and allow more direct transition to oral regimens. Nitroprusside may be particularly beneficial when mitral regurgitation is severe. Nitroglycerin is also a very effective arteriolar vasodilator in the setting of severe vasoconstriction, but may be particularly helpful for initial symptom relief in patients with high pulmonary artery pressures and severe right heart failure in whom diuresis is not proceeding as rapidly as desired.

Oral vasodilator regimens: ACE inhibitors are the vasodilators of choice in stage D heart failure patients awaiting transplantation.³ It is generally not helpful to introduce or increase ACE inhibitors when patients remain unstable despite moderate inotropic support (e.g., dobutamine $\geq 5 \mu\text{g/kg/min}$).

Unfortunately, patients with resting systolic blood pressures of less than 85 mm Hg without vasodilators often do not tolerate ACE inhibitors. Patients with serum sodium less than 132 mM/L are at increased risk for symptomatic hypotension with ACE inhibitors but derive the greatest benefit. An elevated creatinine is not a reason, per se, to withhold ACE inhibitors. However, when effective diuresis is limited by deteriorating renal function, ACE inhibitors are generally withdrawn. Shock and hyperkalemia are contraindications to ACE inhibitor use. ACE inhibitor-induced symptomatic hypotension or significant renal dysfunction could prompt a trial of hydralazine and oral nitrates.²²

Angiotensin receptor blockers (ARBs) can be used as an alternative in ACE inhibitor-intolerant patients or as an addition in tolerant patients already on ACE inhibitors and β -adrenergic receptor antagonists.²³

Precipitating factors. Patients should be closely monitored for conditions that aggravate heart failure. Arrhythmias, anemia, infection, thyroid dysfunction, and medications with adverse hemodynamic effects on cardiac output or fluid retention are frequent culprits. These conditions should be treated as indicated.

Antiarrhythmic and cardiac resynchronization therapy. The technical sophistication, safety, and reliability of electrophysiologic devices have improved in recent years. The majority of heart transplant candidates will have undergone ICD implantation and cardiac resynchronization therapy, if also indicated.²⁴ Generally, these strategies will have been used earlier in the course of disease. The use of cardiac resynchronization therapy in stage D heart failure is rarely, if ever, even palliative.⁴

Patients with frequent or incessant arrhythmias or in whom the arrhythmias appear to be contributing to poor hemodynamics should undergo further therapy, which may include combination drug therapy and in some cases attempts at ablation of arrhythmic foci. Vigorous efforts should be made to establish and maintain sinus rhythm. Amiodarone is frequently the antiarrhythmic drug of choice.

Other medications. Patients taking β -blockers who develop decompensated heart failure should be maintained on β -blockers, if possible. The doses may need to be decreased to achieve hemodynamic goals. As heart failure progresses, β -blockers may not be tolerated at any dose, but, given that β -blockers have been studied in more than 20,000 patients with heart failure and the collective evidence from more than 20 placebo-controlled clinical trials is overwhelmingly positive, β -blockers should be reinstituted if at all possible.²⁵⁻²⁷ They will generally not be tolerated in patients with recurrent fluid retention or other signs of clinical instability. Typically, the combination of β -agonists and β -blockers administered simultaneously makes little sense.

When using aldosterone antagonists, close monitoring of serum electrolytes and renal function is a must, especially when used with ACE inhibitors or ARBs. Renal dysfunction (serum creatinine >2.5 mg/dL in men, >2.0 mg/dL in women), or a serum potassium level greater than 5.0 mmol/L usually prompts discontinuation, especially in older patients.^{28,29}

Digoxin remains an important adjunct. Low-dose digoxin, targeting serum levels between 0.5 and 0.8 ng/mL, may be used.³⁰ Vigilant observation is critical especially when fluctuating renal function is present. Calcium-channel blockers are not encouraged; however, amlodipine can be given for angina pectoris. Current heart failure guidelines do not recommend routine anticoagulation solely on the basis of a low left ventricular function in patients in sinus rhythm. On the other hand, the presence of atrial fibrillation, a previous thromboembolic event, or a left ventricular mural thrombus should prompt anticoagulation. Patients less than 3 months after a myocardial infarction or who have a patent foramen ovale with right ventricular failure are at increased thromboembolic risk, and anticoagulation could be considered.

Nutritional support. Nutritional support should be instituted if oral intake is inadequate. Early intervention with enteral (preferred) or parenteral supplementation is essential. Malnutrition impairs wound healing and increases the risk of perioperative infection.

Physical therapy. The prospect of potentially shorter recovery times, less perioperative functional impairment, and improved quality of life during the waiting period warrant consideration of rehabilitation therapy. Patients unable to participate in active

therapy should at least receive passive exercise. Subsequent rehabilitation should include bedside exercise and supervised walking as soon as possible.

Emotional support. The emotional and psychiatric aspects of chronic illness and uncertainty greatly influence a patient's sense of well-being and perceived benefits of therapy. Regular counseling sessions should be initiated and continue throughout the waiting period. Patients and their families must be informed about all aspects of heart transplantation.

Mechanical Circulatory Support

Mechanical circulatory support, discussed more fully elsewhere in this text, includes percutaneously and surgically implanted mechanical modalities intended to augment univentricular or biventricular function. Temporary devices may also incorporate membrane oxygenators to support gas exchange. Mechanical circulatory support allows patients to be "bridged" to transplantation and improve their chances of posttransplant survival.^{31,32}

The medical management of the mechanical circulatory support patient is challenging. It requires knowledge of individual device characteristics and expertise managing the critical illness related to surgical implant and physiologic changes associated with loading or unloading of native ventricles. Factors in the immediate postoperative period requiring acute intervention involve right ventricular optimization (including management of inotropes, intravascular volume, pulmonary vascular resistance, arrhythmias, tricuspid regurgitation, and interventricular septal shifts), systemic vasodilation, hemorrhage and coagulopathy, mechanical ventilation, and glycemic control.

In recent years, the percentage of patients supported on ventricular assist devices to cardiac transplant has doubled (from 11% to 22%, comparing periods 1999-2001 to 2002-2004).² Out-patient management of left ventricular assist devices in transplant candidates has likewise contributed to the large decline (45% from 72%) in patients requiring hospitalization while they await transplantation.

Surveillance anti-HLA Antibodies

The danger of acute, antibody-mediated rejection markedly increases when high titers of preformed anti-human leukocyte antigen (HLA) antibodies are present in the recipients serum. HLA antibody formation may occur with blood transfusion (e.g., at the time of coronary artery bypass grafting or following a left ventricular assist device implantation). Past pregnancies and infections with HLA cross-reacting bacterial or viral antigens may potentially prompt HLA antibody formation. Therefore, antigen exposure must be minimized. Any required transfusions should be leukocyte depleted. Serial measurement of reactive antibody titers referred to as panel reactive antibodies (PRA) are performed. If the PRA is significantly elevated, prospective cross-matching with a specific donor is performed before transplantation. Different inconclusive immunomodulation interventions have been attempted to lower pretransplant PRA. This process, however, imposes additional limitations on securing a suitable donor heart and increases the pretransplant risk and likely the posttransplant risk.

Immediate Pretransplant Considerations

Donor hearts are allocated based on degree of illness in the recipient, blood type compatibility, size disparity, and how long the candidate has been actively waiting for transplantation.³³

There are three gradations in severity of illness. Status 1A patients receive first priority. These include severely ill candidates who require invasive monitoring and multiple inotropic agents or a high-dose single inotropic agent, or recipients of mechanical circulatory support devices within the first month of implant or with a significant device malfunction. Status 1B includes candidates requiring intravenous inotropes, whereas Status 2 is assigned to any other actively listed candidate.

A blood type O donor can be used for a recipient of any blood type, a blood type A donor for either a blood type A or AB recipient, a blood type B donor for either a blood type B or AB recipient, and a blood type AB donor only for a blood type AB recipient. In general, the donor is usually no less than 80% of the recipients weight, but height disparity and recipient pulmonary hypertension are also considered.

Taking into account blood type and size, allocation is first to Status 1A, then to Status 1B, and finally to Status 2 patients. Within each group, those who have actively waited the longest are given preference on an individual donor.

Once a donor heart becomes available for a specific candidate, the patient is evaluated and prepared for surgery. The evaluation assesses whether any new medical information is manifest that would preclude a successful transplant (e.g., the presence of a new, active infection). Past medical history is reviewed to ensure that postoperatively no issues are forgotten (e.g., the treatment of chronic hypothyroidism). Anticoagulation, if present, is reversed with vitamin K and fresh frozen plasma. Prophylactic antibiotics are prescribed, typically a cephalosporin. Pretransplant immunosuppression is administered and the ICD, if present, is turned off.

Posttransplantation Management in the Critical Care Setting

Immediate Posttransplant Care

The management of a newly transplanted patient is both complex and challenging. The delivery of prompt and attentive care in the immediate postsurgical phase is crucial to future success. Following surgery, recipients return to the intensive care unit immediately, as would any patient undergoing a median sternotomy. Newly transplanted patients are hemodynamically monitored in the intensive care unit for a few days. A unique consideration in these patients is the totally denervated and somewhat dysfunctional heart due to the ischemic insult that occurred at the time of donor heart procurement and recipient implantation. Attempts are made to coordinate the donor heart procurement and subsequent transplant to minimize the ischemic time—time from cross-clamp application in the donor to its release in the recipient—to less than 4 hours.

The transplanted heart usually requires inotropic support and a higher preload (right atrial pressure of 8 to 15 mm Hg and pulmonary capillary wedge or left atrial pressure of 15 to 20 mm Hg) to achieve hemodynamic stability. Isoproterenol in doses of 0.25 to 5.00 $\mu\text{g}/\text{min}$ is an excellent choice because of its chronotropic and inotropic properties. Its lusitropic effect is also an added bonus in enhancing diastolic relaxation of the stiff heart with diminished diastolic compliance. Due to the limited stroke volume early on, heart rates of 110 to 120 beats/min are targeted to maintain adequate cardiac output. When further inotropic

support is needed, dobutamine (5 to 20 $\mu\text{g}/\text{kg}/\text{min}$), milrinone (0.2 to 0.75 $\mu\text{g}/\text{kg}/\text{min}$), and/or epinephrine (1.0 to 5.0 $\mu\text{g}/\text{min}$) may be used. The β -adrenergic receptors of the denervated heart are especially responsive to the full β -adrenergic agonist epinephrine because of the lack of neuronal uptake. On a rare occasion, pure α -adrenergic agonists such as phenylephrine may be used when faced with excessive vasodilation. The duration of inotropic support may be related to the effectiveness of the cardioplegia, donor age, and ischemic time, but typically lasts 2 to 5 days.³⁴

The sinus node is especially susceptible to cold ischemia because of its closeness to the cardiac epicardium. As a consequence, transient sinus bradycardia is not uncommon, especially in recipients previously treated with amiodarone. Cardiac pacing through surgically placed epicardial leads is effective on a temporary basis. Alternatively, theophylline may also be used with moderate success. Fewer than 5% of patients will require permanent pacing due to persistent bradycardia.

Perhaps the most important physiologic alteration of the denervated heart to be aware of is its propensity to respond differently to drugs, both commonly or uncommonly used. For example, cardiac allografts are exquisitely sensitive to adenosine and possibly epinephrine. Adenosine may induce prolonged asystole and, if used, should be initiated at half the usual recommended dose. On the other hand, the inotropic or chronotropic effects of drugs such as dopamine and ephedrine may be diminished. Finally, atrioventricular nodal blockers, such as digoxin, atropine, or quinidine, will have negligible or absent effects due to the lack of vagal innervation.³⁵

Posttransplant Immunosuppression

In the absence of immunosuppression, the patient's immune system will begin a cascade of events that eventually leads to cardiac allograft destruction. As shown in [Figure 48-3](#), this cascade involves antigen recognition, the process whereby the foreign tissue is recognized as non-self; T cell-centered events, which include the generation of growth factors; and cell proliferation and differentiation.³⁶

Multiple drugs are used, sequentially and in combination, to decrease the overall toxicities. Early rejection prophylaxis refers to agents used early after transplantation. Maintenance immunosuppression refers to drugs used early after transplantation but continued chronically. Many of the drugs used in early rejection prophylaxis can also be used to treat established rejection episodes. The commonly used drugs are listed in [Table 48-5](#).^{36,37}

Typically, recipients are treated with a three-drug combination, so called “triple drug therapy,” a calcineurin inhibitor (cyclosporine or tacrolimus), an antiproliferative (mycophenolate mofetil, mycophenolic acid, or azathioprine) or a proliferation signal inhibitor (an inhibitor of the molecular target of rapamycin [mTOR], e.g., sirolimus), and a corticosteroid. In early rejection prophylaxis, an interleukin-2 receptor blocker (basiliximab or daclizumab), a polyclonal antibody (thymoglobulin or antithymocyte globulin), or the murine monoclonal anti-CD3 antibody, may be used resulting in so called “quadruple therapy,” especially to delay the use of nephrotoxic calcineurin inhibitors.

Over time during maintenance immunosuppression, attempts to minimize the doses of all immunosuppressive drugs should be made, especially decreasing the target ranges of the calcineurin inhibitors and minimizing or eliminating corticosteroids.

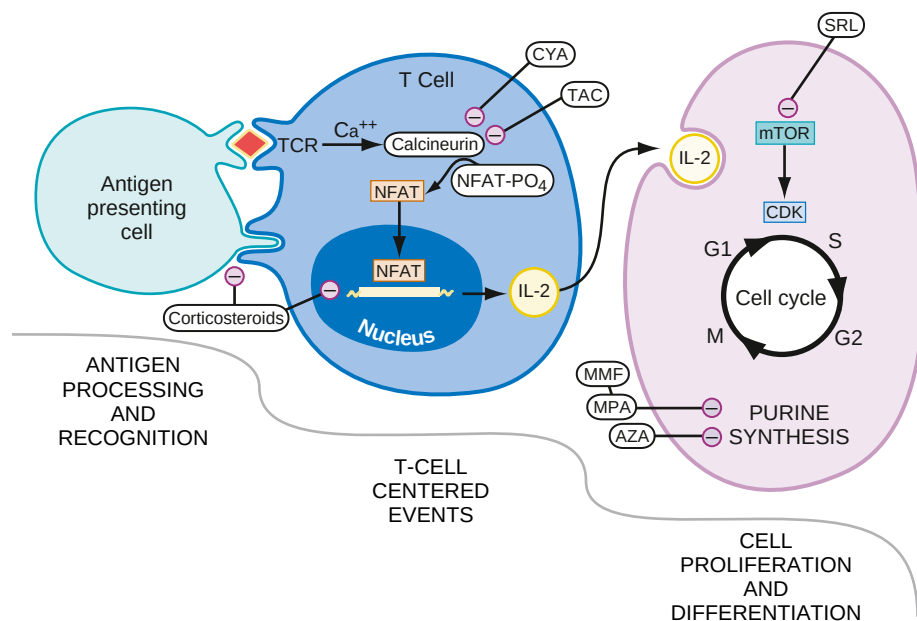


Figure 48-3. Cascade of events leading to cardiac allograft rejection and destruction. Antigen processing leads to the presentation of a donor peptide (depicted as a red diamond) on an antigen presenting cell. Antigen recognition occurs as the T-cell receptor (TCR) is engaged by the donor peptide when coupled with a secondary signal. Calcium-dependent activation of calcineurin occurs, which enables the dephosphorylation of nuclear factor of activated T cells (NFAT). NFAT is able to cross into the nucleus and with other transcription factors synthesize various immune components, including interleukin-2 (IL-2). IL-2 and other growth factors activate the molecular target of rapamycin (mTOR), which activates cyclin-dependent kinases (CDK). CDK initiate the cell cycle, which, with the incorporation of purines and pyrimidines, leads to the synthesis of nucleic acids and cell division. Under the influence of various growth factors, proliferation and differentiation occur resulting eventually in cell-mediated and antibody-mediated immunity.

Posttransplant Complications that may Necessitate Intensive Care

In addition to immediate, postoperative management, transplant recipients may on occasion require evaluation, management, and treatment in cardiac intensive care.³⁸ Typically this will occur for cardiovascular, infectious, or other reasons. The causes of death following transplantation, as shown in Figure 48-4, indicate some of the challenges an intensivist may face.² Early on, cardiac and infectious causes predominate. Later, although cardiac causes diminish, they remain prominent, shifting from acute rejection to cardiac allograft vasculopathy as a cause of death. Also, while deaths due to infections diminish, death due to malignancy and renal failure increase.

The cardiovascular reasons for cardiac intensive care include ventricular dysfunction, arrhythmias, and cardiac allograft rejection, which usually have typical heart failure symptoms, hypotension, palpitations, or simply malaise and fatigue. The infectious causes typically present with fever, hypoxia, or simply malaise and fatigue. Other reasons prompting patients to come to the attention of critical care specialists are other critical care issues (e.g., gastrointestinal hemorrhage or those due to immunosuppressive drug toxicities).

Appropriate intensive care for the heart transplant recipient depends on both the ability to render excellent intensive care as one normally would and the recognition of the unique challenges of the transplant recipient. Care for a transplant recipient with a severe gastrointestinal hemorrhage has more to do with the gastrointestinal hemorrhage than with the transplant status, although the transplant status cannot be ignored.

Ventricular dysfunction. The transplanted heart has normal left and right ventricular function. Thus, any degree of dysfunction is abnormal, potentially life threatening, and requires explanation. The differential diagnosis includes cardiac allograft rejection and cardiac allograft vasculopathy. Once ventricular dysfunction is diagnosed, usually by echocardiography, an endomyocardial biopsy is emergently performed. The false negative rate is low so the absence of histological evidence of rejection prompts urgent coronary angiography.

Treatment of rejection depends on the type of rejection, cell-mediated or antibody mediated, histologic grade, degree of ventricular dysfunction, time after transplantation, past rejection history, and the current doses of immunosuppressive agents prescribed. Table 48-6 provides the grading scheme used and treatments generally prescribed.^{39,40} In situations where there is scant evidence of cellular rejection coupled with significant antibody-mediated rejection, plasmapheresis is recommended.

Treatment of cardiac allograft vasculopathy depends on the location of the disease, proximal or distal, the extent of the disease (focal or diffuse), the degree of disease in distal vessels, and the viability of the myocardium. The cardiac allograft vasculopathy that develops early after transplantation portends a poor prognosis. It is often extensive and diffuse with little, if any, hope of meaningful intervention. Later on, the disease tends to be more proximal and focal. In these situations, percutaneous intervention and even coronary artery bypass surgery may be appropriate. The proliferation signal inhibitors, mTOR inhibitors (e.g., sirolimus), decrease the incidence of cardiac allograft vasculopathy when used early after transplantation and appear to decrease progression of disease once cardiac allograft

Table 48–5. Immunosuppressive Agents in Heart Transplantation

Agent	Type	Use	Side Effects	Considerations
Cyclosporine	Calcineurin inhibitor	M	Nephrotoxicity, HTN, hirsutism, GH, neuro-toxicity, hypatotoxicity, hyperglycemia	Increased levels with ketoconazole, diltiazem, verapamil, erythromycin; decreased levels with phenytoin, phenobarbital, isoniazid, rifampin, carbamazepine
Tacrolimus	Calcineurin inhibitor	M	Nephrotoxicity, HTN neurotoxicity, hepato-toxicity, hyperglycemia	Increased levels with ketoconazole, diltiazem, verapamil, erythromycin; decreased levels with phenytoin, phenobarbital, isoniazid, rifampin, carbamazepine
Mycophenolate mofetil	Antiproliferative	M	Leukopenia, anemia, GI distress	
Mycophenolic acid	Antiproliferative	M	Leukopenia, anemia, GI distress	
Azathioprine	Antiproliferative	M	Leukopenia, anemia, pancreatitis	Increased levels with allopurinol
Sirolimus	Proliferation signal inhibitor	M	Hyperlipidemia, anemia, leukopenia, GI distress, dermatologic	Increased levels with ketoconazole, diltiazem, verapamil, erythromycin; decreased levels with phenytoin, phenobarbital, isoniazid, rifampin, carbamazepine
Prednisone, methylprednisolone, others	Corticosteroids	E M R	Pituitary-adrenal suppression, cushingoid habitus, glucose intolerance, hyperlipidemia, HTN, posterior subcapsular cataracts, myopathy, osteoporosis, skin fragility, peptic ulcer disease	
Basiliximab	Interleukin receptor blocker	E	GI distress	
Daclizumab	Interleukin receptor blocker	E	GI distress	
OKT3	Murine monoclonal anti-CD3 antibody	E R	Fever, chills, GI distress, pulmonary edema, HAMA antibody formation	First-dose reactions with profound vasodilation can occur
Thymoglobulin	Rabbit polyclonal lymphocyte immune globulin	E R	Leukopenia, thrombocytopenia, fevers, chills, arthralgias, serum sickness	
ATGAM	Equine polyclonal lymphocyte immune globulin	E R	Leukopenia, thrombocytopenia, fevers, arthralgias, serum sickness	

E, early rejection prophylaxis; M, maintenance immunosuppression; R, treatment of established rejection; HTN, hypertension; GH, gingival hyperplasia; GI, gastrointestinal; HAMA, human antimouse antibody.

vasculopathy is established.^{41,42} The physician should consider either adding an mTOR inhibitor or substituting one for another antiproliferative.⁴² In some cases, retransplantation is the only viable option, and it is only a viable option if the patient is a suitable transplant candidate. Survival after retransplantation is worse than after primary transplant, especially if the time between transplant and retransplant is short.²

Arrhythmias. Atrial arrhythmias occasionally occur and ventricular arrhythmias uncommonly occur after transplantation. Rhythm disturbances should be approached as in any other patient with the following caveats. In general, cardiac allograft rejection should be excluded as a cause, or treated if diagnosed, regardless of time posttransplant. Digoxin is not likely to be

beneficial in slowing the rate of atrial fibrillation, especially early after transplantation, since its mechanism of action depends primarily on cardiac innervation. Early after transplantation, especially in the postoperative period, β -blockers and the calcium channel blockers verapamil and diltiazem may not be well tolerated as the cardiac allograft is still recovering from an ischemic insult. Additionally, caution should be exercised when using verapamil and diltiazem because they will increase the levels of calcineurin inhibitors and mTOR inhibitors (see Table 48-5).³⁶ With ventricular arrhythmias, not only should cardiac allograft rejection be excluded as a cause and treated if diagnosed, but cardiac allograft vasculopathy should be considered in the differential diagnosis.

Infections. When infections occur, the etiologic agent is usually dependent on the time following transplantation.⁴³ Early after transplantation, usually up to 1 month, most infections are nosocomial and bacterial. Wound and line infections predominate but pneumonias also occur. Often, these infections are predisposed in patients who are poorly nourished and debilitated before transplantation or who have long postoperative intensive care unit stays. Later on, in the 2 to 4 month range, opportunistic infections appear. Cytomegalovirus and *Pneumocystis carinii* occur during this time frame as a result of the high dose immunosuppression used early on. Fortunately, prophylaxis is available and effective, valganciclovir or intravenous immunoglobulin for the former and trimethoprim sulfamethoxazole for the latter. Prophylaxis is used for other

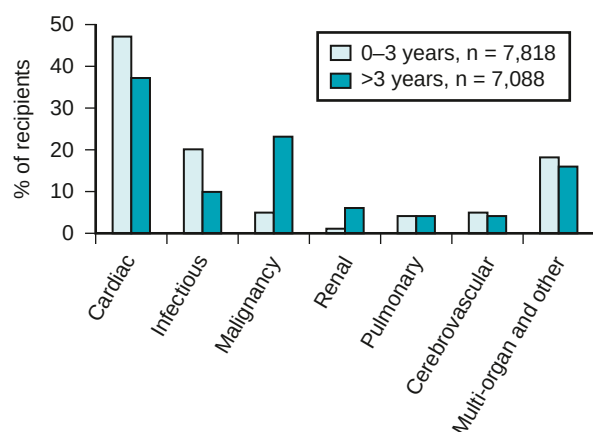


Figure 48-4. Causes of death after transplantation. The cause of death after transplantation is influenced by time after transplantation. Light blue bars indicate recipients dying in the first 3 post-transplant years, and dark blue bars indicate recipients dying after the first 3 years. Although cardiac and infectious causes of death diminish after the first 3 years, deaths resulting from malignancy and renal failure increase. (Adapted from Taylor DO, Edwards LB, Boucek MM, et al: Registry of the International Society for Heart and Lung Transplantation: Twenty-fourth Official Adult Heart Transplant Report—2007. *J Heart Lung Transplant* 2007;26:773.)

common entities (e.g., acyclovir for *Herpes simplex* [if not on valganciclovir] and nystatin for oral candidiasis [when the patient is on high dose corticosteroids], and pyrimethamine for toxoplasmosis [during the first 6 weeks posttransplant if a toxoplasmosis positive donor was used]). Fungal infections peak in the first 1 to 2 months posttransplant and usually occur in patients who also have a bacterial infection treated with broad-spectrum antibiotics at the time they are also heavily immunosuppressed.

Once a transplant recipient is beyond the first 6 to 12 months posttransplant, most infections are typically those found in the general community. In general, this means that a patient having pneumonia at 12 months posttransplant is likely to have a community-acquired pneumonia and the usual approaches and treatments are appropriate. This contrasts sharply with a patient presenting at 3 months posttransplant with hypoxia and interstitial infiltrates. This latter patient should undergo urgent bronchoscopy to search for opportunistic agents.

If a heart transplant recipient presents to the cardiac intensive care unit with virtually any presentation, it is wise to assess the status of the cardiac allograft with an electrocardiogram and an echocardiogram. If ventricular function is not normal, one should proceed as outlined above.

Other. Unfortunately, while the immunosuppressive drugs decrease the risk of rejection and treat established rejection, they, as a group, have multiple side effects. The deleterious effects of the immune suppression are suggested by the increase in the malignancy as a cause of death after the first 3 years following transplant.

Future Directions

The future of cardiac transplantation will continue to be both intriguing and enigmatic. The continued trend of recipient demand exceeding donor heart supply compels continued exploration of alternative therapies for advanced cardiac failure. Further refinement of mechanical alternatives, immune or genetic modulation, and investigational agents are required to meet this challenge. Improved candidate selection and meticulous pretransplant management must suffice until these aspirations are realized.⁴⁴

Table 48-6. Cardiac Allograft Rejection: Grading* and Treatment

Qualitative Grade	Cellular Grade	Antibody-Mediated	Treatment†
None	0	Negative	None
Mild	1R	Positive	No treatment (followed by rebiopsy at shorter time interval), change calcineurin inhibitor, change antiproliferative, add an antiproliferative, or oral corticosteroid augmentation
Moderate	2R	Positive	Oral or intravenous corticosteroids or, if persistent on subsequent biopsy, antilymphocyte antibody + intravenous corticosteroids
Severe	3R	Positive	Antilymphocyte antibody + intravenous corticosteroids

*Based on the International Society for Heart and Lung Transplantation (ISHLT) Grading Scheme.

†In all situations, the dose of calcineurin inhibitor and antiproliferative agent(s) is(are) optimized; R, refers to the revised grading scheme; Oral corticosteroid augmentation, approximately 1 mg/kg/day for 5-10 days followed by tapering to prerejection doses; Intravenous corticosteroid, approximately methylprednisolone 500-1000 mg/day for 3 days followed by a rapid taper to prerejection doses.

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Emergency Airway Management

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CHAPTER 49

Requirements for Safe Airway Management
Techniques of Emergency Airway Management
The Difficult Airway
Emergency Airway Management Complications

Anesthesia Induction Drugs for Rapid-Sequence Intubation
Clinical Scenarios
Conclusion

MAINTENANCE of adequate gas exchange is the fundamental responsibility of the physician managing the airway in emergency (i.e., “code blue”) situations. Failure to maintain a patent airway for more than a few minutes can lead to brain injury or death.¹ This chapter reviews the principles of emergency airway management, placing special emphasis on the critically ill or cardiac intensive care unit (CICU) patient.

This chapter is illustrated with numerous figures and tables demonstrating how to perform various airway management techniques. Emphasis is on illustrating the “when and why” of employing various airway management modalities, rather than merely providing a technical guide.

Regardless of the airway management situation, there are several essential requirements for safe airway management (including evaluation of the patient and the airway), discussed in the second section of this chapter. The third section reviews the various techniques and apparatus used in emergency airway management. The fourth section places the airway techniques in context by reviewing the essential airway complications that must be avoided. Essential components of this “disaster avoidance” discourse include management of the “difficult airway” and avoidance of esophageal intubation, aspiration, and hemodynamic compromise. Following the introduction of these fundamental principles of emergency airway management, several commonly encountered clinical scenarios are reviewed, with focus on their emergency airway management ramifications.

Requirements for Safe Airway Management

Regardless of the emergent nature of the “code blue,” some key drugs and several pieces of emergency airway equipment should be available before manipulation of the airway (Table 49-1).

Oxygen (O₂)

Oxygen should always be applied during assessment of the patient and before implementing airway management techniques. The application of supplemental oxygen can be lifesaving because oxygen deficiency is commonly encountered in

critically ill patients suffering from respiratory failure. Furthermore, the concept of *preoxygenation* (increasing the alveolar oxygen concentration before tracheal intubation) is a critical tenet of emergency airway management.

Supplemental Oxygen

The primary reason for oxygen administration is the prevention or treatment of hypoxemia. Numerous causes of hypoxemia exist and all are improved with the administration of 100% O₂ (Table 49-2).

Hypoxia is defined as oxygen deficiency at the tissue level. Anything that decreases oxygen delivery ($\dot{D}O_2$) may lead to hypoxia. Oxygen delivery depends upon cardiac output ($\dot{Q}$), hemoglobin concentration (Hgb), and arterial oxyhemoglobin saturation (SaO₂), as follows:

$$\dot{D}O_2 \text{ (mL O}_2\text{/min)} = \dot{Q} \text{ (mL/min)} \times \text{Hgb (gm/dL)} \times \text{SaO}_2 \times 1.34 \text{ (mL O}_2\text{/gm Hgb)}$$

Hypoxia occurs when $\dot{D}O_2$ decreases below adequate levels because of impaired myocardial function, anemia, or hypoxemia (due to decreased fraction of inspired O₂ [FiO₂] or increased shunt). Hypoxia can also occur secondary to increased metabolic rate or decreased utilization at the tissue level (e.g., cyanide poisoning). By administering oxygen to critically ill patients in respiratory failure, one can increase SaO₂, thereby improving $\dot{D}O_2$ until anemia, myocardial dysfunction, or right-to-left transpulmonary shunting abates.

Preoxygenation (Before Induction and Intubation)

Preoxygenation of the lungs is an essential component of any intubation technique that might involve a period of apnea. Preoxygenation is especially important for a rapid-sequence intubation because it allows for a reserve of oxygen in the lungs during apnea. For a patient who has been rendered apneic there is a finite period before arterial oxyhemoglobin desaturation. This period is related to the reservoir of oxygen in the lungs, or functional residual capacity (FRC), and is inversely related to the oxygen consumption (Fig. 49-1). Preoxygenation with 100% O₂ allows for up to 10 minutes of oxygen reserve following apnea (in a patient with healthy lungs); however, the patient

Table 49–1. Essential Preparatory Requirements for Safe Airway Management “Code Box”

Requirement	Equipment
Oxygen	BVM with oxygen inflow tubing
Ventilation	Soft nasal airway Rigid oral airway Emergency cricothyroidotomy device, or transtracheal jet ventilation (TTJV) equipment, LMA, ETC
Intubation	Laryngoscope with new tested batteries No. 3 and No. 4 Macintosh blades with functioning light bulbs No. 2 and No. 3 Miller blades with functioning light bulbs Endotracheal tubes - various sizes styletted with balloon pretested Laryngeal mask airway Esophageal-tracheal Combitube Tracheal tube guides (semirigid stylets, ventilating tube changer, light wand) Flexible fiberoptic intubation equipment Retrograde intubation equipment Adhesive tape or umbilical tape for securing ETT
Suction	Yankauer, endotracheal suction
Monitor	PETCO ₂ monitor, esophageal detector device
Drugs	IV induction and paralytic medication Topicalization drugs DeVilbiss sprayer for application of topical drugs Resuscitation drugs (epinephrine, atropine, etc.)
Miscellaneous	Various syringes, needles, stopcocks, IV connector tubes

Abbreviations: BVM, bag-valve mask; EDD, esophageal detector device; ETC, esophageal tracheal Combitube; ETTs, endotracheal tubes; IV, intravenous; LMA, laryngeal mask airway; PETCO₂, end tidal CO₂; TTJV, transtracheal jet ventilation.

who is preoxygenated with only room air (21% O₂) would have only about one fifth the time (or 2 minutes) before desaturation. Patients in respiratory failure frequently desaturate sooner owing to higher O₂ consumption, reduced FRC, and possibly lung disease with increased right-to-left transpulmonary shunting (Fig. 49-2).

Mask Ventilation Capability

It is critical to ensure the ability to apply oxygen in the CICU using positive pressure via a bag-valve-mask (BVM) device, along with oral and nasal airway adjuncts. BVM ventilation devices, such as an AMBU bag, deliver a significantly higher FIO₂ than either nasal cannulae or a mask alone (Table 49-3). Additionally, a BVM device enables one to ventilate a patient who is apneic or to assist ventilation in the patient with respiratory failure. The keys to using BVM devices are to provide adequate flow (10 to 15 L/min) and to ensure a tight seal between the mask and the patient's face so as not to entrain any room air during ventilation.

Intubation Equipment Check

Typically, the anesthesiologist, or other airway expert, brings the essential emergency intubation equipment to the resuscitation site in a “code box” (see Table 49-1). The user must inspect the “code box” each time he or she comes on call to make sure that the items listed in Table 49-1 are present and in working order before he or she is summoned to respond to a “code blue” situation and use the equipment.

All code box items need to be verified as present and in good working condition. The BVM device, styletted endotracheal tubes (ETT), and the laryngoscope, however, require some special notes about preparation and checkout.

The BVM device should be tested for integrity of the system and ability to generate positive pressure without leaks at connections. This can be done by using one's thumb to occlude the 15-mm exit flow orifice of the elbow connector (where it connects to a mask) while flowing O₂ through the O₂ connection tubing. The bag should inflate at a rate proportionate to the O₂ gas flow until one's occluding thumb is removed from the elbow connector exit flow orifice. If a self-inflating (AMBU) type of bag-mask device is used, pressure testing can be accomplished as already described, except that the bag will already be filled when the pressure test is begun.

The various sized styletted ETTs (balloon pretested) should be prepared as follows: An adult-sized ETT (size 7.0 or 8.0) should have a malleable stylet passed through its interior to a position just short of the tip (by approximately 5 to 10 mm). The malleable stylet allows the distal end of the ETT to be molded into a configuration that will most easily pass through the patient's vocal cords. Additionally, a styletted 6.0 ETT (or 5.0 ETT) should be prepared as a backup for patients who have small glottic openings or a difficult airway. The smaller ETTs commonly pass through a swollen or small glottic opening and into the trachea when a larger tube will not.

The rigid direct laryngoscope (RDL) with several blades is another critical piece of equipment. First, one must make sure the laryngoscope handle is clean and that the electrical connections are free of any corrosion or debris. Next, one should check that the batteries are fresh and generating a bright beam of light when the laryngoscope blades are attached. There must be at least two sizes of Miller and Macintosh blades (No.3 and No.4) so that various types of airway problems can be solved.

All of the items listed in Table 49-1 are essential and constitute the minimum airway equipment that the anesthesiologist or other airway expert should bring to the “code blue” situation.

Suction

Patients in respiratory failure may have thick secretions and/or may have vomited. To protect against aspiration and to better visualize the laryngeal anatomy, suctioning of the airway is frequently required during a “code blue.” The suction apparatus should be continuous (not intermittent) and of sufficient force to allow rapid clearance of thick oropharyngeal secretions or vomitus. During initial airway management, a Yankauer suction tip should be used to suction debris out of the oropharynx. After tracheal intubation, however, endotracheal suction catheters may be useful to clear secretions and aspirated material out of the airways.

Table 49–2. Causes of Hypoxemia in Critical Illness Requiring Emergency Airway Management

Causes	Example	P(A-a)O ₂	Response to 100% O ₂ *	Paco ₂	Therapy
Environmental causes (low P _{IO₂})	Low P _B (altitude)	Normal	↑ P _a O ₂	Normal	Give O ₂
	Low F _{IO₂} (e.g., excess N ₂ O)	Normal	↑↑ P _a O ₂	Normal	Give O ₂
Hypoventilation	- Respiratory depressant - Heroin OD - SCI	Normal	↑ P _a O ₂	↑↑	Give O ₂ then ↑ V _A
$\dot{V}_A/\dot{Q}_t$ mismatch	- Hypovolemia - Excessive V_T - Excessive PEEP	↑↑	↑↑ P _a O ₂	Normal	Give O ₂ then ↑ intravascular volume and adjust ventilation
Shunt($\dot{Q}_s/\dot{Q}_t$ R→L trans-pulmonary shunt)	- Lung collapse (HTX, PTX, atelectasis) - Pneumonia (aspiration) - Pulmonary contusion - Fat embolus - TRALI - ARDS (Sepsis/SIRS)	↑↑	No improvement in Q _s /Q _t units, but never all 2° to shunt	Normal	Give O ₂ then add PEEP, ↑ I:E ratio as tolerated
Diffusion	- Massive fluid resuscitation (interstitial edema) - ARDS	↑↑	↑ P _a O ₂	Normal	Give O ₂ then ↑ PEEP, diurese when clinically applicable
Anemia	Hemorrhage	↑	↑ P _a O ₂ (↑O ₂ content)	Normal	Give O ₂ , then transfuse PRBCs
↓ $\dot{Q}$	- Hypovolemia - Myocardial ischemia - Cardiac tamponade - PTX/HTX	↑↑	↑ P _a O ₂ (↑O ₂ content)	May ↓ in response to metabolic acidosis	Give O ₂ , then treat 1° cause
Histocytic hypoxic conditions	- CN toxicity - CO toxicity	↑↑	↑ P _a O ₂	May ↓ initially then ↑ as respiratory failure occurs	Give O ₂ , then add HBO for CO poisoning and d/c SNP for CN ⁻ toxicity

*Compared to F_{IO₂} = 0.21

↑, increased; ↓, decreased; P_{IO₂} (partial pressure of inspired O₂), F_{IO₂} × P_B; P_B, barometric pressure; F_{IO₂}, fraction of inspired oxygen; N₂O, nitrous oxide; P(A-a)O₂, partial pressure difference in O₂ between the alveolus (A) and arterial blood (a); P_aCO₂, partial pressure of CO₂ in arterial blood; O.D., overdose; SCI, Spinal cord injury; V_A, alveolar ventilation; $\dot{V}_A/\dot{Q}_t$ mismatch, alveolar ventilation/perfusion mismatch; V_T, tidal volume; PEEP, Positive end-expiratory pressure; PTX, pneumothorax; HTX, hemothorax; Asp, aspiration; TRALI, Transfusion related acute lung injury; ARDS, Acute respiratory distress syndrome; PRBCs, Packed red blood cells; $\dot{Q}$, Cardiac output; CN⁻, Cyanide; CO, Carbon monoxide; HBO, Hyperbaric oxygen.

Functioning Intravenous Catheter

A functioning intravenous catheter (IV) is mandatory when airway control is urgent but not emergent. The ability to administer fluids and cardiovascular support drugs is essential. Thus, after application of O₂ by mask, assessment of the airway, and establishment of ventilation, an IV line should be established before any attempts at airway manipulation. In a patient in full arrest, the trachea must be intubated first, and IV access may be secured secondarily. All advanced cardiac life support (ACLS) protocol drugs can be administered via the ETT except for ionic compounds (calcium, bicarbonate, and magnesium).

Monitoring (Pulse Oximetry, Blood Pressure, Electrocardiogram)

The airway expert must ensure that the patient is monitored with pulse oximetry, blood pressure cuff, and electrocardiogram (ECG) before attempting to intubate the trachea (whenever time allows). Vital sign stability and adequate arterial oxyhemoglobin

saturation are the goals of supportive measures before airway instrumentation and during and after intubation of the trachea.

Vasopressors and Inotropic Drugs

Vasopressors and inotropic drugs must be available for immediate use because hypotension is a common side effect of tracheal intubation. Hypotension can occur from the administration of anesthetic drugs, the use of positive pressure ventilation (PPV), or from relief of endogenous catecholamines elevated during respiratory failure and normalized following tracheal intubation. Furthermore, premorbid conditions in previously ill or elderly patients will further increase the likelihood of hypotension following intubation.

Airway Evaluation

Before attempting endotracheal intubation, the clinician should obtain historical and physical examination information to assess the patient's airway for technical ease of ventilation/intubation. If evaluation reveals that the patient's airway will be difficult to

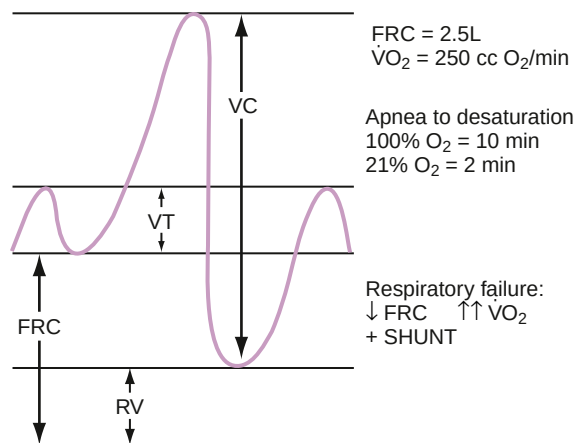


Figure 49-1. FRC and relationship of oxygen reserve. This figure illustrates the factors that determine the time from apnea until desaturation, including the functional residual capacity (FRC), the concentration of oxygen in this reservoir (F_{IO_2}), and the oxygen consumption ($\dot{V}O_2$) of the patient. The spirometric trace on the left side of the figure depicts the relative volumes of the FRC, tidal volume (V_T), residual volume (RV), and vital capacity (VC). The reservoir of oxygen in the lungs at end exhalation (FRC) in a normal 70 kg patient is approximately 2.5 L, and the resting $\dot{V}O_2$ is approximately 250 mL/min. If the patient is breathing 100% oxygen, then there is theoretically 10 minutes before desaturation. Whereas, if the patient is breathing room air (21% oxygen), there is only 2 minutes before desaturation. Furthermore, ICU patients are typically sicker with lower FRCs, increased $\dot{V}O_2$, and increased shunting, all of which can cause more rapid desaturation following apnea. (From Wilson WC: *Emergency airway management of the ward*. In Hannowell LA, Waldron RJ (eds): *Airway Management*. Philadelphia, Lippincott-Raven Publishers, 1996, pp 443-451; with permission.)

intubate, the patient should be intubated while awake. Several outstanding reviews on evaluation of the difficult airway exist.^{2,4} In this section, a definition of the difficult airway is provided, and historical and physical examination keys for predicting airway difficulty are described.

Definition of Difficult Airway

Airway difficulty can occur during mask ventilation or during endotracheal intubation. The two are not synonymous, and indeed, some patients who are difficult to ventilate with a mask (edentulous, large-jawed) may be quite easy to intubate. The difficulty of maintaining gas exchange with mask ventilation can range from zero to infinite (Fig. 49-3, top).

Difficulty of intubation using direct laryngoscopy proceeds along a similar continuum from easy to nearly impossible (Fig. 49-3, bottom). *Difficult intubation* has been defined as requiring multiple attempts with multiple maneuvers, including external laryngeal pressure, multiple blades, and/or multiple endoscopists.

Probably the best definition of difficult intubation for documentation (from one anesthesiologist to another) or for research purposes involves the grading of laryngoscopic views (Fig. 49-4): Grade I is visualization of the entire laryngeal aperture; grade IV is visualization of the soft palate only; grades II and III are intermediate views.³ Grade III or IV laryngoscopic views correlate well with difficult intubations in the vast majority of patients.^{3,5} There are, however, some clinically relevant situations that provide exceptions to this rule. First, the skill of the endoscopist in manipulating the endotracheal tube and laryngoscope may have a significant effect on the grade of laryngoscopic view. Second, a grade III laryngoscopic view has been described differently by different investigators.^{3,6} Third, the blade used for laryngoscopy affects the grade applied to the situation. A long floppy epiglottis

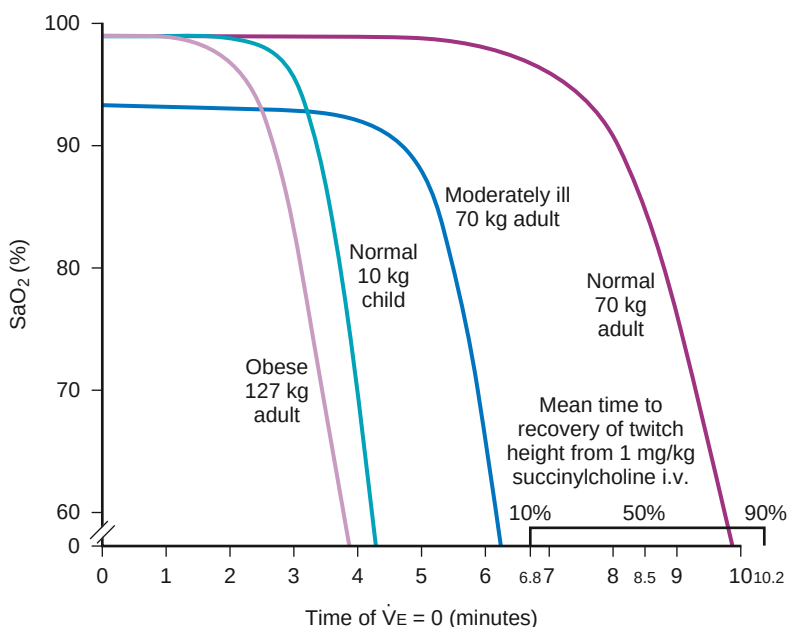


Figure 49-2. SaO_2 versus time of apnea (in minutes) for various types of patients. Time to hemoglobin desaturation with initial F_{IO_2} is 0.87. The physiologic characteristics of these patients can be obtained from the author upon request. The SaO_2 versus time curves were produced by the computer apnea model. The mean times to recovery from 1 mg/kg intravenous succinylcholine are shown in the lower right hand corner. (From Benumof JL: *Critical hemoglobin desaturation will occur before return to an unparalyzed state following 1 mg/kg IV succinylcholine*. *Anesthesiology*, 1997;87:979-982, with permission.)

may yield a high grade view (III or IV) with a MacIntosh blade and a relatively low grade (I or II) with a straight blade. Finally, traumatic conditions such as cervical spine injury (inability to move the neck into “sniffing” position), laryngeal fractures, or expanding hematomas may disassociate the laryngoscopic view from the difficulty of tracheal intubation.

Historical Indicators of Airway Difficulty

Any patient who is awake and capable of coherent conversation should be queried about prior intubation and ventilation successes or failures. Commonly, patients in the intensive care

unit (ICU) or CICU requiring emergent airway management are disoriented and unable to contribute historical data. Regardless of the patient's mental state, if time permits, the physician must review the patient's chart for details of previous intubations (easy or difficult) and other concurrent problems that may complicate the intubation plan. A good place to look is the anesthetic record for patients who have had prior surgery. If an obese patient relates that he or she requires nasal continuous positive airway pressure (CPAP) at night to sleep, mask ventilation or intubation may be more difficult than in a thin patient without such a history. Once the patient is recognized to have a difficult airway, the clinician should plan to secure the airway with the patient awake.

Table 49-3. Actual Fio_2 Achievable with Commonly Used Oxygen Administration Devices in Patients with Normal Ventilatory Breathing Patterns

Device	Flow Rate (L/min)	Achievable Fio_2
Nasal prongs	2	0.28
	6	0.44
Simple face mask	5-6	0.44
	7-8	0.6
Bag-mask device	6	0.6
	10	0.8+
	15	0.9+

Data from Gibson RL, Comer PB, Beckham RW, et al: *Anesthesiology* 1976;44:71-73.

Fio_2 , fraction of inspired O_2 .

Pathologic and Anatomic Predictors of Airway Difficulty

The patient who presents with stridor and cyanosis (from infectious, malignant, or traumatic causes) is easily recognized as having a potentially difficult airway. More subtle anatomic or pathologic causes of airway difficulty can go unrecognized in the ICU or CICU patient, however, owing to a hasty preintubation evaluation or to preoccupation with other aspects of the patient's care (e.g., acute myocardial ischemia or congestive heart failure [CHF]).

Pathologic Causes of Airway Difficulty

Several pathologic causes of airway difficulty are known to cause difficulty with mask ventilation (bull neck, thick beard, massive jaw, edentulousness, large tongue, mandibular fractures). Only some of these (bull neck and large tongue), however, are associated with difficulty of intubation. Indeed, edentulousness

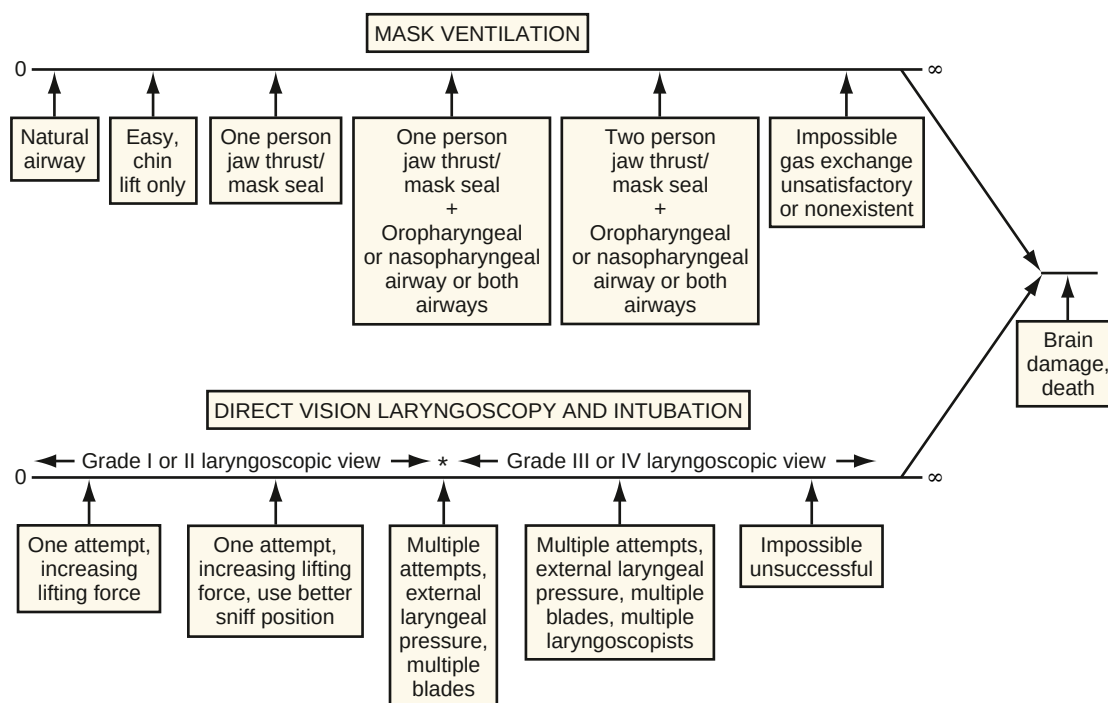


Figure 49-3. Degree of airway difficulty continuum for mask ventilation and direct vision laryngoscopy at intubation. This illustration serves to provide a conceptual frame work for the definition of airway difficulty with mask ventilation (*top*) and direct vision laryngoscopy (*bottom*). The degree of difficulty ranges from zero degrees of difficulty to the impossible or infinitely difficult airway. The amount of difficulty can vary in the same patient with different anesthesiologists using various techniques. The grade of laryngoscopic view refers to grades defined by Cormack and Lehane (see Fig. 49-4). (From Benumof JL: *Management of the difficult airway. Anesthesiology* 1991;75:1087, with permission.)

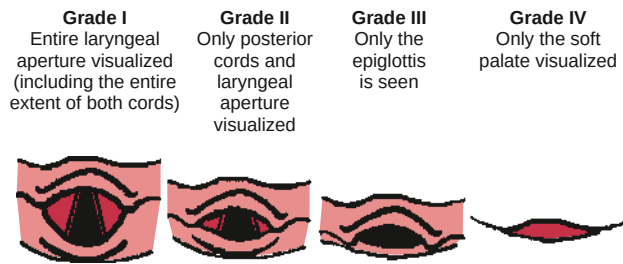


Figure 49-4. Four grades of laryngoscopic view. The grading of laryngoscopic view is based upon the anatomic features that are visualized during the performance of direct laryngoscopy. (From Cormack RS, Lehane J: *Difficult tracheal intubation in obstetrics. Anesthesia* 1984;39: 1105, with permission.)

and mandibular fractures can actually make intubation of the trachea easier.

Pathologic factors associated with difficult intubation include congenital facial and upper airway deformities, cervical trauma, rheumatoid arthritis (because of decreased neck movement), intraoral tumor or abscess, and maxillary or facial airway trauma (in which edema, blood, and pus may obscure the view).

Anatomic Characteristics That Impair Laryngoscopy

Anatomic characteristics that are known to impair direct laryngoscopy are listed in Table 49-3. Of the seven predictors shown in Table 49-3, none is by itself predictive of airway difficulty. However, when taken in combination, airway difficulty can be predicted. Receding mandible or anterior larynx is evaluated in the fully extended adult neck. When the distance between the mandible and the upper border of thyroid cartilage is less than 6 cm, visualization of the vocal cords is predictably difficult.⁶

Airway Examination Principles

The 11-Step Airway Exam of Benumof

Although emergency conditions do not always allow for enough time, a physical examination of the airway should be conducted before the initiation of airway management of all patients. The intent of the airway examination is to detect anatomic and pathologic physical characteristics that may indicate that airway management will be difficult.

Currently, the American Society of Anesthesiologists Difficult Airway (ASA DA) guidelines have endorsed an easily performed 11 step airway physical examination, as originally proposed by Benumof (Table 49-4).⁷ The decision to examine all or some of the components listed in Table 49-4 depends upon the clinical context and judgment of the practitioner. The order of presentation in the table follows the “line of sight” that occurs during conventional oral laryngoscopy and intubation. Of note, several of the examination components listed in Table 49-4 require an awake, cooperative patient. Even in the noncooperative, semi-urgent situation, the airway expert can check the length of the upper incisors, the mandibular space compliance, thyromental distance, and neck length and neck thickness to assess the relative difficulty of intubation, as the aforementioned components do not require patient cooperation. Because certain elements of this 11-step examination cannot be practically evaluated in the all critically ill patients, an abbreviated airway examination is recommended.

Table 49-4. Anatomic/Pathologic Predictors of Difficult Intubation/Ventilation

Anatomy	Difficult Ventilation	Difficult Intubation
Neck	Bull neck Obesity	Bull neck Obesity Decreased head extension or neck flexion
Tongue	Large tongue	Large tongue
Mandible	Thick beard	Receding mandible Decreased jaw movement
Teeth	Edentulousness	Buck teeth
Pathology		
Maxillofacial	Facial plethora Facial fractures and lacerations	Facial fractures Facial plethora
Oropharyngeal	Edema Hematoma Inflammation Foreign body Tumor	Edema Hematoma Inflammation
Glottis	Edema Vocal cord paralysis	Edema Vocal cord paralysis
Neck	Subcutaneous emphysema Penetrating trauma	C-spine injury Cervical mass/hematoma Subcutaneous emphysema

Three Easy Airway Evaluation Tests

Missed signs of a difficult airway can be minimized if one looks carefully for both pathologic and anatomic abnormalities. Investigators have sought to determine anatomic characteristics that correlate with intubation difficulty. Three airway evaluation tests that are easy to perform have emerged as highly predictive indicators of intubation difficulty: Mallampati class, thyromental distance, and atlanto-occipital (AO) extension. When these three tests are used in the same patient, their combined predictive power becomes quite substantial.

Relative Tongue/Pharyngeal Size (Mallampati Class)

Mallampati and associates⁸ in 1985 proposed the size of the tongue in relation to the size of the oral cavity as a clinical sign of the difficulty of tracheal intubation (Fig. 49-5). Lewis and colleagues⁹ have demonstrated that the Mallampati classification is best obtained with the patient in the sitting position, with the head in full extension, with tongue out, and with phonation, because the test is more predictive and easier to perform under these conditions.

Thyromental Distance or Mandibular Space

Space anterior to the larynx—thyromental distance—greater than 6 cm suggests that direct laryngoscopy will be relatively easy.¹⁰ Because the tongue must be moved anteriorly and caudad

(in a supine patient) by the laryngoscope, the mandibular space must be large enough to accommodate the tongue and allow exposure of the glottis.

Atlanto-Occipital Joint Extension

Normally, 35 degrees of atlanto-occipital (AO) extension are possible at the AO joint. Bellhouse and Dore¹¹ have demonstrated that AO joint extension can be easily measured clinically, and that the measurement is highly predictive of the ease of intubation.

Evaluating the Airway of the Trauma Patient

In trauma patients (with suspected cervical spine injury), the neck must not be moved until radiographically and clinically confirmed as uninjured. Thus, such patients are analogous to those with little or no AO extension. Fortunately, the combined power of a favorable thyromental distance (>6 cm) and low Mallampati classification (I or II) provides quite strong predictors of an easy intubation.^{12,13}

Patient Preparation and Positioning

Regardless of whether an awake, topicalized technique or a rapid-sequence technique is chosen, proper patient positioning and preparation are important.

Preparation for Awake Technique

If a blind nasal or fiberoptic intubation is planned, the head of the patient's bed should be elevated at least 45 degrees to facilitate intubation. The patient should be psychologically prepared, and the airway expert must be thorough in ensuring that the nasopharynx, oropharynx, and larynx are properly anesthetized with topically applied local anesthesia before beginning intubation.

"Sniffing" Position (Preparation for Rapid-Sequence Technique)

The "sniffing" position is the optimum position for direct laryngoscopy and endotracheal intubation using a rapid-sequence technique. One of the most common reasons for difficulty with laryngoscopy and intubation is failure to place the patient in an adequate sniffing position. The sniffing position involves forward flexion of the neck on the chest and atlanto-occipital extension of the head at the neck. This maneuver aligns the oropharyngeal, laryngeal, and tracheal axes (Fig. 49-6). The easiest way to accomplish this is to place at least two folded towels under the head of the supine patient. The first attempt at laryngoscopy should be a well-prepared one. Once the patient is placed in an adequate sniffing position, a helper should apply cricoid pressure to protect against regurgitation of gastric contents.

Alternative Plan and Extra Help

After assessing the airway and evaluating the patient's underlying pathologic condition, one must devise a plan for intubation. If there is any concern that the patient's airway will be difficult to intubate, an awake technique with spontaneous ventilation should be chosen. Regardless of the primary plan, there must always be a "plan B."

Whenever securing the airway, one must make sure to have extra help available. The expert should communicate with the patient and the assistants to ascertain that everyone understands the plan.

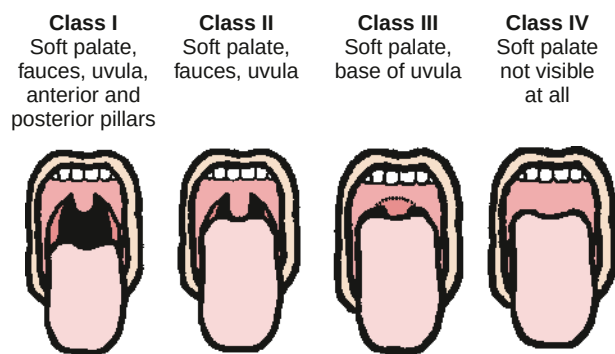


Figure 49-5. Mallampati classification. Classification of the upper airway relating to the size of the tongue to the pharyngeal space based upon the anatomic features seen with the mouth open and the tongue extended. (Modified from Mallampati, SR et al. *A clinical sign to predict difficult tracheal intubation: a prospective study.* *Can J Anaesth* 1985;32:429, with permission.)

Techniques of Emergency Airway Management

Mask Ventilation

Types of Masks Used for Ventilation

Face masks come in a variety of shapes, but most airway experts prefer anatomically shaped masks because they fit the patient's face and the clinician's hand best. Adult masks come in small, medium, and large (sizes 3, 4, and 5). Most adults can be ventilated with a size 3 or 4 mask, but occasionally, a patient with a large jaw requires a size 5 mask.

Mask Ventilation Technique

The face mask must be applied firmly to the patient's face to ensure an adequate seal, although care must be taken not to injure the bridge of the nose with excessive pressure. A single-hand technique is acceptable if the airway is easy to ventilate (Fig. 49-7). If, however, ventilation is not easy, two hands should be used to hold the mask in place while another person depresses the bag in an attempt to ventilate the patient (Fig. 49-8). Frequently, the application of jaw thrust (backward and upward pull of the jaw in a supine patient) opens an airway and allows ventilation.

Oropharyngeal and Nasopharyngeal Airways

When the tongue and other soft tissues are maintained in the normal forward position, the posterior pharyngeal wall remains nonobstructed, and the airway is generally open (Fig. 49-9, A).

The most common cause of airway obstruction is falling back of the tongue and epiglottis in supine, unconscious patients (Fig. 49-9, B). This can be alleviated by the jaw thrust maneuver. Regardless of whether jaw thrust is successful, an oral or nasal airway as an adjunct to bag-mask ventilation can open up a closed airway.

Both oral (Fig. 49-9, C) and nasal (Fig. 49-9, D) airways restore airway patency by separating the tongue from the posterior pharyngeal wall. A rigid oral airway may elicit a gag response from an awake patient, which may be followed by emesis. Soft nasal airways provoke less gag response than rigid oral airways. Soft nasal airways are commonly inserted in patients suffering from ventilatory failure, who are more awake and prone to gagging on the rigid oral airway. Coagulopathies and nasal or basilar skull fractures are relative contraindications to nasal airways.

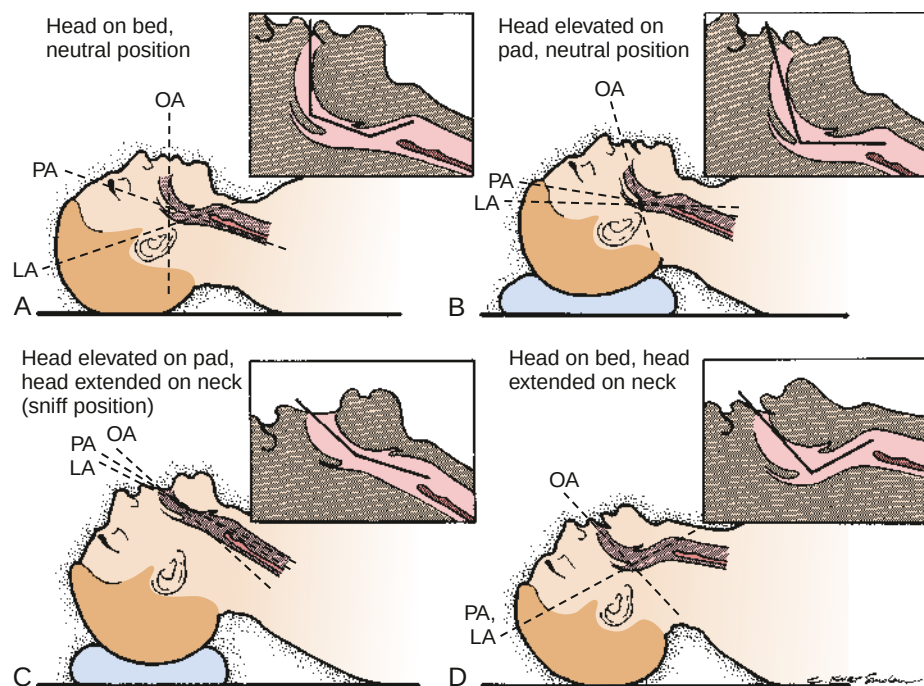


Figure 49-6. Head position and the axis of the upper airway. This diagram demonstrates the various head and neck positions in the supine patient and the corresponding oral axis (OA), pharyngeal axis (PA), and laryngeal axis (LA) in four different head positions. Each head position is accompanied by an inset that magnifies the upper airway and superimposes the continuity of these three axes within the upper airway. The upper left panel (A) shows the head in the neutral position with marked nonalignment of the various axes. In the upper right panel (B), the head is resting on a pillow, which causes forward flexion of the neck on the chest and serves to align the pharyngeal axis and the laryngeal axis. However, the oral axis remains nonaligned. The lower right panel (D) shows extension of the head on the neck without concomitant elevation of the head on the pad resulting in nonalignment of the oral pharyngeal with the laryngeal and pharyngeal axes. The lower left panel (C) shows the head resting on a pad that flexes the neck forward on the chest along with extension of the head on the neck, which brings all three axes into alignment (sniff position). This position allows for a direct view from the oral pharynx to the larynx providing the tongue and soft tissues are elevated out of the way with a rigid direct laryngoscope. (From Benumof JL: *Conventional (laryngoscopic) orotracheal and nasotracheal intubation (single lumen type)*. In Benumof JL (ed): *Clinical Procedures in Anesthesia and Intensive Care*. Philadelphia JB Lippincott Co, 1992, p 123, with permission.)

Laryngeal Mask Airway (LMA)

Ventilatory obstruction above the level of the cords (supraglottic) can be alleviated by the LMA because of its supraglottic placement (Fig. 49-10). However, the LMA is not an effective ventilatory device in cases of periglottic or subglottic pathology (e.g., laryngospasm, subglottic obstruction).¹⁴

The LMA is inserted blindly into the oropharynx forming a low pressure seal around the laryngeal inlet, thereby permitting gentle positive pressure ventilation with a leak pressure in the range of 15 to 20 cm H₂O. Therefore, LMA is relatively contraindicated in the presence of a known supraglottic hematoma or other expanding lesion (e.g., abscess) that might rupture. However, it can be very useful in other supraglottic obstructive conditions such as those due to swelling, edema, or redundant tissues. Placement of an LMA requires a completely anesthetized airway or an anesthetized patient.¹⁵ The LMA has been shown to rapidly restore efficient ventilation in numerous cannot intubate-cannot ventilate situations.¹⁵⁻¹⁷

Rigid Direct Laryngoscopy

Before performing laryngoscopy, the airway expert should test the laryngoscope blade and handle to ensure proper functioning. The laryngoscope is held in the left hand, so that the right hand is free to place the styletted endotracheal tube through the

cords and into the trachea. The patient's mouth is opened by simultaneously extending the head on the neck with the right hand, and using the small finger of the left hand (while holding the laryngoscope) to push the anterior part of the mandible in a caudal direction and opening the mouth (Fig. 49-11).

As the blade enters the oral cavity, gentle pressure is applied on the tongue, sweeping it leftward and anteriorly (Fig. 49-12) so as to expose the glottic aperture. Two basic types of blades are in common use: a curved (MacIntosh) blade and a straight (Miller and Wisconsin) blade. The curved MacIntosh blade (Fig. 49-13) tip is placed in the vallecula after the tongue is slid leftward and anteriorly and while the laryngoscope handle is lifted in a forward and upward direction (stretching the hyoepiglottic ligament). This causes the epiglottis to move upward, exposing the arytenoid cartilages and eventually the vocal cords. The straight Miller blade (Fig. 49-14) is inserted until the epiglottis is visualized, and then the epiglottis is elevated to expose the glottic aperture.

Six common errors can occur during RDL use. First, the blade can be inserted too far into the pharynx, elevating the entire larynx which exposes the esophagus instead of the glottis. Second, for optimal laryngoscopy, the tongue must be completely swept to the left side of the mouth with the flange on the RDL blade. This is slightly more difficult to accomplish with the Miller blade

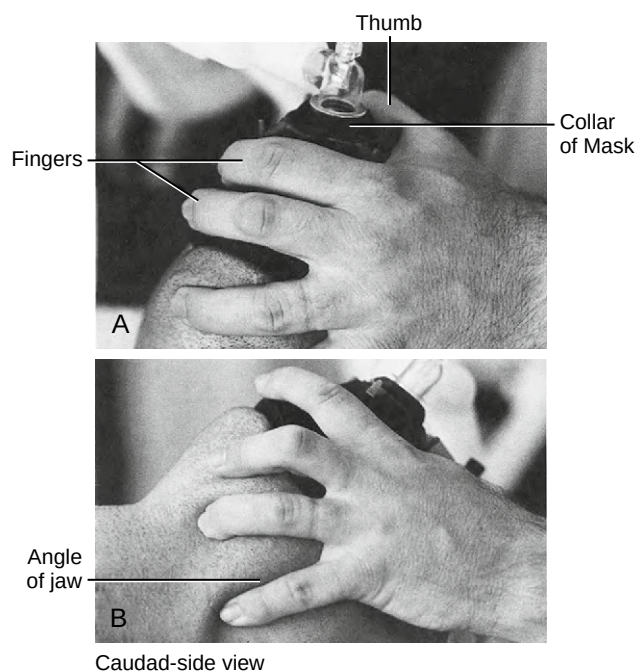


Figure 49-7. Mask ventilation one-hand technique. This figure shows the one-handed technique in holding a mask properly on a patient's face. The top figure (A) demonstrates the standard one-handed grip of the mask on the face. The thumb encircles the upper part of the patient's mask while the second and third finger are applied to the lower portion of the mask with the fourth and fifth fingers pulling the soft tissue under the mandible up toward the mask. The lower panel (B) demonstrates the one-handed mask grip while maintaining jaw thrust. The hand positions are altered such that only the thumb and the second finger encircle the mask while the third, fourth, and fifth fingers maintain upward and backward pull of the mandible "jaw thrust." Typically an oral airway would have been placed in the patient's oropharynx before manipulating the mandible with the "jaw thrust" maneuver. (Modified from McGee JP, Vender JS: *Nonintubation management of the airway*. In Benumof JL (ed): *Clinical Procedures in Anesthesia and Intensive Care*. Philadelphia JB Lippincott Co, 1992, p 107, with permission.)

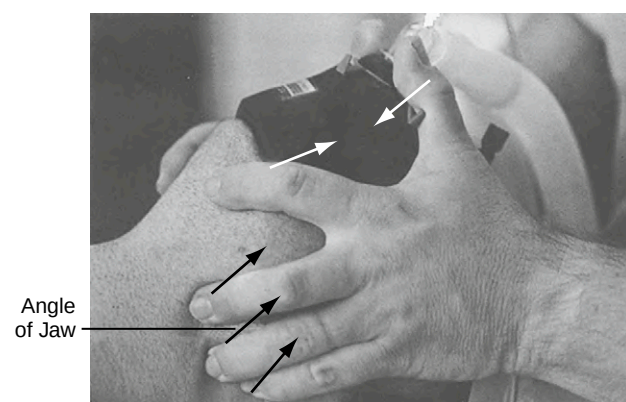


Figure 49-8. Two-hand mask ventilation technique. With the two-handed technique, the thumbs are hooked over the collar of the mask while the lower fingers maintain jaw thrust and the upper fingers are pulling the mandible into the mask while extending the head (arrows indicate direction of force). (Modified from McGee JP, Vender JS: *Nonintubation management of the airway*. In Benumof JL (ed): *Clinical Procedures in Anesthesia and Intensive Care*. Philadelphia JB Lippincott Co, 1992, p 109, with permission.)

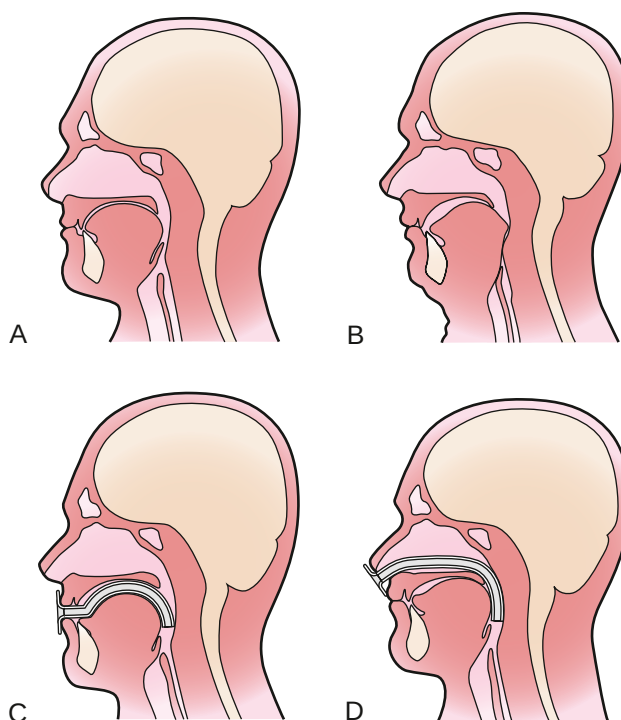


Figure 49-9. Normal airway, soft tissue obstruction, and use of laryngeal and nasopharyngeal airways. This series of four panels describes in sequence the normal (unobstructed) airway (A), the obstructed airway (B), and use of the oral (C) and nasal (D) airways. The normal airway (A) maintains the tongue and other soft tissues in the forward position, allowing unobstructed passage of air. The next panel (B) demonstrates the typical obstructed airway of an unconscious supine patient. The tongue and epiglottis fall back to the posterior pharyngeal wall and occlude the airway. In panel C, the use of oral pharyngeal airway is demonstrated. The oral pharyngeal airway follows the curvature of the tongue and pulls it and the epiglottis away from the posterior pharyngeal wall providing a channel for air passage. In the last panel (D), the use of the nasal pharyngeal airway is demonstrated. This airway passes through the nose and ends at a point just above the epiglottis clearing the air passage. (Modified from Stone DJ, Gal TJ: *Airway management*. In Miller RD (ed): *Anesthesia*, 4th ed. New York, Churchill Livingstone 1994; 1403–1436, with permission.)

because the flange is less prominent. Third, novice laryngoscopists frequently rock the RDL in the patient's mouth using the upper incisor as a fulcrum in a self-defeating attempt to visualize the glottis. This can chip the patient's upper incisors and moves the glottic aperture further anterior out of view. The correct approach is to lift the handle anterior and forward at an approximately 45° angle (see Fig. 49-14). Fourth, proper sniffing position is not always achieved or indicated. Fifth, in obese barrel-chested patients and large breasted women, it can be difficult to insert the blade in the mouth. Use of a short handled RDL or removal of the blade from the scope handle and reattaching once the blade is positioned in the mouth helps with this predicament. Finally, improper blade selection may hinder laryngoscopy and intubation. If the patient has a long floppy epiglottis, a Miller blade may be best; a large wide tongue may be best managed using a Macintosh blade.

Numerous developments have been made in the last decade combining fiberoptic technology with various configurations of

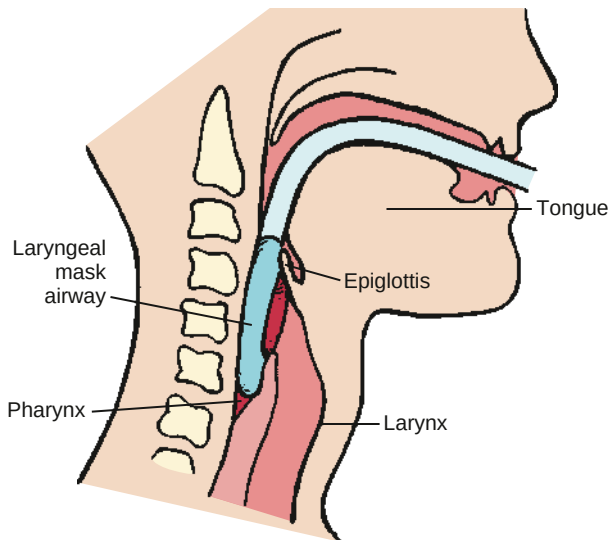


Figure 49-10. LMA. The normal anatomic position of the laryngeal mask airway. The proximal portion of the laryngeal mask rests upon the epiglottis, whereas the distal end extends into the pharynx at the upper end of the esophagus. The opening on the laryngeal mask overlies the laryngeal inlet. This figure demonstrates a prototypical LMA and is not meant to represent any particular commercially available device. (Modified from Brain AJJ: *The laryngeal mask: a new concept in airway management*. *Br J Anaesth* 1983;55:801, with permission.)

the laryngoscope, with the goal of improving intubation success, and decreasing the need to move the neck when manipulating the airway. Such laryngoscopic devices as the Bullard Laryngoscope (Circon, ACMI, Stamford, Conn.) and the WuScope (Achi Corp., Dublin, Calif.) are representative of this approach and have been in use for more than a decade. More recent innovations include the GlideScope (Verathon, Inc., Bothell, Wash.) (Fig. 49-15, 49-16). In recent studies of simulating easy and difficult airways with novice GlideScope users, the laryngoscopic view was either the same or superior in the difficult intubation scenario.¹⁸

Rapid Sequence Intubation

Patients who require emergency intubation are at increased risk of regurgitation and aspiration, partly because they have not fasted before induction. To minimize the likelihood of regurgitation and aspiration, RSI techniques were developed. Classically, RSI includes preoxygenation with 100% O₂ for 5 minutes (as discussed above), followed by the application of cricoid pressure, and in rapid sequence order an induction drug and a rapid acting neuromuscular blockade (NMB) drug (e.g., succinylcholine 1 to 2 mg/kg or Rocuronium, 1.2 mg/kg) are administered without testing ventilation beforehand. As soon as airway reflexes are lost, the RDL is used to visualize the glottis and facilitate placement of a styletated ETT. Cricoid pressure is maintained until P_{ET}-CO₂ is detected from the putative ETT, equal bilateral breath sounds are auscultated and the intubating anesthesiologist declares that it may be released.

Cricoid pressure (Sellick maneuver) denotes downward (posterior) pressure on the neck overlying the cricoid cartilage. This

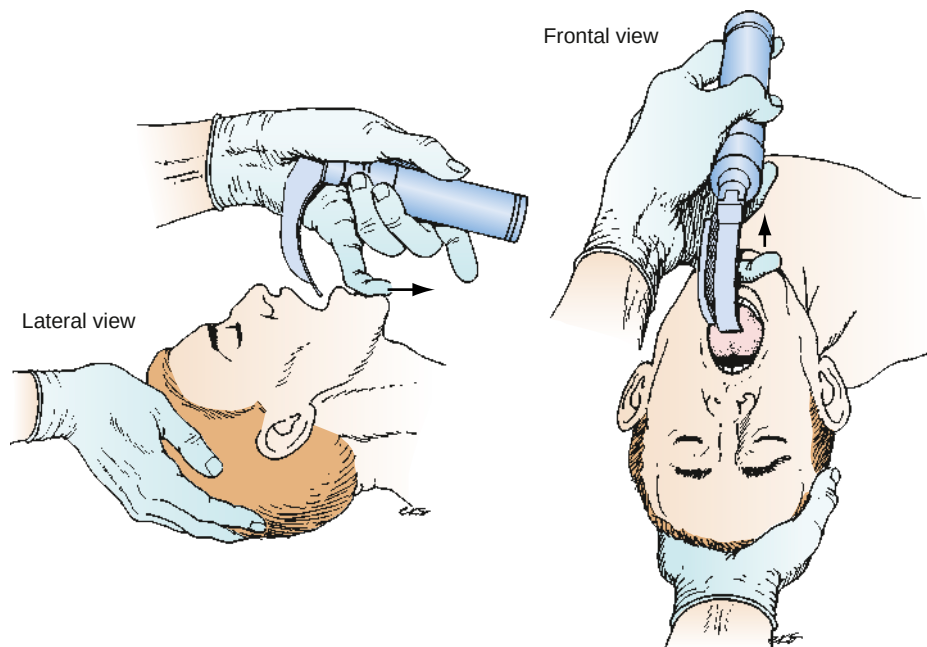


Figure 49-11. Opening the mouth for laryngoscopy: use of the little finger. The mouth can be opened wide by concomitantly extending the head on the neck with the right hand while the small finger and the medial border of the left hand pushes the anterior aspect of the mandible in a caudad direction. The laryngoscope is held in the left hand while opening the mouth with this technique. As the blade approaches the mouth, it should be directed to the right side of the tongue. Gloves should be worn during laryngoscopy and the hands should be kept out of the oral cavity to limit contact with the patient's secretions. (From Benumof JL: *Conventional (laryngoscopic) orotracheal and nasotracheal intubation (single lumen type)*. In Benumof JL (ed): *Clinical Procedures in Anesthesia and Intensive Care*. Philadelphia JB Lippincott Co, 1992, p 124, with permission.)

cricoid pressure compresses the esophagus and is intended to decrease the likelihood of gastric contents leaking into the pharynx. Occasionally, cricoid pressure can impair the laryngoscopic view. “Laryngeal manipulation” is not analogous to cricoid pressure; it is the movement of the thyroid cartilage posterior to bring the laryngeal aperture into view. Use of a rigid stylet also increases the likelihood of intubation success in difficult-to-intubate patients.^{19,20} During intubation attempts, the patient should be carefully monitored by pulse-oximetry, heart rate (HR), blood pressure (BP), and ECG. Intubation attempts should be interrupted by reoxygenation using BVM ventilation if the

procedure takes more than 30 seconds or when desaturation ($\text{SpO}_2 < 90\%$) occurs. If intubation attempts fail and adequate oxygenation cannot be achieved with BVM ventilation, a laryngeal mask airway (LMA) should be considered as per the ASA DA algorithm.¹⁴

Modified RSI Techniques

The RSI technique can be modified in at least two major ways: (1) institution of BVM ventilation before placement of the ETT and (2) allowing spontaneous ventilation (SV) to be maintained during placement of the ETT (Table 49-5).

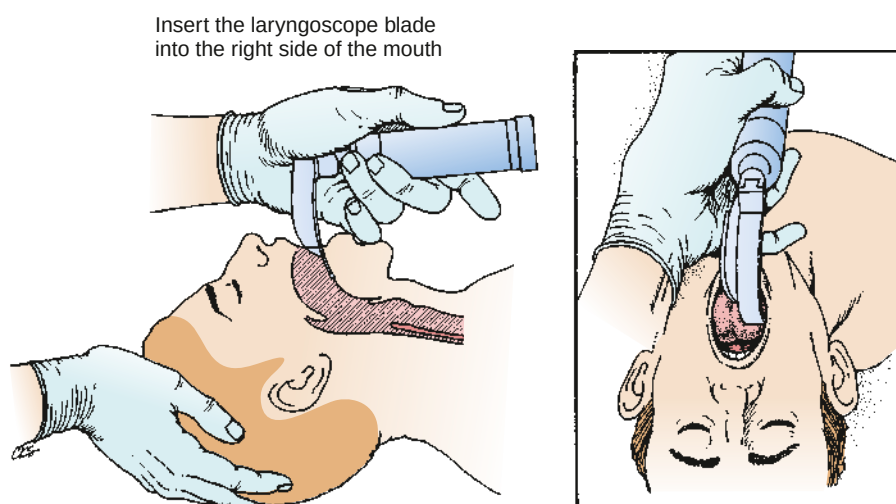


Figure 49-12. Inserting the laryngoscope blade into the right side of the mouth. This figure demonstrates the proper head and neck positioning for insertion of a curved (Macintosh) laryngoscope blade. The inset shows the blade entering the right side of the oral cavity so that the tongue will be moved toward the left side of the mouth with the large flange on the Macintosh blade thereby creating a view of the larynx. (From Benumof JL: *Conventional (laryngoscopic) orotracheal and nasotracheal intubation (single lumen type)*. In Benumof JL (ed): *Clinical Procedures in Anesthesia and Intensive Care*. Philadelphia JB Lippincott Co, 1992, p 125, with permission.)

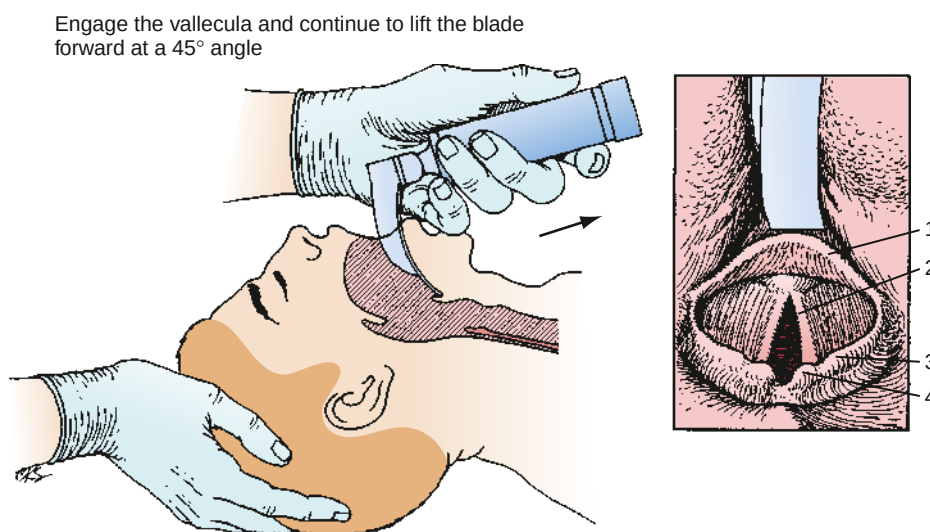


Figure 49-13. Correct position of the Macintosh laryngoscope blade in the vallecula. This figure demonstrates the correct position of the curved (Macintosh) laryngoscope blade in the vallecula and the angle of pressure that should be applied (45 degrees from the patient's axial line). The inset demonstrates the laryngeal view obtained when the Macintosh blade is used. 1 = epiglottis, 2 = vocal cords, 3 = cuneiform part of arytenoid cartilage, and 4 = corniculate part of arytenoid cartilage. (From Benumof JL: *Conventional (laryngoscopic) orotracheal and nasotracheal intubation (single lumen type)*. In Benumof JL (ed): *Clinical Procedures in Anesthesia and Intensive Care*. Philadelphia JB Lippincott Co, 1992, p 127, with permission.)

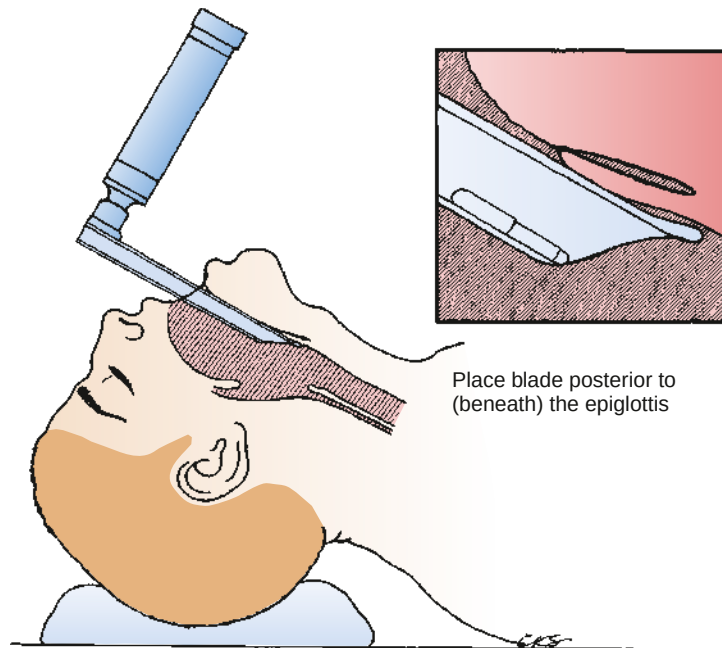


Figure 49-14. Laryngoscopic technique with a straight (Miller) blade. A straight (Miller) laryngoscope blade should pass underneath the laryngeal surface of the epiglottis; then the handle of the laryngoscope blade should be elevated at a 45-degree angle similar to that used with a Macintosh blade. By lifting up the epiglottis, the laryngeal aperture should come clearly into view. (From Benumof JL: *Conventional (laryngoscopic) orotracheal and nasotracheal intubation (single lumen type)*. In Benumof JL (ed): *Clinical Procedures in Anesthesia and Intensive Care*. Philadelphia JB Lippincott Co, 1992, p 128, with permission.)



Figure 49-15. GlideScope video laryngoscope Cobalt. Single-use, sterile Cobalt GVL Stat with reusable Video Baton. (Images courtesy of Verathon, Inc.)

The application of BVM ventilation during RSI is indicated in instances where apnea is likely to result in rapid desaturation despite properly performed preoxygenation. Trauma and critically ill patients often suffer from conditions causing increased right-to-left transpulmonary shunting (e.g., pulmonary contusion, pneumonia) and thus require additional O_2 and ventilation after induction and before full effect of NMB drugs. This modification to the RSI technique involves gentle BVM ventilation with 100% O_2 while maintaining cricoid pressure (to prevent gastric insufflation and decrease the risk of regurgitation and/or aspiration).

The RSI technique can also be modified by maintaining SV. This modification is employed in situations where apnea may lead to the inability to ventilate (e.g., patients with partial airway obstruction manifested by audible stridor) and when positive pressure ventilation might extend a partial airway disruption into a complete separation (e.g., tracheal or main stem bronchus

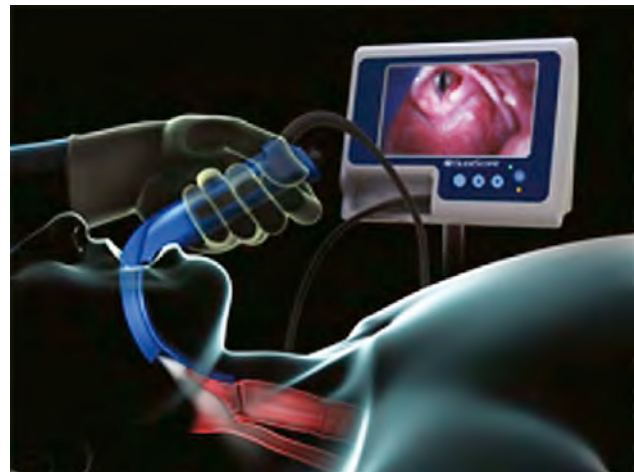


Figure 49-16. GlideScope video laryngoscope. Actual airway view achieved by the GlideScope video laryngoscope. (Images courtesy of Verathon, Inc.)

tears). The maintenance of SV is also indicated in a patient who cannot tolerate the hemodynamic consequence of positive pressure ventilation (e.g., severe cardiac tamponade). An uncooperative patient with an obvious DA represents another patient condition where the maintenance of SV may be indicated. In this setting, a small dose of sedation should be administered to gain control of the situation and SV is preserved while employing cricoid pressure.

In situations where SV is maintained and the patient is sedated as needed, the trachea is often intubated using a fiberoptic bronchoscope (FOB) through an intubating mask (described in detail

Table 49–5. Rapid Sequence Intubation Principles: Classic Versus Modified Techniques

Elements	PRE-O ₂	Cricoid Pressure	Induction Drug Followed by NMBD	BVM Ventilation Deferred until ETT Confirmed	Confirm ETT with Paco ₂
Classical	+	+	+	+	+
Modified: by allowing BVM ventilation (with cricoid pressure) before ETT	+	+	+	(–) Can BVM vent as needed to avoid hypoxemia	+
Modified: By maintaining spontaneous ventilation until ETT placement confirmed*	+	+	(–) Small amounts of sedative or induction drug used, but SV maintained. No NMB given until ETT position confirmed.	(–) Can assist ventilation some, but goal is to maintain SV until ETT placed.	+

*No NMB drugs given until ETT in place or laryngoscopist convinced ETT placement will be easy.

Abbreviations: +, element is used during the technique of classical or modified Rapid Sequence Technique; (–) = not utilized; BVM, bag-valve-mask; ETT, endotracheal tube; NMBD, neuromuscular blockade drug; SV, spontaneous ventilation.

later).²¹ The proper amount of drug required to sedate the patient enough to manipulate the airway, but not so much as to result in apnea, varies based upon the size of the patient, the amount of blood loss, and the levels of other drugs already administered.

The Difficult Airway

The ASA Difficult Airway (DA) Algorithm

Practice guidelines for management of the DA were originally published in 1993²² and were updated recently in a report published by the ASA Task Force on Management of the DA.⁷

The original practice guidelines (1993) were developed by a taskforce of ASA members who expounded upon the original ideas put forth in a medical intelligence article written by Dr. Jonathan L. Benumof in 1991, entitled “Management of the DA.”⁴

In 1996, Dr. Benumof wrote another landmark article discussing the development and use of the LMA and its implications on the ASA DA algorithm.¹⁴ This article contributed to the ASA's decision to revise the 1993 algorithm. The current version has emerged after the ASA Task Force reviewed the literature published over the last 60 years and obtained expert opinions from other ASA members to build a consensus.

There are several critical decision tree elements present in the ASA DA algorithm. These include recognition of the difficult airway, awake intubation techniques, and anesthetized intubation techniques (whether recognized or not) (Fig. 49-17).

Recognition of the Difficult Airway

The ASA DA algorithm begins with recognition of airway difficulty. The patient who sustained penetrating trauma to the neck with stridor and cyanosis is easily recognized as a potentially difficult airway. However, there may be more subtle anatomic or pathologic causes of airway difficulty that can go unrecognized in the traumatized patient due to hasty preoperative evaluation or preoccupation with other aspects of the patient's care. Missed signs of a difficult airway can be minimized if one looks carefully for both pathologic and anatomic abnormalities as previously described. Whenever the patient is recognized to have a difficult airway, the clinician should consider securing the airway using an awake technique, as long as the patient is cooperative, hemodynamically stable, and spontaneously ventilating.

Awake Limb of the ASA Difficult Airway Algorithm

An “awake” intubation technique is recommended for patients with known or anticipated difficult airways provided they are cooperative, stable, and spontaneously ventilating. To optimize the conditions for successful intubation, cooperation is enhanced with proper mental and physical preparation. Although the ASA DA guidelines⁷ do not endorse any particular awake intubation tool or methodology, an awake FOB-guided technique is generally the safest and most appropriate for stable scenarios (discussed later in detail). It does emphasize, however, that the patient must be properly prepared (both mentally and physically) for an awake technique, the physician must ensure that spontaneous ventilation continues and O₂ saturation is maintained throughout the procedure. Even when a tracheostomy is planned, performing an awake FOB assisted intubation under direct vision is recommended whenever able to achieve airway protection before performing the formal tracheostomy.

The basic ASA DA algorithm recommends considering abandoning the airway attempt while maintaining spontaneous ventilation, and allowing the patient to recover from topicalization or sedative medications and resume management later with a better plan (other equipment/personnel). However, stopping is rarely an option in emergency airway management situations (i.e., the patient with cardiorespiratory failure). If at any time during the awake intubation manipulation, the patient is unable to ventilate by mask and intubation is not successful, then consideration should be given to use of emergency airway adjunct devices such as the LMA, esophageal tracheal Combitube (ETC), transtracheal jet ventilation (TTJV), or a surgical airway.

Unstable, Uncooperative, or Apneic Patients with Difficult Airways

There are three scenarios in which the need arises to intubate the trachea of an unstable, uncooperative, or apneic patient with pre-existing difficult airways. These situations include: (1) when the airway is not recognized to be difficult, (2) the DA patient is already unconscious before presentation to the “code blue” scenario, and (3) the DA patient is hemodynamically unstable or unable to cooperate with an awake technique. In all of these conditions, the generally anesthetized limb of the ASA DA algorithm is followed. In the uncooperative patient,



DIFFICULT AIRWAY ALGORITHM

1. Assess the likelihood and clinical impact of basic management problems:
 - A. Difficult Ventilation
 - B. Difficult Intubation
 - C. Difficult with Patient Cooperation or Consent
 - D. Difficult Tracheostomy
2. Actively pursue opportunities to deliver supplemental oxygen throughout the process of difficult airway management.
3. Consider the relative merits and feasibility of basic management choices:
 - A. Awake Intubation vs. Intubation Attempts After Induction of General Anesthesia
 - B. Non-invasive Technique for Initial Approach to Intubation vs. Invasive Technique for Initial Approach to Intubation
 - C. Preservation of Spontaneous Ventilation vs. Ablation of Spontaneous Ventilation

4. Develop primary and alternative strategies:

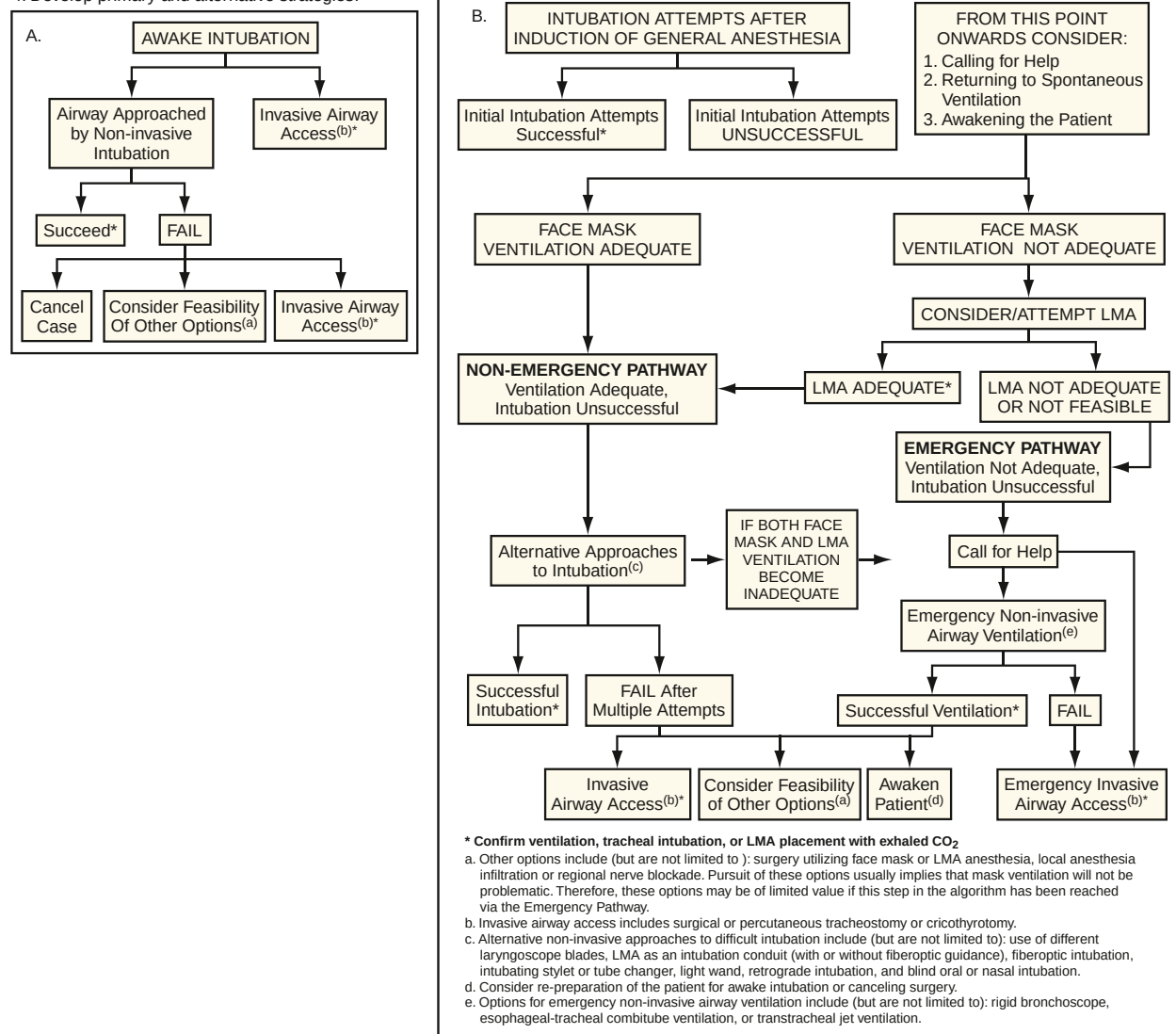


Figure 49-17. ASA difficult airway algorithm. (Modified from ASA Task Force: Practice guidelines for management of the difficult airway: an updated report by the American Society of Anesthesiologists' task force on management of the difficult airway. *Anesthesiology* 2003;98(5):1269-1277, with permission.)

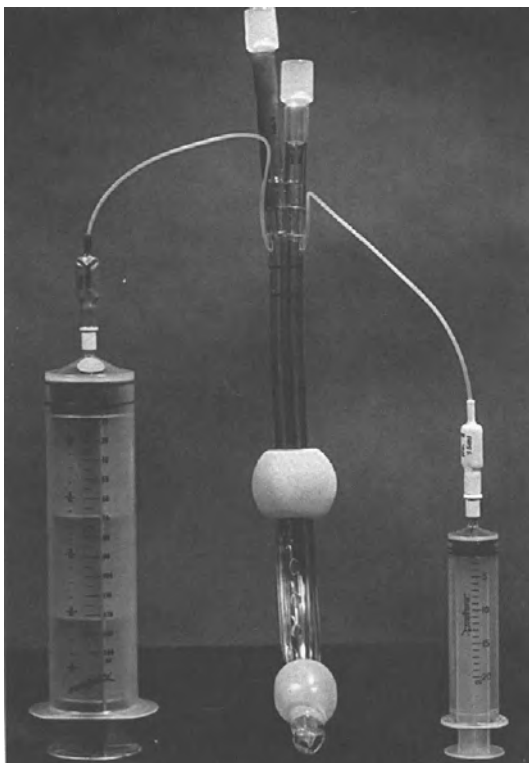


Figure 49-18. Frontal view of the esophageal-tracheal Combitube. This figure demonstrates the two longitudinally fused tubes comprising the Combitube; both cuffs are inflated with their corresponding syringes. Lumen No.1 is the longer tube located on the left and lumen No.2 is on the right. (Modified from Wissler RN: *The esophageal-tracheal Combitube*. *Anesthesiol Rev* 1993;20:147-151, with permission.)

preinduction assessment should have identified factors that might make intubation of the trachea difficult and the airway expert should consider using a technique that maintains spontaneous ventilation despite the need for anesthesia. If intubation cannot be achieved, BVM ventilation should be attempted with enriched O₂ while applying cricoid pressure. In the cannot intubate-cannot ventilate (CNI-CNV) patient, the emergency limb of the ASA DA algorithm (Fig. 49-17) is followed. Various intubation modalities can be employed to maintain oxygenation before definitive ETT placement, the LMA being first. If ventilation is not successful with the LMA, other secondary emergency airway tools are tried including the ETC, TTJV, and the rigid ventilating bronchoscope. Various surgical airway techniques (cricothyroidotomy, tracheostomy) can also be considered.

Esophageal-Tracheal Combitube

The esophageal-tracheal Combitube (Sheridan Catheter Corporation, Argyle, N.Y.) was developed specifically for emergency airway management.²³ The Combitube consists of longitudinally fused tubes made of polyvinylchloride (PVC) with a standard 15-mm airway connector on the proximal end of each tube. There are two inflatable balloons on the Combitube: a proximal 100-mL latex pharyngeal balloon, and a 15-mL PVC balloon near the distal tip (Fig. 49-18). The Combitube has a distal curve to match the adult human hypopharynx. More than 96% of the times that a Combitube is inserted blindly into the oropharynx, esophageal placement results.²⁴

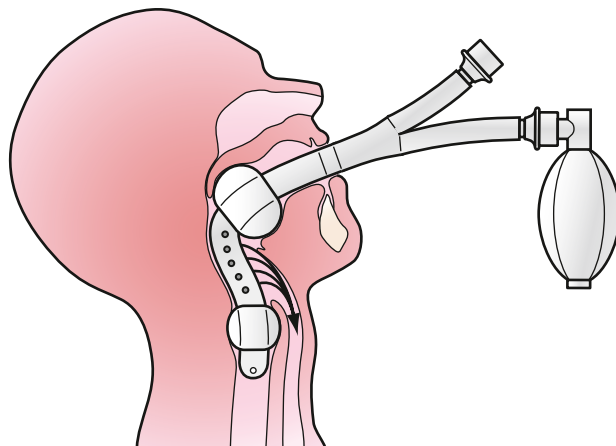


Figure 49-19. Esophageal trachea Combitube in the usual (esophageal) position. This figure demonstrates the ventilatory pattern usually encountered when the Combitube is blindly placed in the esophagus. (Modified from Wissler RN: *The esophageal-tracheal Combitube*. *Anesthesiol Rev* 1993;20:147-151, with permission.)

The Combitube is inserted until the two proximal black rings lie between the patient's upper incisors. At this time, the proximal balloon is inflated with 100 mL of air via the blue pilot tube. Next, the distal balloon is inflated with 15 mL of air via the white pilot tube. Ventilation is then initiated via the No. 1 tube, and CO₂ should be detected. Detection of CO₂ indicates that the Combitube was placed esophageally, so the air enters tube No. 1 and then enters the laryngeal aperture (Fig. 49-19). In the rare cases (less than 3%) in which the Combitube enters the trachea, ventilating with tube No.1 will not move the lungs, and CO₂ will not be detected from the exhalate of tube No.1.²³ At this point, tube No.2 should be ventilated and assessed for CO₂ (Fig. 49-20). The ETC is a commonly employed rescue method for gaining emergency airway access, especially in the "cannot intubate-cannot ventilate" patient.²¹

Laryngeal Mask Airway

The LMA is not only an emergency aid used to establish ventilation in the CNI-CNV situation; it can also serve as a conduit for intubation once ventilation has been established. The ASA DA Algorithm and guidelines do not endorse a particular brand or subtype of LMA (Classic, Fastrach, ILA). However, whenever gastric volumes are expected to be large (e.g., following large meal, known bowel obstruction), the ProSeal may be superior. Whenever the LMA will likely be used as a conduit for FOB-assisted intubation, the Cookgas ILA (Fig. 49-21) may be better because the ventilation tubing is wider and shorter than the other conventional LMAs, and does not have the epiglottis elevating bar that is present with the Fastrach.

Only in situations where there is absolutely no concern of airway swelling (i.e., partial airway obstruction), stridor, or abscess should the Fastrach be used with blind ETT insertion. In all of the aforementioned conditions, blind manipulation is contraindicated. The LMA is inserted blindly into the pharynx, forming a low-seal around the laryngeal inlet (Fig. 49-22). The special design features of the Fastrach, specifically, include a rigid, anatomically curved conduit that is wide enough to accept an 8.0 ETT with an epiglottic elevating bar to facilitate the blind passage of the special ETT (Fig. 49-23). As with all LMAs, the

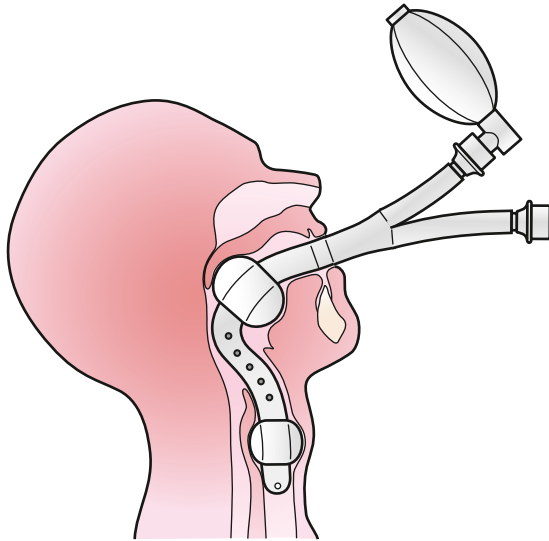


Figure 49-20. Esophageal trachea Combitube in the tracheal position. This figure demonstrates the ventilatory pattern achieved when the Combitube is placed in the trachea. Tracheal positioning of the Combitube is rare as greater than 97% of the time the Combitube will enter the esophagus when placed blindly. (Modified from Wissler RN: *The esophageal-tracheal Combitube*. *Anesthesiol Rev* 1993;20:147-151, with permission.)

Fastrach is placed blindly and the cuff is inflated. Once ventilation is confirmed, the ETT can be blindly passed via the LMA conduit into the trachea. The blind intratracheal placement must be confirmed with P_{ETCO_2} , an EDD, or by FOB. The LMA can be kept in place until airway stability is achieved. Once successful, ETT placement through the LMA is verified, the LMA can be deflated and removed using a push device to help keep the ETT in place. If intubation is not successful, ventilation can occur via the LMA between attempts.

Passage of a FOB through the LMA or Fastrach has a much higher chance of success and is nearly 100% successful in most series.¹⁴ A 6.0 mm ID cuffed ETT (a nasal RAE tube is most suitable due to its additional length) may be passed over the fiberoptic bronchoscope and through the shaft of the Nos. 3- and 4-sized LMA whereas a 7.0-mm ID cuffed ETT will only fit through the shaft of the No. 5-sized LMA. Subsequently, if a larger ETT is required, the 6.0- or 7.0-mm ID cuffed ETT can be exchanged for a larger ETT using an airway exchange catheter (AEC).¹⁴ The various sized ETTs that fit through all sized LMAs and the FOBs that fit through these ETTs are displayed in Table 49-6. Alternatively, and preferably, when the glottic chink is expected to be of normal size, the authors recommend using the newer blue intubating LMA (ILA-by Cookgas, Mercury Medical, Clearwater, Fla.). A large size of 4.5 will allow passage of an 8.0 or 8.5 ETT (Fig. 49-21).

Generally, the largest FOB that will fit through the ETT is best to maximize the ability of passing the ETT through a normally sized adult glottis. The possibility of the ETT to hang up at the glottis is more common with use of the pediatric-sized FOB. However, if the patient has a small glottic chink, then a smaller FOB and ETT is better. If a 4.0 or less mm OD FOB is used with either the 6.0- or 7.0-mm ID ETT, the lungs can be continuously ventilated around the FOB while contained within the ETT by passing the FOB through the self-sealing diaphragm of a bronchoscopy elbow adapter. The distal and proximal ends of

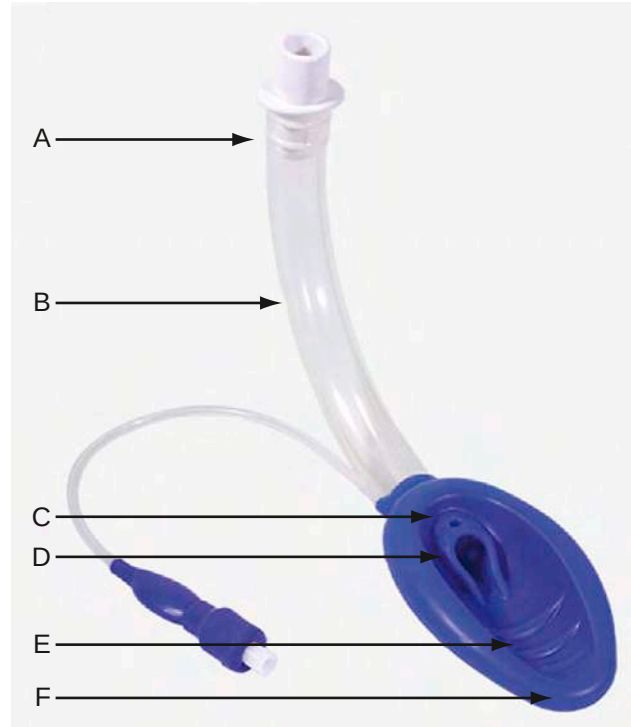


Figure 49-21. Cookgas Intubating Laryngeal Airway (ILA). The Cookgas ILA has several benefits over other LMAs for emergency airway use: **A**, 15-mm airway connector ridges facilitate easy removal for fiberoptic airway management and improved tube seal upon replacement. **B**, Oval-shaped hypercurved airway ventilation tube resists kinking. In addition, the relatively large internal diameter accommodates large-sized adult endotracheal tubes (ETTs): 2.5 ILA allows 6.5 ETT; 3.5 ILA allows 7.5 ETT; and 4.5 ILA allows 8.5 ETT. Furthermore the relatively short length of ventilation tube facilitates fiberoptic intubation. **C**, The auxiliary airway hole improves airflow and prevents suction effects from drawing up the epiglottis inside the airway tube. **D**, The keyhole-shaped airway outlet directs both FOB and ETTs toward the laryngeal inlet, and is anatomically engineered to align with the glottic chink. **E**, The mask ridges move against posterior larynx improving anterior seal. **F**, Recessed front improves posterior pharyngeal fit and ILA stability. Available through Mercury Medical, Clearwater, Fla.

the bronchoscopy elbow adapter are connected to the ETT and ventilatory apparatus, respectively. Figure 49-24 shows the use of the bronchoscopy elbow adapter, 6.0-mm ID ETT and LMA for the continuous ventilation FOB intubation technique for both a nasal RAE and standard 6.0-mm ID ETTs. With a 4.0-mm OD FOB/6.0-mm ID ETT combination, the space available for ventilation around the FOB corresponds to a 4.5-mm ID ETT.

The LMA, as a ventilatory device and/or intubating conduit, can be placed into the ASA DA algorithm in three different places. These are (1) on the “awake intubation” limb of the algorithm as a conduit for FOB guided tracheal intubation, (2) on the “anesthetized” limb as both a life saving ventilatory device, and (3) as a conduit for FOB assisted tracheal intubation.

Rigid Bronchoscope

A rigid bronchoscope is a straight, metal, lighted tube capable of visualizing the large airways with ventilatory capacity through the associated ventilating side port (Fig. 49-25). The rigid bronchoscope is effective in cases of large airway masses

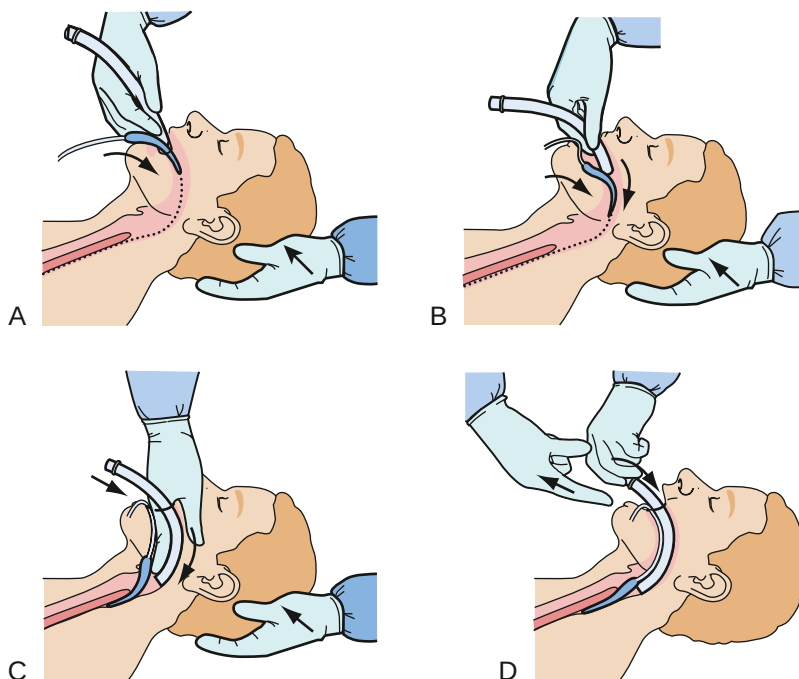


Figure 49-22. LMA insertion. With the neck extended and the head flexed, flatten the deflated cuff against the hard palate and advance until resistance is met. Once in place, inflate the cuff enough to achieve an adequate seal. (Images courtesy of LMA North America, Inc., San Diego.)

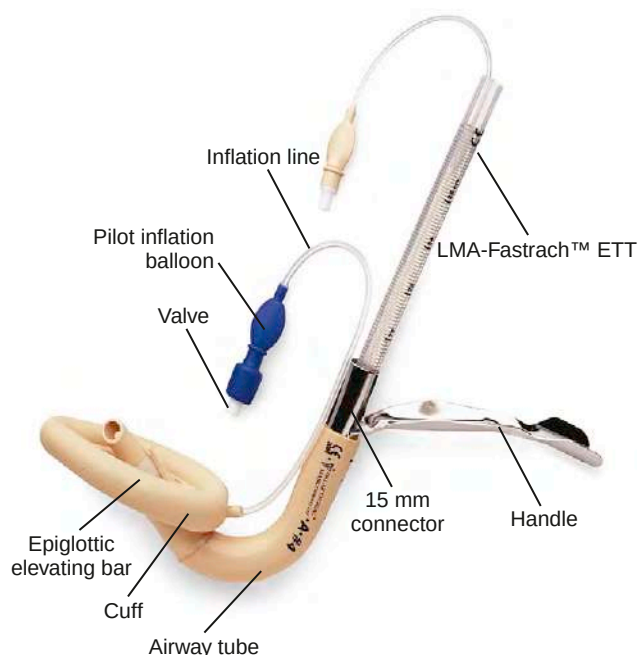


Figure 49-23. Fastrach LMA.

and bleeding. In the ASA DA algorithm, the application of the rigid bronchoscope is recommended as an emergency airway tool in the CNI-CNV situation, especially when LMA ventilation has failed or its use is not feasible. Similarly, the Bainton pharyngolaryngoscope (Figs. 49-26, 49-27) is a straight blade with a shallow vertical portion at the proximal end and incorporates a tubular distal portion (with an intraluminal light source

protected from secretions and obstruction); a tracheal tube with an inner diameter of 8 mm or smaller, optionally with the adapter removed, is easily passed through the tube of the blade without significantly obstructing the view.

Surgical Airway

Transtacheal Jet Ventilation

Transtacheal jet ventilation (TTJV) is another method of gaining emergency ventilation in a “cannot intubate-cannot ventilate” patient. The technique consists of palpating the cricothyroid membrane and advancing a 14-gauge catheter through the membrane and into the trachea with the needle tip pointed proximally 30 to 45 degrees caudad from the axis of the neck (Fig. 49-28). Once the catheter is in the trachea, its transtacheal position must be verified by attaching a syringe to the catheter and attempting to aspirate air. If air is not aspirated, the catheter may not be in the trachea and should be removed. After air aspiration has occurred, the needle stylet is withdrawn, and the hub of the intravenous catheter is connected to a transtacheal jet ventilation system (Fig. 49-29).

The TTJV system must have 25 to 50 pounds per square inch (psi) of pressure to allow flow down the small-bore (14-gauge) catheter. The natural airway must be maintained during exhalation; occasionally, some jaw thrust is required. Transtacheal jet ventilation can maintain oxygenation and adequate ventilation for more than 40 minutes.²⁵ Indeed, TTJV can take place while an alternative form of airway establishment is performed, such as fiberoptic bronchoscopy intubation.

Cricothyroidotomy - Percutaneous

The same technique described for TTJV is used to place a thin-wall (14-G or larger) needle into the trachea. Once the needle is confirmed intratracheal, a wire is passed through the needle

Table 49-6. Relevant Diameters of the Different Sized Laryngeal Mask Airways (LMAs), Endotracheal Tubes (ETTs), and Fiberoptic Bronchoscopes (FOBs) That Fit into the ETTs

LMA MFR	Size	Patient Weight (kg)	LMA Internal Diameter (ID mm)	Cuff Volume (mL)	Largest ETT Inside LMA (ID mm)	Largest FOB Inside ETT (mm)
Classic	1	<6.5	5.25	2-5	3.5	2.7
Classic	2	6.5-20	7.0	7-10	4.5	3.5
Classic	2.5	20-30	8.4	14	5.0	4.0
Classic	3	30-70	10	15-20	6.0 cuffed	5.0
Classic	4	>70	10	25-30	6.0 cuffed	5.0
Classic	5	>90	11.5	25-30	7.0	6.5
Cookgas	2.5	20-50	10	20-25	6.5	6.5
Cookgas	3.5	50-70	12	25-30	7.5	6.5
Cookgas	4.5	>70	14	25-30	8.5	6.5

Classic LMA (LMA North America, Inc. San Diego).

Cookgas ILA (Mercury Medical, Clearwater, Fla.)

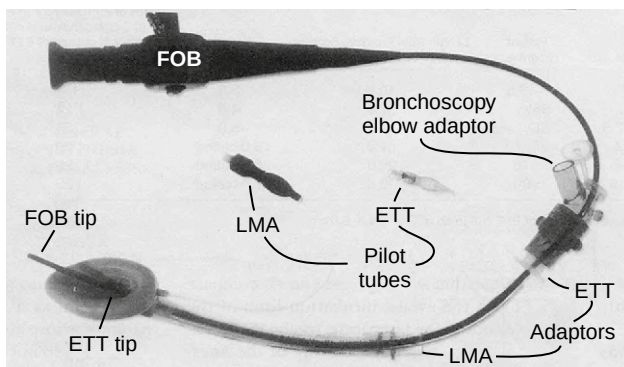


Figure 49-24. A patient can be continuously ventilated during fiberoptic intubation using the laryngeal mask airway (LMA) as a conduit for the fiberoptic bronchoscope (FOB). By passing a 4.0-mm OD fiberscope through the self-sealing diaphragm of a bronchoscopy elbow adaptor and the tip of a cuffed 6.0-mm ID endotracheal tube (ETT) to the level of the grille on the LMA, ventilation can occur around the FOB but within the lumen of the ETT; the deflated cuff of the ETT inside the shaft of the LMA makes a tight enough seal to permit positive-pressure ventilation. Once the FOB is passed well into the trachea, the 6.0-mm ID ETT is pushed over the FOB into the trachea until the adaptor of the ETT is against the adaptor of the LMA (From Benumof JL: Laryngeal mask airway and the ASA difficult airway algorithm. *Anesthesiology* 1996;84:686-699, with permission.)

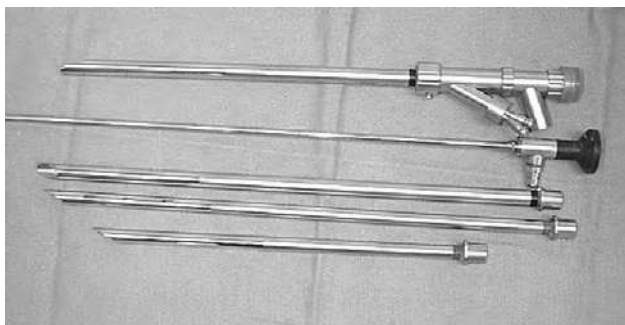


Figure 49-25. Rigid bronchoscope with ventilating side port, optic guide, and several sizes shown.

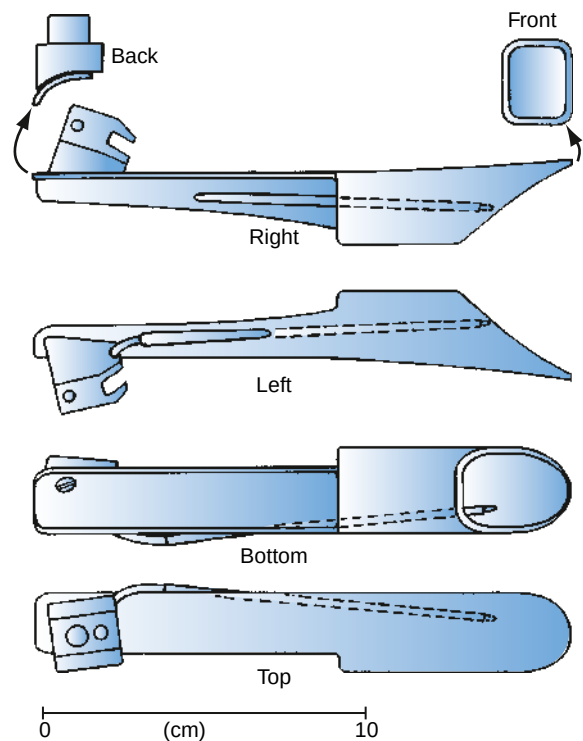


Figure 49-26. Bainton pharyngolaryngoscope. Scale drawing of the Bainton pharyngolaryngoscope. (From Bainton CR: A new laryngoscope blade to overcome pharyngeal obstruction, *Anesthesiology* 1987;67:767, with permission.)

into the trachea using the Seldinger technique (Fig. 49-28). Maintaining the guidewire several centimeters into the trachea, the cricothyrotomy site is dilated. Then, using the Seldinger technique, the cricothyrotomy tube is advanced, confirmed to be intratracheal and secured in place. Of note, whenever a formal tracheostomy can be performed, it is favored over the emergency cricothyroidotomy to prevent the subglottic stenosis frequently seen with cricothyrotomy.

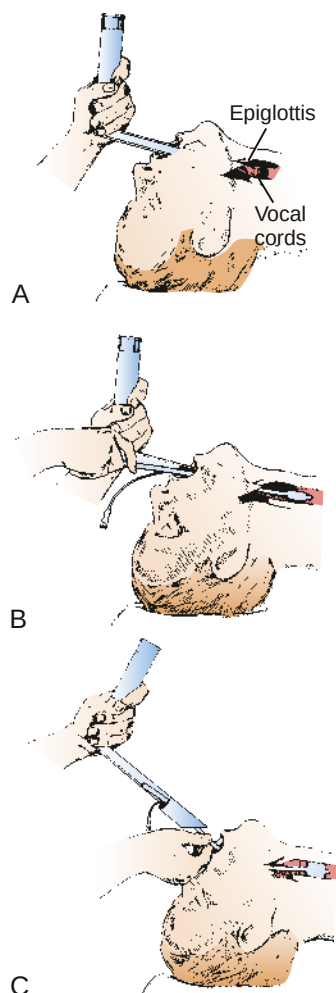


Figure 49-27. Schematic of intubation technique with Bainton pharyngolaryngoscope. **A**, Tubular portion fits within the pharyngeal space. Tip of blade elevates epiglottis to permit laryngeal view. **B**, ETT without an adapter (stylet optional) is inserted into tubular portion of blade and advanced into larynx. ETT cuff is inflated. **C**, syringe and stylet are removed from ETT and pharyngolaryngoscope is withdrawn from mouth. Right hand of operator stabilizes ETT as blade is elevated over proximal end of ETT and cuff pilot tube. (From Bainton CR: A new laryngoscope blade to overcome pharyngeal obstruction, *Anesthesiology* 1987;67:767, with permission.)

Cricothyroidotomy - Open

Cricothyroidotomy is the emergency surgical airway of choice (versus tracheostomy) primarily due to the ease of determining anatomic landmarks (Fig. 49-30). The thyroid cartilage is stabilized and an incision is made through the skin and subcutaneous tissue overlying the cricothyroid membrane. The membrane is then opened with a stab incision and an endotracheal tube or cricothyrotomy tube is inserted and placement confirmed in the usual fashion.

Tracheostomy

Tracheostomy is less desirable in emergency airway scenarios than cricothyroidotomy because it is slower, requires additional steps, and has greater potential for bleeding. Optimally, a transverse skin incision is made in midline position (for cosmetic and healing purposes). However, in emergency situations with

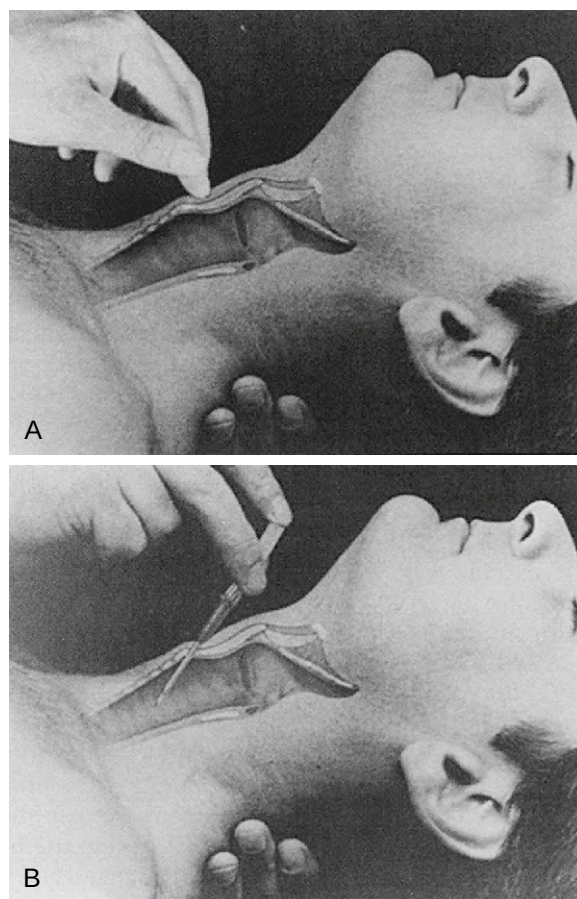


Figure 49-28. This figure demonstrates a 14-gauge angiocatheter passing through the cricothyroid membrane at an angle approximately 30 degrees caudad from the skin. After achieving this position, the metal stylet is withdrawn and a syringe is applied to the catheter to confirm intratracheal position; aspiration of air is the expected end point if the 14 gauge catheter is truly in the tracheal lumen. (From Benumof JL, et al: *Transtacheal ventilation*. In Benumof JL (ed): *Clinical procedures in Anesthesia and Intensive Care*. Philadelphia, Lippincott-Raven Publisher, 1992, p. 199, with permission.)

novice surgeons, a vertical incision can be made in the neck (to minimize bleeding and avoid the anterior jugular veins) overlying the trachea and the cricoid cartilage (Fig. 49-31). Next, skin and subcutaneous tissue are divided with a scalpel through the platysma, the strap muscles, and potentially the thyroid isthmus. Once the first few tracheal rings are exposed, a horizontal incision is made between the first and second tracheal rings and the tube is introduced into the trachea. Percutaneous placement of a tracheostomy tube can be performed but is recommended under bronchoscopic guidance as to reduce the chance of paratracheal insertion and to document real time intratracheal position of the needle, wire, dilators, and the tracheostomy tube.

Blind Intubation Techniques

Generally, blind intubation techniques are rarely used as a "first-line" method and typically, in fact, are employed when other safer techniques have failed. Some techniques include the frequently used blind nasal approach (in awake, spontaneously ventilating patients) and techniques that are typically relegated

to anesthetized patients (including light wand, esophageal-tracheal Combitube, and retrograde wire). The blind nasal technique, being the most commonly employed blind technique, is described here in some detail.

Blind Nasal Intubation

Positioning, preparation, and topical anesthesia for a blind nasal intubation are the same as for fiberoptic bronchoscopy. For a blind nasal intubation, the patient should be spontaneously ventilating and, if possible, awake and cooperative. The ETT is placed in the already dilated and anesthetized nasal passage, and the airway expert's ear is placed near the 15-mm connector end of the endotracheal tube to listen for breath sounds. As the

ETT is passed down the nasal passage and toward the glottic aperture, the airway sounds from the patient will become much louder than previously noted. At this point, the airway expert should ask the patient to pant or take some deep breaths (both maneuvers tend to open the glottic aperture). During each inhalation, the ETT should be advanced. With this maneuver, the ETT can be essentially sucked into the larynx.

It is occasionally beneficial to use a flexible-tipped type of ETT known as an Endotrol tube. The Endotrol tube gives the intubator the ability to flex the ETT anteriorly while advancing the tube (Fig. 49-32). Clinical end points alerting the physician that the ETT is inside the patient's trachea are (1) the patient is no longer able to speak, (2) increased secretions are heard in the ETT, and (3) frequently, coughing is elicited as the ETT passes down the larynx advancing into the trachea. Following placement of the ETT, however, its position must be confirmed just as with other methods of intubation. In this case, an end-tidal CO₂ monitoring device is recommended.

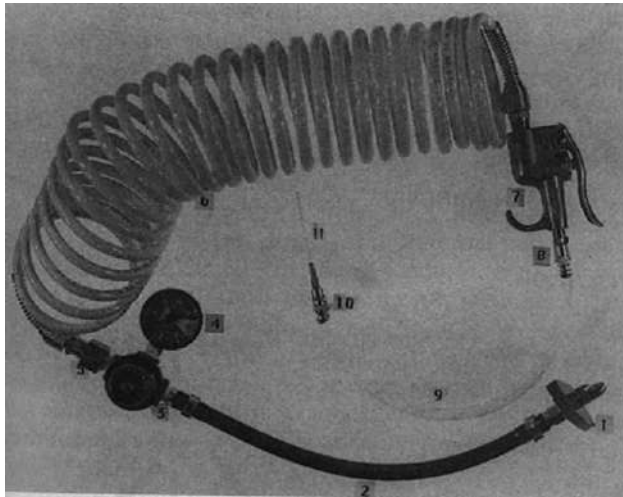


Figure 49-29. This figure demonstrates the equipment used for pressurizing the already placed transtracheal catheter. (1) Wall oxygen pressure quick disconnect device. (2) Green Chemtron O₂ hose. (3) NPT hose barb connector. (4) Bird regulator gauge (0 to 50 psi). (5) NPT air hose connector. (6) High pressure self-coiling air hose. (7) Jet injector valve. (8) NPT hose barb connecting the injector valve to clear soft flexible tubing (9). (10) Hose barb connecting to the clear tubing with a standard Becton/Dickinson male Luer lock connector. (11) Transtracheal ventilation intravenous catheter with standard hub. (From Benumof JL, Scheller MS: *The importance of transtracheal jet ventilation in the management of the difficult airway*. *Anesthesiology* 1989;71:769-778, with permission.)

Intubation Using a Light Wand

The light wand is a rediscovered technique for intubating the trachea using a blind approach. The light wand is typically relegated to elective use in anesthetized patients, but it can also be a useful adjunct in the "cannot intubate-cannot ventilate" patient. The light wand was first described by Macintosh and Richard²⁶ in 1957. Several commercial versions of the light wand are now available. All are similar devices comprising a lighted stylet over which an ETT fits.

The patient is anesthetized, and the ETT with lighted stylet is passed into the oropharynx. Pulling the tongue out can frequently facilitate passing the light wand into the trachea. Once the ETT passes through the cords and enters the larynx, it produces a jack-o-lantern effect because of transillumination (Fig. 49-33). This effect is very prominent when the room lights are dimmed, but it can be difficult to appreciate in the bright lights of the CICU. Once the light wand is in the larynx, the endotracheal tube is advanced, and the stylet is withdrawn. At this point, confirmation that the ETT is in the larynx must be accomplished using end-tidal CO₂ monitoring or other technique.

Retrograde Wire Intubation

The retrograde technique of intubation was first described by Waters in 1963.²⁷ Waters employed a Tuohy needle passed in a cephalad direction through the cricothyroid membrane. An

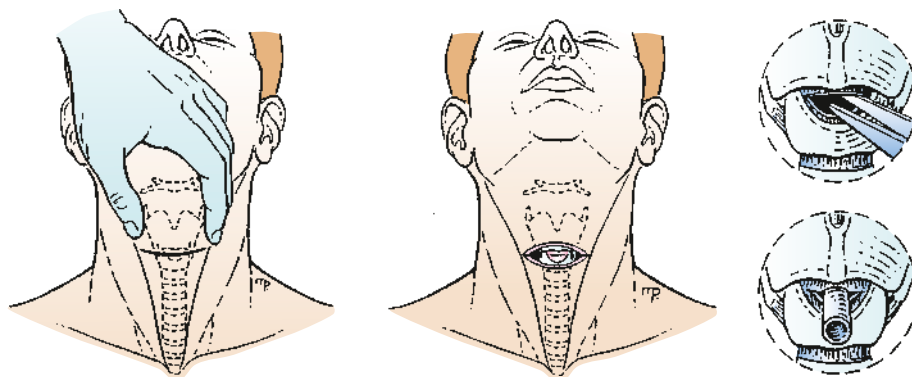


Figure 49-30. Surgical cricothyroidotomy. Horizontal skin incision, incision of cricothyroid membrane, dilation of the opening, and introduction of a ventilation tube. (From Biro P, et al: *Transtracheal access and oxygenation techniques*. *Acta Anesth Scand* 1998;42:169, with permission.)

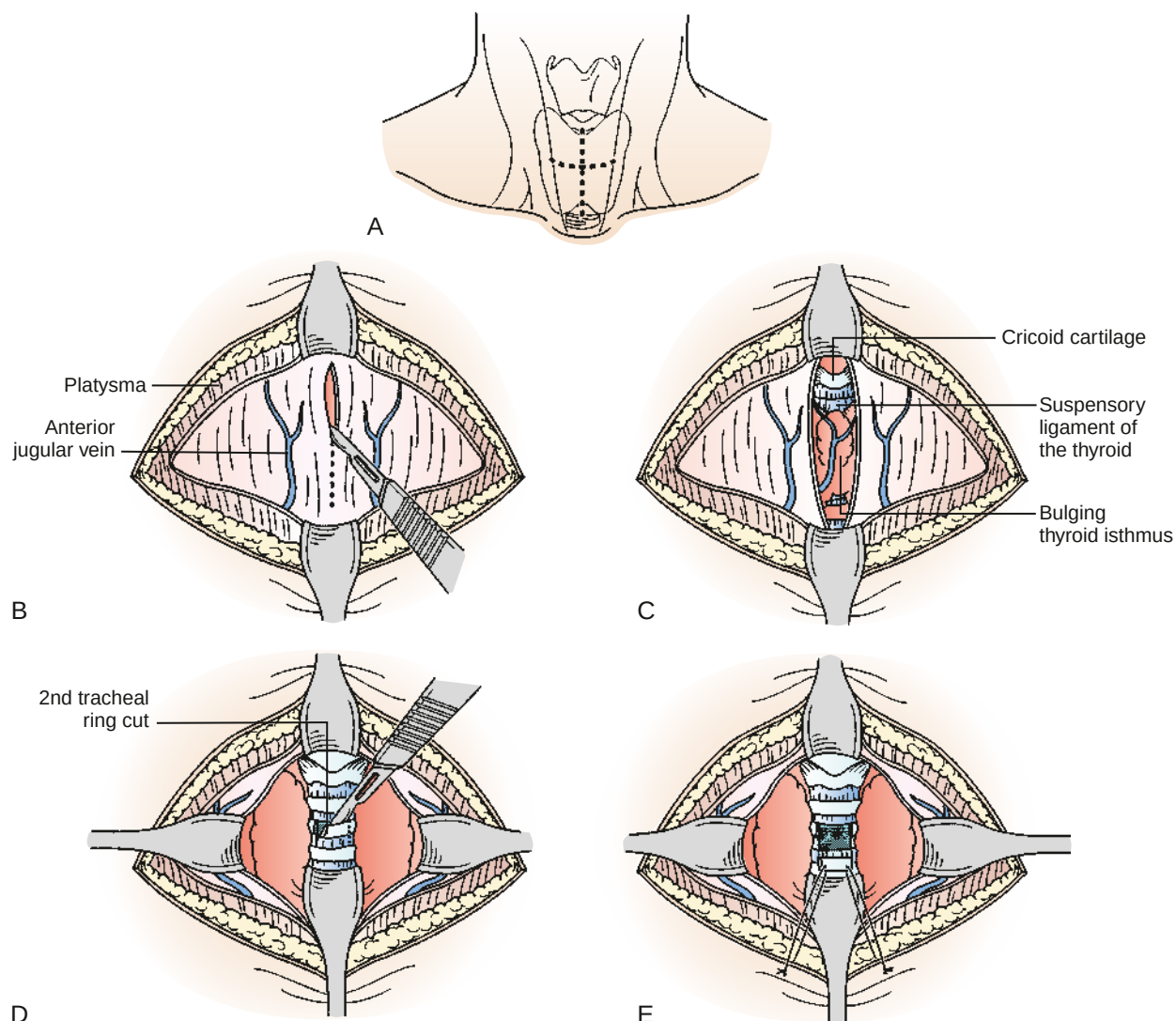


Figure 49-31. Tracheostomy. **A**, Transverse incision made usually for elective tracheostomy but a vertical incision allows for less bleeding when emergent procedure done. **B**, The strap muscles are separated and **(C, D)** thyroid isthmus retracted caudally. **E**, After the second tracheal ring is cleaned off, an inferiorly based flap is developed in the tracheal wall and sutured to the skin to allow easy access to the trachea while tract matures. (Neifeld JP *Head and Neck in Greenfield LJ, et al. (eds): Surgery: Scientific Principles and Practices. Philadelphia Lippincott-Raven Publishers, 1997, p 644, with permission.*)

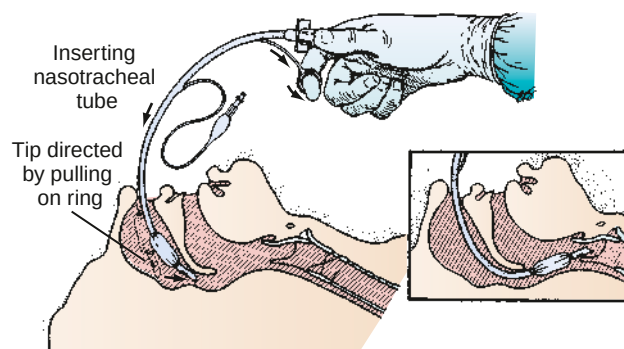


Figure 49-32. Flexible tipped (Endtrol) nasotracheal tube. The flexible tipped nasotracheal tube can greatly aid blind nasal tracheal intubation. By pulling the ring, the endotracheal tube (ETT) flexes more anterior, this helps direct the tip around the soft palate and into the laryngeal inlet. (See inset). (From Ward CF, Salvatierra CA: *Special intubation techniques for the adult patient*. In Benumof JL (ed): *Clinical Procedures in Anesthesia and Intensive Care*. Philadelphia JB Lippincott Co, 1992, p 154, with permission.)

epidural catheter was then threaded through the Tuohy needle, and the catheter was retrieved from the oropharynx using a plastic dressmaker's hook. Next, both the tube and the catheter were pulled through the vocal cords into the trachea by pulling on the catheter from the cricothyroid membrane. In 1967, Powell and Ozdil²⁸ introduced a wire-through-the-needle retrograde technique; in their modification, the wire was placed through the Murphy sidehole. This wire placement allowed the endotracheal tube to pass farther through the cords than it can when the wire passes out the tip of the endotracheal tube.²⁸ Other modifications of these techniques have been described,²⁹ but the basic technique remains the same. Indeed, the Cook Critical Care (Bloomington, Ind.) division has developed a commercially available emergency retrograde intubation kit.

Fiberoptic Bronchoscopy

Fiberoptic bronchoscopy (FOB) intubation can be performed in awake patients who are spontaneously breathing and in anesthetized or apneic patients. The technique for awake nasal

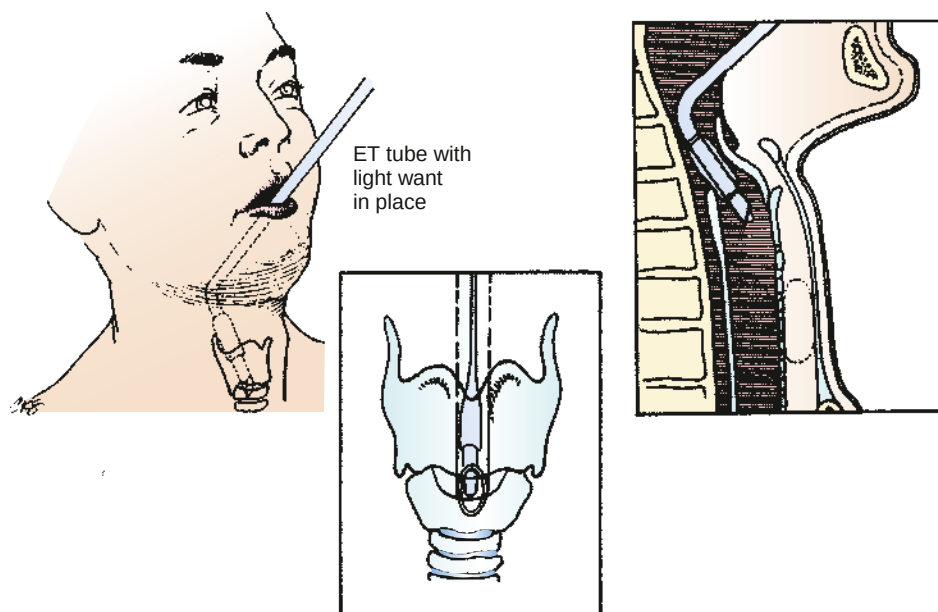


Figure 49-33. Transillumination of the larynx with light wand. This diagram demonstrates the jack-o'-lantern effect caused by transillumination of the soft tissues on the neck when the light wand enters the larynx. The left panel demonstrates the position of the light wand upon entry into the laryngeal inlet. The middle panel demonstrates this view from the anterior orientation and the right panel shows a side view of the light wand in position to cause transillumination of the anterior structures. (From Ward CF, Salvatierra CA: *Special intubation techniques for the adult patient*. In Benumof JL (ed): *Clinical Procedures in Anesthesia and Intensive Care*. Philadelphia JB Lippincott Co, 1992, p 175, with permission).

fiberoptic intubation is described here in detail; FOB intubation of the anesthetized patient is only briefly described. There are many recipes for accomplishment of FOB intubation. Success with any of these techniques requires appropriate patient selection, sufficient patient preparation, and adequate endoscopist experience and skill (Table 49-7).

Patient Selection

Indications for fiberoptic bronchoscopy intubation are (1) situations in which alignment of the oral pharyngeal and laryngeal axes is difficult or ill-advised (e.g., cervical spine injury or neck fixed in a halo brace) and (2) any situation in which direct laryngoscopy is predicted to be difficult (i.e., HMD <6 cm, Mallampati class III or IV; see Fig. 49-5), especially in patients with a small mouth opening and in temporomandibular disease. Contraindications to FOB intubation include massive oropharyngeal bleeding or life-threatening airway obstruction, which would not allow time for adequate topicalization and severe hemodynamic instability, which similarly would not allow sufficient preparation or FOB intubation time.

Relative contraindications to FOB intubation are copious secretions and friable tissues that cannot be managed with antisialagogues and careful manipulation of the FOB. Tumors, abscesses, and maxillofacial trauma are all good indications for fiberoptic intubation, provided that the endoscopist can avoid the tumor, pus, and blood and see the entire way into the trachea.

Patient Preparation

Positioning for FOB

The patient is placed in a sitting position, nasal cannula oxygen is administered, and pulse oximetry and other monitoring devices are applied. The sitting position allows secretions to run down into the esophagus and out of the bronchoscopic view.

Additionally, gravity helps direct the fiberoptic bronchoscope toward the larynx as compared with the supine position, where gravity tends to favor the posterior esophageal orifice.

Intravenous Analgesia, Sedation, and Antisialagogue

Patients should receive an antisialagogue (glycopyrrolate, 0.2 mg) and sedation before the start of the procedure. Opiates, benzodiazepines, and neuroleptic drugs have all been used successfully. Low-dose opiates alone (fentanyl, 1 to 4 $\mu\text{g}/\text{kg}$) are sufficient in patients not tolerant of opiates. Midazolam should not be routinely used because it causes some patients to become hyperalgesic and uncooperative. Fentanyl provides adequate sedation and analgesia, both of which are useful while topicalization is occurring. Dexmedetomidine can also be used as it provides excellent sedation, decreases the opioid requirement, and does not depress ventilation.

Local Anesthesia and Vasoconstriction

The following description of mucosal topicalization and vasoconstriction can be used for any blind technique, not just FOB intubation. The patient should receive phenylephrine (Neo-Syneprine) or oxymetazoline (Afrin) nasal spray in both nares before initiation of topicalization. Then the patient is asked to report which nares allows for better air flow. This will identify the nares that should be intubated and primarily topicalized. However, both nares should be anesthetized to block the superior laryngeal nerve (SLN) on both sides and thus anesthetize the supralaryngeal structures (as described subsequently).

Next the nasopharynx, oropharynx, base of the tongue, and larynx are anesthetized. The nasopharynx is anesthetized with 4% cocaine or 4% lidocaine with Neo-Syneprine. For nasopharyngeal anesthesia, 4% cocaine provides intense vasoconstriction and has a more rapid onset and longer duration than lidocaine.

Table 49–7. Causes of Failure to Intubate with Fiberoptic Bronchoscope

Cause of Failure	Comments and Solutions
Patient Selection Factors	
Massive bleeding	Unable to see adequately is a relative contraindication to FOB. Small amounts of bleeding can be controlled with frequent suctioning. A vasoconstrictor added to topical agents helps limit bleeding.
Uncooperative patient	Patient will not hold still and/or is very belligerent. Rare problem in elective surgery, but may occur in trauma and emergency situations.
Patient too unstable	Does not allow time to properly anesthetize airway.
Patient Preparation Factors	
Inadequate topical anesthesia	Be patient, take time to topicalize properly. Dry the mucosa (glycopyrrolate) and suction secretions from the oropharynx so that topical anesthesia can get to the mucosa to work. Anesthetize the nose, nasopharynx, oropharynx, larynx, and trachea. Nerve blocks, used by some, are not usually necessary when proper anesthetization is performed.
Presence of secretions or small amounts of blood	Treat with proper suctioning, use of an antisialagogue (glycopyrrolate) and a vasoconstricting agent (Neo-Syneprine), or use cocaine. Attach O ₂ to suction port of FOB, blowing secretions away.
Patient desaturates during FOB	Patient should be wearing nasal prongs or mask O ₂ during FOB whenever significant right-to-left shunt is present. Also, endoscopist can attach O ₂ to the suction channel of the FOB and instruct patient to pant during intubation.
Endoscopist Experience Factors	
Inability to navigate normal anatomy	Most common problem of novice is too little practice with airway models and mannequins before attempting to intubate patients.
Distorted anatomy due to tumors or abscess	These are excellent indications for using an FOB, because intubation with direct laryngoscopy may be difficult. However, the endoscopist must be well grounded in normal anatomy before negotiating abnormal anatomy in a difficult intubation. Use of a small ETT may help in these circumstances.
Inability to visualize cords due to a large floppy epiglottis	Have patient say “Ahh” and/or “pant like a puppy.” (If patient is anesthetized, helper should apply jaw thrust or pull the tongue forward.)
Fogging of objective	Use a dilute detergent (Hibiclense) to wipe the FOB lenses before use, and warm the FOB before use.
Inability to advance tube into trachea	Inadequate topical anesthesia—perform nerve block or use more topical. Large discrepancy between ETT and FOB—use the largest FOB that will fit easily through the ETT yet still allow easy removal with proper lubrication. Hung up at glottic opening—pull back the ETT and rotate 90 to 180 degrees either right or left to allow the ETT to pass through the cords more easily.
Inability to remove the FOB	Beware that the FOB may exit the Murphy eye of the ETT. This can be avoided if the FOB is threaded through the ETT before attempting intubation. Some endoscopists place the lubricated ETT through the naris into the nasopharynx blindly and then pass the FOB through the ETT. This technique has greater risk that FOB might exit the Murphy eye. Also, be sure that the FOB is well lubricated with silicone before placing it through the ETT.

ETT, endotracheal tube; FOB, fiberoptic bronchoscope.

The toxic dose of cocaine is 3 mg/kg, whereas the toxic dose of lidocaine is 7 mg/kg when used with vasoconstriction.

Cocaine is applied to each nare using Krause forceps (Fig. 49-34) or a cotton-tipped applicator. The nares are painted first, and then the applicator is passed down the nasopharynx. Advancing the applicator into the pyriform fossa also blocks the superior laryngeal nerve (SLN). This nerve innervates the epiglottis, aryepiglottic folds, and mucous membranes of the laryngeal structures down to the false cords. When the applicator can be inserted without causing discomfort, a soft 34 French nasal airway is passed. If the patient tolerates this maneuver, topicalization of the nasopharynx is complete.

While the nasopharynx is being anesthetized, the oropharynx and larynx can be simultaneously anesthetized by spraying a fine mist of 4% lidocaine via a DeVilbiss nebulizer. The DeVilbiss

sprayer can be modified by connecting it to a low-flow O₂ source after removing the squeeze bulb, thus providing a continuous source of aerosolized lidocaine (Fig. 49-35). The patient should be asked to “pant like a puppy” so as to entrain the aerosolized lidocaine into the trachea as well. When the DeVilbiss sprayer can enter the oropharynx without causing the patient to gag, oropharyngeal and base of tongue anesthesia is adequate for FOB intubation. Provided that the patient has breathed enough lidocaine mist into the airways, the trachea is usually adequately anesthetized at this point as well.

Some endoscopists prefer performing nerve blocks of the glossopharyngeal nerve (at the palatoglossal arch) (Fig. 49-36) and the superior laryngeal nerve (externally, where it crosses the superior cornu of the hyoid) (Fig. 49-37), and administering transtracheal lidocaine (Fig. 49-38).³⁰ These maneuvers are not

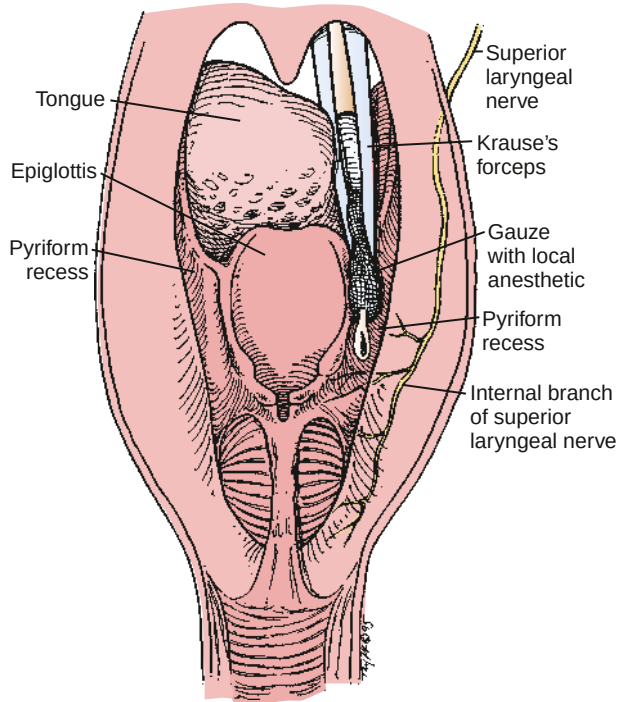


Figure 49-34. Superior laryngeal nerve block by external approach ("topicalization"). Posterior view of the nasopharyngeal area showing the perforating branches of the superior laryngeal nerve. Krause forceps are used with gauze soaked in local anesthetic fluid at the level of the pyriform sinus. (From UCI Department of Anesthesia D.A. Teaching aids (with permission).

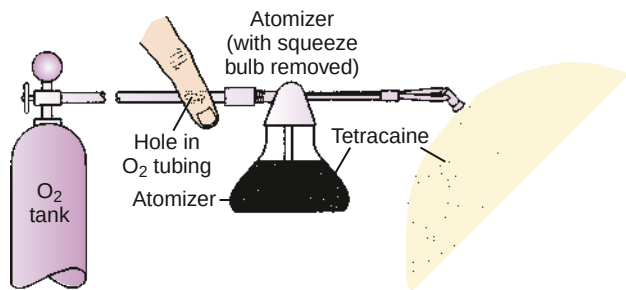


Figure 49-35. Continuous oxygen flow atomizer apparatus. Oxygen tubing is connected from an oxygen tank to the bulb attachment site of a DeVilbiss atomizer. A hole is cut in the oxygen tubing near the attachment site. Oxygen is allowed to flow into the tubing and out of the cut hole until a finger is applied covering the hole; then oxygen flows to the nebulizer and a fine mist of local anesthetic is emitted. The size and velocity of the spray is directly related to the flow of oxygen through the tubing. (Reproduced with permission from Benumof JL: *Anesthesia for Thoracic Surgery*, Philadelphia, WB Saunders, 1987, pp 241-243; with permission).

necessary for FOB aided or blind nasal intubation techniques in properly topicalized patients (i.e., following above recipe). However, if awake laryngoscopy is planned with either a normal RDL or a Bullard laryngoscope, the deep pressure receptors may still be active causing the patient to gag. When pressure-inducing laryngoscopic devices are used to intubate awake patients, supplemental glossopharyngeal nerve blocks should also be performed (see legend in Figure 49-36 for instructions).

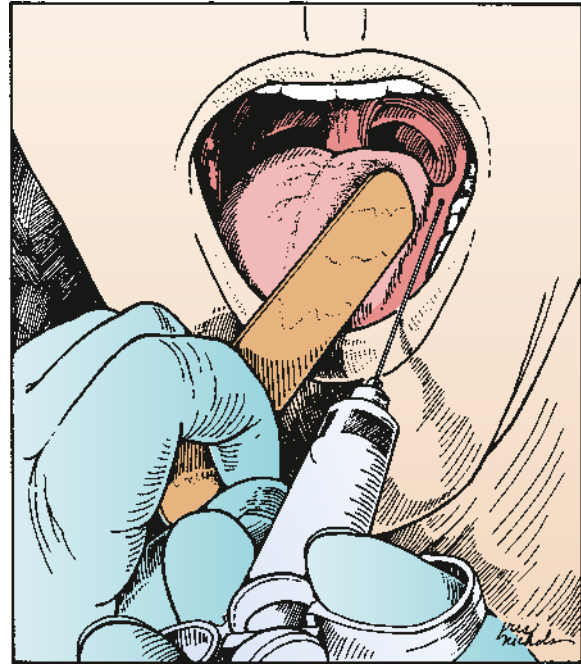


Figure 49-36. Glossopharyngeal nerve (lingual branch) block. The tongue is pushed medially with a tongue depressor, and a 3-inch spinal needle is inserted into the base of the anterior tonsillar pillar 0.5 cm lateral to the base of the tongue and advanced 0.5 cm deep. After negative aspiration, 2 mL of local anesthetic is injected. Both sides are injected for adequate block of the gag reflex. (From Mulroy MF: *Regional Anesthesia: An Illustrated Procedure Guide*, 3rd ed. Lippincott Williams and Wilkins, 2002, p 229, with permission.)

Technique of Fiberoptic Intubation

Awake Nasal Technique

The largest ETT that will fit the patient's nasal passage should be used; most adults can accept an 8.0 ETT. If the patient's naris can be easily dilated with a 34 French soft nasal airway, an 8.0 ETT will almost always fit. This is because the external diameter of a 34 French soft nasal airway is approximately 11.0 mm, whereas that of an 8.0 ETT is approximately 10.5 mm.

Following topical anesthesia, the FOB (with an already loaded ETT) (Fig. 49-39) is inserted into the patient's naris. Alternatively, an ETT can be placed in the naris to serve as an introducer, and the fiberoptic bronchoscope can then be placed through the endotracheal tube and into the nasal passage. The advantage of the first technique is to eliminate the possibility that the FOB will exit the Murphy eye of the ETT because the ETT is preloaded on the FOB. The advantage of the second technique is that the ETT serves as a dilating airway and a guide for the FOB. When the FOB exits the ETT, it is frequently aiming right into the laryngeal aperture.

When manipulating the FOB, it is useful to remember that small movements at the end of the FOB result in very large changes in the view. Regardless of the technique chosen to introduce the FOB into the naris, the endoscopist next advances the FOB under direct vision until the epiglottis or the laryngeal aperture is identified. The FOB should never be advanced blindly because structures that are not clearly identified may be damaged. Once the glottic opening or the epiglottis is in view (Fig. 49-40), the FOB is maneuvered around the epiglottis, through the vocal cords, and into the trachea. The FOB is then

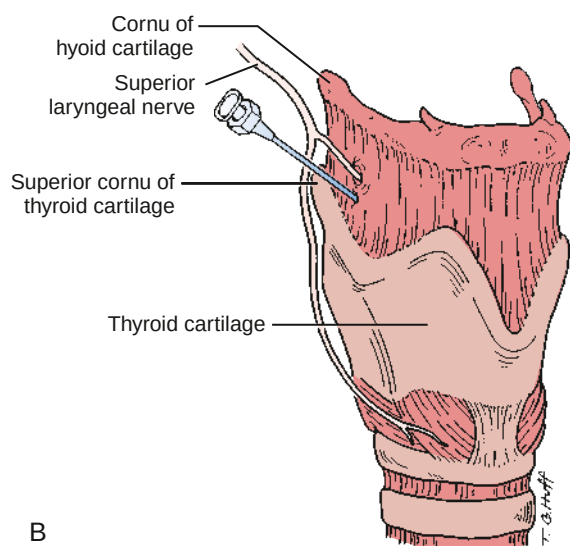
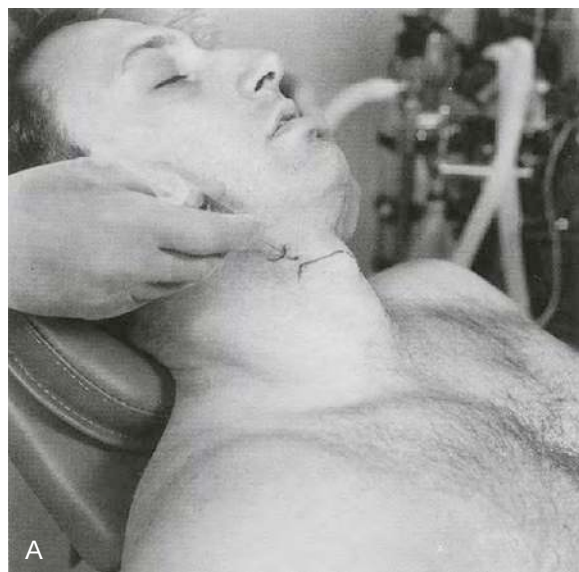


Figure 49-37. Superior laryngeal nerve block. The 23- or 25-gauge needle is introduced onto the superior border of the lateral wing of the thyroid cartilage or caudad to the greater cornu of the hyoid bone. After negative aspiration deep to the thyrohyoid membrane, 2 to 3 mL of local anesthetic are injected into the space below the membrane. (From Norton ML: *Atlas of the Difficult Airway: Topical and Regional Anesthesia of the Upper Airway*, Mosby Publishing, 2002, p 91, with permission.)

advanced further down the trachea to a position just above the carina. At this point, the ETT is threaded over the FOB through the larynx and into the trachea.

If the ETT does not advance easily, it may be hung up at the arytenoids or at the laryngeal aperture. This problem can be due either to a size discrepancy between the internal diameter of the ETT and the outer diameter of the FOB because the ETT is simply too large for the glottis. Often, rotating the ETT 90 to 180 degrees either clockwise or counterclockwise will facilitate passage of the ETT through the glottic aperture.

If the ETT will not pass despite the use of these maneuvers, the ETT and FOB should be removed together as a unit, and a smaller ETT used. If secretions become a problem during

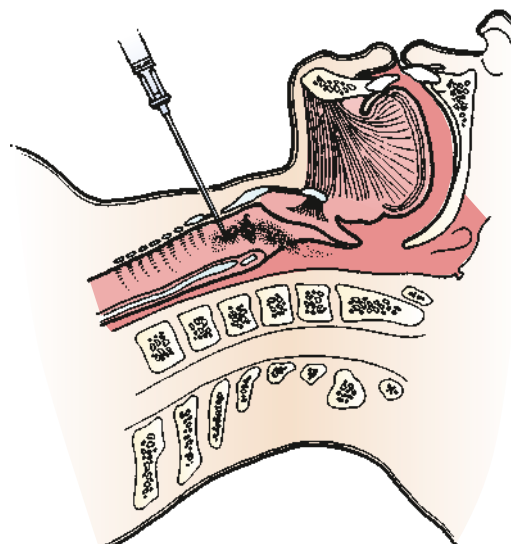


Figure 49-38. Transtracheal injection (topical subglottic anesthesia—recurrent laryngeal nerve distribution). A 20-gauge IV catheter is introduced through the cricoid membrane. Once tracheal entry is confirmed by air aspiration, 4 mL of topical anesthetic is injected as the patient inspires; the inward air flow carries the solution down the trachea, and the cough reflex will spread it up to the undersurface of the vocal cords. (From Mulroy MF: *Regional Anesthesia: An Illustrated Procedure Guide*, 3rd ed. Lippincott Williams and Wilkins, 2002, p 230, with permission).

bronchoscopy, they can be removed by flushing saline down the working channel of the FOB or passing oxygen through it, providing the additional benefit of increasing the FiO_2 in spontaneously breathing patients.

Once the ETT is positioned approximately 3 to 4 cm above the carina, the FOB is removed. If it becomes difficult to remove the FOB, the nasal passage may be narrow and may be crimping the ETT, or the FOB may have passed out the Murphy eye. If this occurs, the fiberoptic bronchoscope and the ETT must be removed as a unit, and the procedure begun again.

Oral Technique

The FOB can be advanced through the oropharynx in both awake, spontaneously ventilating patients, and those who are asleep and being ventilated with a mask or LMA. The sedation and local anesthesia preparation is the same as that required for a nasal intubation (details described above).

With oral intubation in a spontaneously ventilating patient, the FOB is advanced into the airway through a rigid plastic Ovassapian oral airway intubator (Fig. 49-41, A). The oral intubation can be more difficult in some patients because the FOB must take a more acute bend at the oropharynx to be directed toward the larynx (compared with the more gentle curvature required for the nasal intubation).

When FOB-assisted intubation is performed in patients under general anesthesia, concomitant ventilation can be achieved using an LMA, Intubating Fastrach LMA, or the Patil intubating mask with self-sealing diaphragm (Fig. 49-41, B), along with the Ovassapian oral airway intubator, as described by Rogers and Benumof.³¹ Entry into the glottis is generally easier with an LMA-FOB-assisted intubation compared with an intubating mask-FOB-assisted technique.

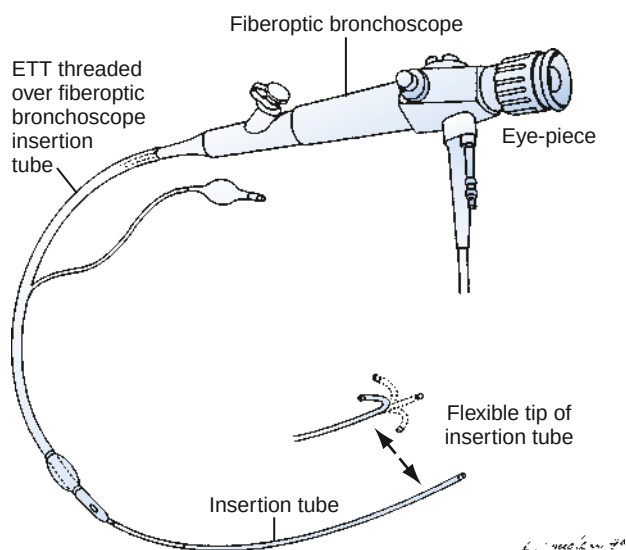


Figure 49-39. Fiberoptic bronchoscope with endotracheal tube (ETT) threaded over the insertion end of the FOB. The 15-mm airway connector has been removed, and the ETT is secured to the body of the FOB with a piece of tape. The distal (insertion) end of the FOB is lubricated with a silicone-based fluid, the cuff of the ETT is deflated. The tip of the FOB can only be flexed in one plane. To maneuver the FOB in other planes, the scope itself must be longitudinally twisted. (From Zupan J: *Fiberoptic bronchoscopy in anesthesia and critical care*. In Benumof JL (ed): *Clinical Procedures in Anesthesia and Intensive Care*. Philadelphia JB Lippincott Co, 1992, p 258, with permission.)

Emergency Airway Management Complications

Complications of emergency airway management are numerous. However, four life-threatening emergency airway complications that must be avoided in the management of airways of critically ill patients are: (1) failure to intubate/ventilate the “difficult airway,” (2) unrecognized esophageal intubation, (3) aspiration of gastric contents, and (4) hemodynamic compromise.

Failure to Intubate or Ventilate

Failure to maintain a patent airway for more than a few minutes can lead to brain damage or death, and is the single most common cause of anesthesia-related morbidity and mortality.¹ CICU patients in cardio-respiratory failure are at an even higher risk because they are starting out with a more compromised hemodynamic and respiratory status than elective patients in the operating room. Furthermore, difficulty can occur because proper equipment and help may be missing. The ASA DA algorithm was developed by a task force of academic clinicians with the goal of reducing airway related catastrophes. Although not specifically created for emergency situations, the ASA DA algorithm provides logical guidance for emergency airway management of the CNI-CNV situation (as reviewed in detail previously).

Unrecognized Esophageal Intubation

An esophageal intubation is not an error of commission; it is an error of omission (that is failure to recognize it). Once the airway is secure, confirmation of placement and ventilation

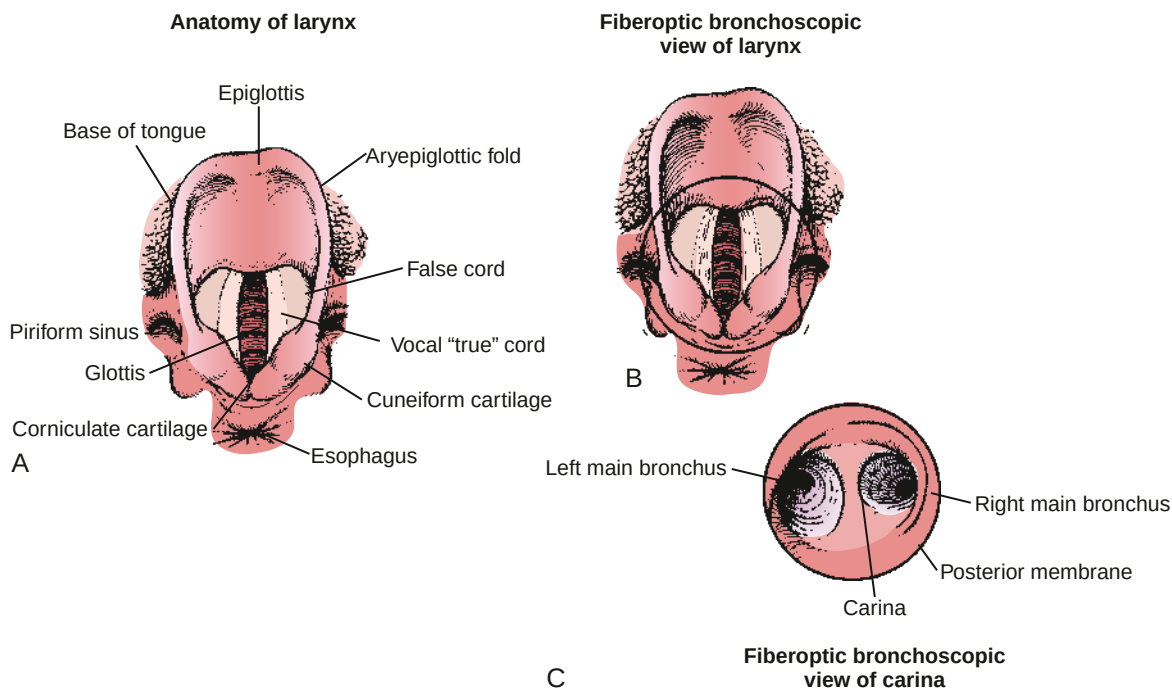


Figure 49-40. View of the larynx and carina via an FOB. This figure demonstrates the normal anatomy of the larynx (A) and the view obtained from a fiberoptic bronchoscope positioned just above the laryngeal inlet (B). After passage of the FOB through the vocal cords and down the trachea the carina comes into view (C). The tracheal cartilages are c-shaped and are joined posteriorly with a membrane. This anatomy allows for identification of the various portions of the tracheal bronchial tree. (From Zupan J: *Fiberoptic bronchoscopy in anesthesia and critical care*. In Benumof JL (ed): *Clinical Procedures in Anesthesia and Intensive Care*. Philadelphia JB Lippincott Co, 1992, p 258, with permission.)

must occur immediately. Depending on the patient's underlying condition, confirmation of ETT position can be complicated and can lead to disastrous results if not properly verified. Endotracheal tube confirmation techniques can be characterized as direct and indirect methods.

Direct Confirmation of Intratracheal Position

Direct vision of the endotracheal tube passing through the cords is considered "the gold standard." The only foolproof techniques for confirming an endotracheal position are seeing the tube pass through the cords and looking through the endotracheal tube and visualizing the tracheal rings with an FOB, or in penetrating neck trauma, the trachea may be exposed and the tube can be placed inside under direct vision.

Indirect Confirmation of Intratracheal Position

All of the usual clinical end points are indirect methods and error-prone including: auscultating equal bilateral breath sounds, observing symmetrical chest rise, and fogging of the ETT. Two specific indirect methods for determining ETT position are used for all emergency intubations. These include $P_{ET}CO_2$ measurement and the esophageal detector device (EDD).

The $P_{ET}CO_2$ can be detected by capnography or by a portable calorimetric device made by Nellcor Puritan Bennett called the Easy Cap II. These devices are good predictors of esophageal intubation in patients with normal cardiovascular status. However, in code situations with little or no cardiac output, very little blood will traverse the pulmonary circulation and consequently very little CO_2 will be exhaled with each breath and be available to be detected. Indeed, $P_{ET}CO_2$ has been used to quantify the efficacy of CPR.

Conversely, patients with high levels of CO_2 in their stomach (from $NaHCO_3$ or soft drinks) can give a false positive test on the first couple breaths. After six breaths, esophageal/gastric CO_2 levels drop. Barring these two relatively rare events, end tidal CO_2 measurement is a reliable indication of ETT position.

Recently, an esophageal detector device has been described by Wee.³² The Wee esophageal detector device (comprised of an Ellicks evacuator applied to the supposed "tracheal" tube) has proven to be highly sensitive and specific for detection of esophageal intubation (Fig. 49-42). If the tube is in the esophagus, the deflated bulb fails to re-expand when released because suction applied to the esophageal wall causes the mucosa to close in on and obstruct the ETT. In contrast, when the tube is in the trachea, air flows out of the lungs into the trachea and reinflates the bulb because the tracheal rings keep the airways from collapsing around the ETT.

Extubation or Endotracheal Tube Change in the Difficult Airway

Extubation of the trachea or tube change in the ICU or CICU patient with a known difficult airway should be considered a high-risk endeavor and should be performed over a jet stylet ETT changer, as described by Bedger and Chang.³³ If there is any difficulty placing the new ETT, ventilation can be performed using the jet stylet according to the method of Goskowitz and associates.³⁴

Aspiration of Gastric Contents

The severity of gastric aspiration is a function of the volume, pH, and nature of the material aspirated. Patients at high risk for aspiration either should receive a rapid-sequence induction

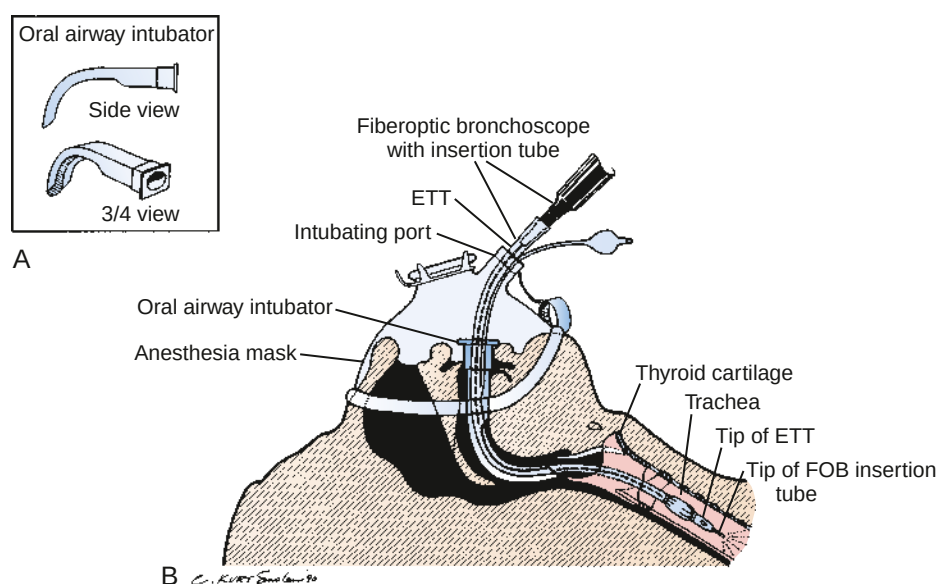


Figure 49-41. The oral airway intubator and the intubating anesthesia mask. The oral airway intubator (A) has a channel large enough to pass an 8.0-mm endotracheal tube (ETT). The intubating anesthesia mask fits over the patient's face as a normal mask does and is equipped with the usual 15-mm airway connector. Additionally, there is an intubating port with self-sealing diaphragm through which a fiberoptic bronchoscope and previously threaded ETT may pass (B). The scope passes via the intubating port through the intubating oral airway and then into the trachea. The ETT (previously threaded over the bronchoscope) is then advanced into the trachea. The bronchoscope is withdrawn, the endotracheal tube is grasped near the patient's mouth, and the anesthesia mask is removed with care not to pull the ETT out the trachea in the process. (From Zupan J: *Fiberoptic bronchoscopy in anesthesia and critical care*. In Benumof JL (ed): *Clinical Procedures in Anesthesia and Intensive Care*. Philadelphia JB Lippincott Co, 1992, p 261, with permission.)



Figure 49-42. Collapsed self-inflating bulbs (SIBs) were connected simultaneously to tracheally and esophageally placed tubes. The SIB connected to the tube in the trachea instantaneously reinflated, while the SIB connected to the tube in the esophagus remained collapsed. (From Salem MR, Wafai Y, Joseph NJ, et al: *Efficacy of the self-inflating bulb in detecting esophageal intubation. Does the presence of a nasogastric tube or cuff deflation make a difference?* *Anesthesiology* 1994;80:42-48, with permission.)

or should undergo an awake, topical anesthesia intubation technique.³⁵

The purpose of the rapid sequence induction (with cricoid pressure) is to seal the airway with a cuffed endotracheal tube as soon as possible after the loss of airway reflexes. A rapid-sequence induction is used when contraindications to a blind nasal intubation are present and when the risk of aspiration of gastric contents is high (bowel obstruction, obesity, hiatal hernia). Death can occur when the concern for a full stomach supersedes more important issues such as difficult airway and severe hypovolemia.

Hemodynamic Compromise

Patients in the CICU who are in respiratory failure may be hovering on the edge of cardiopulmonary arrest from the primary process. Also, they may be at risk from the elevated circulating catecholamines, which increase myocardial O_2 consumption and SVR (except in the rare circumstance of concomitant anaphylaxis, sepsis, or drug overdose). Furthermore, elevated catecholamines and $Paco_2$ (if respiratory failure present) sensitize the myocardium to ventricular ectopy.

More importantly, the elevated catecholamines tend to support the patient's BP before intubation. Therefore, the cardiovascular system of the critically ill patient frequently requires some exogenous catecholamine or vasopressor support during or following intubation. This support can come in

the form of pharmacologic therapy or intravascular volume expansion.

Hypotension following emergent intubation occurs secondary to lysis of endogenous catecholamine output and due to the heart-lung interactions of positive pressure ventilation (especially in hypovolemic patients).

Causes of Preinduction Increases of Catecholamines

Before induction and intubation of trauma patients, a hyperadrenergic state exists serving to buoy the patient's blood pressure. Several factors promote this hyperadrenergic state through increased endogenous catecholamine elaboration: (1) stress (fear of dying and dyspnea), (2) pain, (3) elevated $Paco_2$ (ventilatory failure), (4) pump failure, and (5) hypovolemia and hemorrhage.

Causes of Hypotension Following Induction and Intubation

Following induction/intubation the BP frequently falls in patients with respiratory failure (especially following a rapid sequence induction). The hypotensive response can be attributed to four factors.

Loss of Consciousness (Decrease in Sympathetic Tone)

All intravenous (IV) induction drugs such as etomidate, ketamine, propofol, and sodium pentothal (STP) lead to a loss of consciousness and thereby a loss of preinduction stress, fear, and anxiety mediated catecholamine production. Loss of this catecholamine elaboration can cause the BP to drop.

Direct Myocardial Depression and Vasodilation

Some IV drugs cause direct myocardial depression (e.g., thiopental, propofol, ketamine) and decreased SVR (thiopental and propofol). Etomidate is associated with very little myocardial depression. Ketamine causes some myocardial depression but its sympathomimetic effect can sometimes buoy the blood pressure (providing the patient is not already secreting the maximal amount of endogenous catecholamines).

Decreased Right Ventricular (RV) Preload and Increased RV Afterload

Positive pressure ventilation (PPV) will decrease venous return to the right heart and thus decrease preload and increase RV afterload (when alveolar pressure is greater than pulmonary capillary pressure). These changes in turn decrease filling of the left heart, tending to decrease stroke volume. These effects are especially pronounced when the patient is intravascularly volume depleted.

Decreased $Paco_2$

Hyperventilation will blow off the previously elevated $Paco_2$, resulting in a further decrement in the stimulus for catecholamine release. The combination of hypovolemia with now decreased endogenous catecholamine elaboration along with mechanical factors inhibiting cardiac output (positive pressure ventilation) can lead to catastrophic hypotension.

Techniques to Limit Hypotension Following Intubation

Avoid using a RSI technique when not necessary. A patient with an obvious difficult airway and full stomach should be intubated awake unless he or she becomes uncooperative or grossly unstable. Use small doses of induction drugs when required.

The airway is expected to be difficult to intubate, maintain spontaneous ventilation with cricoid pressure in particularly debilitated patients (i.e., those with pericardial tamponade). Pretreat with a fluid load (except in the case of myocardial ischemia related to high preload). Have vasopressors drawn up available for administration and do not hyperventilate following intubation.

Anesthesia Induction Drugs for Rapid-Sequence Intubation

For emergent intubations, a rapid-sequence technique is the preferred mode for intubating the trachea. However, the stable patients anticipated to have a difficult airway should undergo intubation using an awake technique. Selection of the correct hypnotic drug for rapid-sequence anesthesia induction can be problematic.

Drug or Dosage: What is the Important Factor?

It has been frequently said that more soldiers were killed in World War II by pentothal than by bullets. Indeed, Halford³⁶ wrote a compelling negative critique of the use of pentothal following the Pearl Harbor experience. In the same volume of *Anesthesiology*, however, appeared a case report by Adams and Gray³⁷ (and an accompanying editorial) revealing that pentothal was not the lethal factor but rather the *dosage* that was typically administered to the traumatized patient.

In general, severely ill patients should not receive pentothal or propofol for induction. If the patient is comatose upon arrival of the airway expert to the resuscitation scene, no drug other than oxygen and possibly a neuromuscular blocking drug is required until the patient's blood pressure and heart rate indicate that he or she can tolerate hypnotic agents.

Specific Drugs for Anesthesia Induction

Etomidate

An imidazole derivative, etomidate provides remarkable hemodynamic stability in critically ill patients. Thus, it is the induction drug of choice for hemodynamically unstable patients. The standard induction dose for etomidate is 0.2 to 0.3 mg/kg IV. In stable patients with ischemic heart disease and valvular disease, etomidate does not cause significant alteration in hemodynamic parameters.³⁸ Like any drug that causes loss of consciousness, however, etomidate can lead (indirectly) to hypotension in patients who are maintaining their cardiovascular system via a high resting catecholamine state. In repeat doses, etomidate can cause adrenal suppression. Etomidate is metabolized primarily in the liver, with the majority of metabolites excreted via kidneys (85%) and bile (13%); only 2% is excreted unchanged.³⁹

Ketamine

Ketamine, a phencyclidine derivative, is a unique dissociative anesthetic that produces amnesia and intense analgesia. The standard induction dose for ketamine is 2 to 5 mg/kg IV, or 5 to 10 mg/kg IM. When very small doses (0.5 to 2 mg/kg) of ketamine are used, respiration and airway reflexes usually remain intact. Larger doses can cause a release of endogenous catecholamines that often leads to hypertension and tachycardia. Ketamine does, however, cause myocardial depression. Thus, in cardiomyopathy patients or in patients with hypovolemia and baseline maximal endogenous sympathetic tone, ketamine may

still lead to hypotension. Ketamine is a bronchial smooth muscle relaxant,⁴⁰ making it suitable for use in asthmatic patients. Recovery from ketamine can be associated with hallucinations. Ketamine is metabolized in the liver by the microsomal enzymes to metabolites, which are then altered to the glucuronide form and excreted into the urine.

Thiopental

A derivative of barbituric acid, sodium thiopental is the standard intravenous induction drug used by many anesthesiologists. The standard induction dose in stable patients is 4 to 6 mg/kg. The induction dose in hemodynamically unstable patients must be significantly decreased (i.e., 0.25 to 0.5 mg/kg in patients with congestive heart failure or following trauma). The major side effects of thiopental are dose-dependent depression of respiration and hypotension secondary to a combination of cardiac depression and systemic vasodilation. Hypotension with thiopental and other induction agents can be life-threatening in volume-depleted patients. Lack of analgesic properties makes barbiturates incomplete general anesthetic agents.

Propofol

Propofol, an alkylphenol derivative, is a relatively new hypnotic agent that appears to have several advantages over thiopental for certain procedures.⁴¹ Emergence from brief anesthesia with propofol is extremely rapid because it is cleared more rapidly from the brain than thiopental. This is due to propofol's larger volume of distribution and high clearance from the blood (clearance actually exceeds hepatic blood flow). Propofol has intrinsic antiemetic properties, and patients can emerge from anesthesia hungry, euphoric, and, occasionally, in a noticeably amorous mood.

Despite these benefits, propofol is relatively contraindicated in hemodynamically unstable patients. The hemodynamic side effects of propofol are similar to those of thiopental. Propofol causes irritation and discomfort during intravenous administration. These effects are reduced by administering the drug into larger veins, using a rapidly running IV, and pretreating with intravenous lidocaine (0.5 mg/kg) or fentanyl (2 µg/kg). A typical induction dose of propofol (2 mg/kg) may be followed by a continuous infusion (100 to 200 µg/kg/min) for maintenance of anesthesia. The induction and maintenance doses of propofol (like pentothal) must be decreased in the unstable patient. Propofol is metabolized in the liver by conjugation to glucuronide and sulfate and is eventually excreted via the kidneys.

Clinical Scenarios

When called to the bedside of a patient for a "code blue," the airway expert must first determine whether the patient is truly in full cardiopulmonary arrest or in cardiopulmonary distress with impending arrest, the so called pseudocode. Several specific clinical examples of "pseudocode" are provided in this section.

True "Code" (Full Cardiopulmonary Arrest)

In the patient in full arrest, no drugs are necessary; however, oxygen, suction, proper preparation, and patient positioning are important. Management begins with implementation of the ABCs (airway, breathing, and circulation): apply cricoid pressure, open the airway, mask ventilate, and use a direct

laryngoscopic technique to intubate the trachea with a styletted endotracheal tube.

Following intubation, endotracheal position is verified using both clinical signs—symmetric chest movement, equal bilateral breath sounds, fogging of the endotracheal tube—and the more reliable devices for documenting endotracheal positioning: end-tidal CO₂ with a typical device (Nellcor, Easy Cap) or with an infrared measuring device (available in the operating room and some CICUs and ICUs). Alternatively, a fiberoptic bronchoscope or Wee esophageal detector device can confirm tracheal positioning. The airway expert must be sure to attach the endotracheal tube securely to the patient's maxilla following intubation, and should be cautious when manipulating the patient's head or body. This is the time during emergency airway management when medical personnel let their guard down (because the airway is secured), and someone may inadvertently pull the endotracheal tube out of the trachea while reaching over to move the patient for some other manipulation. The ETT should be secured at 21 cm from the upper incisors in normal adult females and at 23 cm in normal adult males. Finally, a chest radiograph should be ordered and reviewed to verify that the ETT is resting in the midtracheal position (see Fig. 49-43).

Pseudocode (Cardiopulmonary Arrest Imminent)

The pseudocode is characterized by the anesthesiologist's being called *stat* for a “code blue” to the CICU, ICU, or ward and finding upon arrival that the patient is still ventilating and has a pulse and blood pressure. The patient may or may not be in need of definitive emergency airway management. The airway expert must first decide whether intubation is indeed necessary, and if so, how urgently intubation must be performed,

and whether the patient is in the optimum setting. While these issues are being decided, the airway expert should apply oxygen to the patient, listen to the patient's chest with a stethoscope, and (if necessary) assist ventilation with a bag-mask device. Next, the anesthesiologist or airway expert should ask members of the patient's primary team what history has led to this event. The patient should also be interviewed regarding significant past medical problems, drug allergies, and current medications, including monoamine oxidase inhibitors (MAOs) and cardiac, pulmonary, or diuretic medications. The airway expert should then verify that the 10 prerequisites for safe airway management (described earlier) are available and should proceed with guidelines provided in the next section.

Airway Management Guidelines for Specific Clinical Scenarios

Several frequently encountered clinical scenarios occur on the ward, in the emergency room, and in critical care units. Each scenario has several specific and identifiable management points. Although the scenarios presented here represent patients who are in cardiopulmonary failure but have not yet gone into full arrest, improper or delayed therapy can lead to full arrest.

Ventilatory Failure Due to Airway Compromise

The airway expert should always be prepared to use transtracheal jet ventilation (TTJV) or to perform an emergent cricothyroidotomy for the patient who has a compromised airway. Clinical signs of airway compromise are stridor, chest retractions, CO₂ retention, and, ultimately, hypoxia. Airway compromise can occur secondary to tumor, foreign body, trauma, epiglottitis, laryngeal edema associated with anaphylaxis or drug allergy, and postoperative complications. Common postoperative causes of stridor include bleeding into a fresh surgical wound following neck surgery (carotid endarterectomy, thyroid, or parathyroid surgery) and soft tissue swelling following operations on the neck (i.e., anterior cervical discectomy) and massive blood transfusion.

For the stridorous patient with impending airway obstruction, the primary directive should be to maintain airway patency and spontaneous ventilation until the airway is secured (i.e., a partial airway obstruction should not be transformed into a complete airway obstruction). Therefore, a controlled awake technique with topical anesthesia and using a fiberoptic bronchoscope or direct vision is the recommended approach. Blind techniques are not recommended because they may cause complete airway obstruction. Furthermore, emergency airway management in a patient with a suspected difficult airway or with stridor should be performed in the presence of another physician (preferably a surgeon) with particular expertise in obtaining a surgical airway.

Respiratory Failure Due to Gas Exchange Problems (Shunt)

Primary pulmonary parenchymal problems, such as aspiration pneumonia, *Pneumocystis* pneumonia, adult respiratory distress syndrome, and sepsis, cause a large and variable right-to-left transpulmonary shunt. Affected patients typically exhibit signs of air hunger, have a high minute ventilation with a rapid shallow breathing pattern, and are ideally managed via a blind nasal intubation technique. Such a patient tends to suck the endotracheal tube into the trachea as it is placed carefully through the

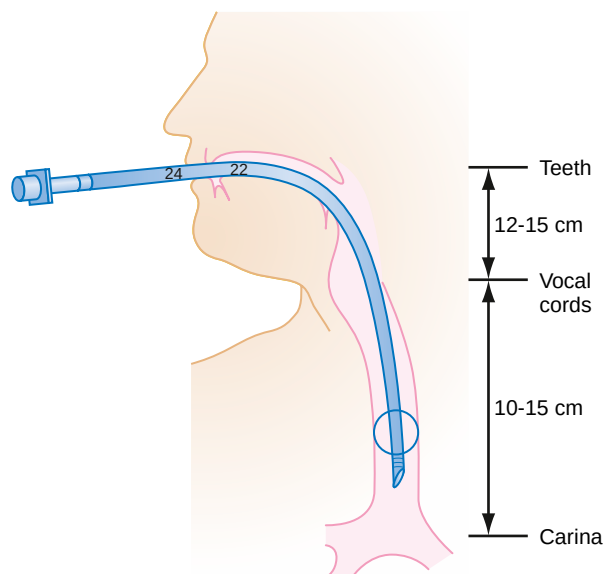


Figure 49-43. Anatomic distances for endotracheal tube positioning. The usual satisfactory position of the endotracheal tube in a 70-kg adult male (23 cm from the upper incisors). This position allows the tip of the endotracheal tube to be 3 to 4 cm above the carina. In the normal adult male patient, distance between the vocal cords and the carina is 10 to 15 cm, and that between the dental line and the vocal cords, 12 to 15 cm. (From Bogdonoff DL: *Airway considerations in the management of patients requiring long-term endotracheal intubation*. *Anesth Analg* 1992;74:276.)

anesthetized nares. The patient may not require quite as much topical anesthesia and analgesia as a patient who presents for an elective operation because of the air hunger. When time allows, however, proper anesthesia induction and patient preparation are humane and can be the critical difference leading to success in securing the airway in such a patient.

Congestive Heart Failure

Congestive heart failure has many etiologies. The patient who has respiratory insufficiency attributable to CHF has, by definition, inadequate cardiac output and invariably manifests a high resting catecholamine state. The high sympathetic output serves to maintain what little cardiac reserve and vascular tone the patient has. One can occasionally temporize the patient with pulmonary edema with high-flow oxygen and medical therapy. If the patient requires intubation, however, consideration should be given to initiating support with inotropic agents and invasive monitoring before commencing airway management. Furthermore, only very small doses of sedative hypnotics should be administered.

Alternatively, a blind nasal intubation with careful topical anesthesia is a very acceptable technique in the patient with CHF. It is essential, however, to take the time to carefully anesthetize and prepare the patient so that he or she does not become more distressed and increase catecholamine output even further, leading to ventricular or supraventricular dysrhythmias.

If renal failure is the etiology of CHF, consideration should be given to the qualitative platelet defect that accompanies renal failure and the increased risk of nasal bleeding. Renal failure is not a contraindication to a nasal technique, provided that anesthetization of the airway is careful and complete.

Congenital Heart Disease

The maneuvers used to intubate the trachea in a patient with congenital heart disease can significantly alter the pathophysiologic expression of that disease. The airway expert must consider not only the effects of the drugs used on heart rate, rhythm, preload, afterload, and contractility but also the relative effects on pulmonary vascular resistance versus systemic vascular resistance and the resultant pulmonary versus systemic blood flow.⁴² Some lesions typically cause a predominant left-to-right shunt, whereas others cause a right-to-left shunt. Several lesions (i.e., hypoplastic left heart, transposition of the great vessels) can cause either shunt, depending on the patient's specific anatomy (caliber of the pulmonary vessels, size of an atrial septal defect, relative ventricular outflow obstruction, etc.) and physiologic state. Table 49-8 shows the common congenital lesions and the hemodynamic manipulations that should be attempted.

Lesions that increase pulmonary blood flow are said to cause a left-to-right shunt. Emergency airway manipulations for patients with such lesions are designed to limit the pulmonary perfusion and to increase systemic perfusion. This goal is achieved through manipulating the pulmonary and systemic vascular resistance (PVR and SVR). If the PVR/SVR ratio is increased, less blood will flow to the lungs. Increasing PVR promotes the shunting of blood away from the lungs. The goal in these patients is not to increase PVR, but rather to avoid manipulations that decrease PVR. Maneuvers that decrease PVR include any that cause high FiO_2 , hypocarbia, alkalosis, low mean airway pressure, and abolition of sympathetic stimulation.

In patients with diminished pulmonary blood flow, anesthetic manipulations should be designed to improve flow through the pulmonary vasculature. Pulmonary blood flow can be promoted and right-to-left shunting reduced by decreasing the right heart to left heart pressure ratio. This can be done by maintaining a high FiO_2 , promoting hypocarbia (through hyperventilation), eliminating acidosis, maintaining a low mean airway pressure, and achieving a normal or slightly elevated SVR. In the case of a fixed pulmonary outflow obstruction (such as tetralogy of Fallot), changes in systemic vascular resistance may alter pulmonary blood flow more than similar changes in pulmonary vascular resistance. In a patient with a tetralogy of Fallot, infusion of phenylephrine frequently reduces intracardiac shunting and increases blood flow through the pulmonary system, improving oxygenation.

Anesthetic drug-induced depression of cardiac contractility is not always detrimental in congenital heart disease. Obstruction in patients with idiopathic hypertrophic subaortic stenosis (IHSS) with infundibular left ventricular outflow obstruction can be exacerbated by tachycardia and hypovolemia as well. This is in contrast to patients who suffer from aortic stenosis or pulmonic stenosis at the valvular level, in whom contractility must be maintained to eject blood out of the stenotic valves. Drugs used for induction and for hemodynamic support should be selected according to the recommendations in Table 49-8.

Valvular Heart Disease

Just as in congenital heart disease, anesthetic drug administration and emergency airway management in valvular heart disease can have a significant impact upon the patient's baseline physiology.⁴⁶ Other chapters in this textbook have more completely addressed the pathophysiology of the various valvular lesions, and the subject will not be duplicated here. Nevertheless, a brief overview of the basic physiology and important hemodynamic goals suggested for safe emergency airway management are provided (Table 49-9).

Aortic stenosis (AS) is the most common cardiac valvular abnormality. The pathophysiology results from obstruction of the left ventricular outflow at the valvular level, which leads to concentric hypertrophy of the left ventricular muscle. The left ventricular end-diastolic pressure (LVEDP) is generally elevated to promote filling of the hypertrophied left ventricle. Similarly, sinus rhythm is critical because left atrial contraction is required to fill the stiff left ventricle. Myocardial contractility is typically preserved and is very important for stability in patients with AS. Hemodynamic goals include maintaining a low heart rate to give the ventricle a longer time to fill and to increase the relative diastolic time, which is when the coronary arteries are perfusing the hypertrophic left ventricle. Preload should be higher rather than lower, and SVR must be maintained on the relatively high side to augment coronary artery blood flow. Also, it must be recognized that the resistance that the left ventricle ejects against in AS is at the valvular level and is not related to the SVR.

Patients with aortic insufficiency (AI) typically have volume overload physiology; stroke volume and ejection fraction are generally maintained through preload reserve and afterload reduction. The hemodynamic goals here are to maintain the heart rate in a relatively higher range to keep left ventricular preload on the higher side and to minimize SVR to help promote forward flow. Contractility should be maintained but not increased.

Table 49–8. Anesthesia Induction Considerations for Patients with Congenital Heart Disease*

	<i>Pathophysiologic Expression of Disease</i>			
	Right-to-Left Shunt	Left-to-Right Shunt	Right Ventricular Obstruction	Left Ventricular Obstruction
<i>Lesions responsible</i>	ASD (late) TGV Tetralogy of Fallot† Tricuspid atresia	ASD (early) AV canal PDA‡ TAPVR vsd	Pulmonary stenosis	Coarctation of the aorta Aortic stenosis§
<i>Hemodynamic goals</i>				
Heart rate	↔, ↓†	↔	↓	↔, ↓, §
Rhythm	Sinus	Sinus	Sinus	Sinus
LV Preload	↑	↑	↑	↑
SVR	↑↑	↓↓	↔	↓, ↑, §
PVR	↓↓	↑↑	↓	↔
Contractility	↔	↔↑	↔	↔
<i>Induction drug considerations</i>	R-to-L shunts are increased by decreasing SVR (large induction dose of sodium pentothal) or by increasing PVR (excessive positive-pressure ventilation, hypoxia, acidosis, hypercarbia)	Avoid pulmonary vasodilators; maintain on lower FiO ₂ ; and avoid myocardial depressants. (If chest open, hypotension can be aided by surgically applied PA obstruction)	Fairly fixed RV output. Will be made worse by increasing the PVR, or by decreasing the perfusion pressure to the hypertrophic RV (do not decrease the SVR or contractility)	Strong ventricle and necessarily so (do not decrease the contractility) For coarctation of aorta, may decrease SVR. For AS, keep rate slower and SVR high

*ASD, atrial septal defect; AV, arteriovenous; PA, pulmonary artery; PDA, patent ductus arteriosus; PVR, pulmonary vascular resistance; RV, right ventricular; SVR, systemic vascular resistance; TAPVR, totally anomalous pulmonary venous return; †, slightly increased; ↑↑, significantly increased; ↓, slightly decreased; ↓↓, significantly decreased; ↔, maintained stable without need for increase or decrease; TGV, transposition of the great vessels; VSD, ventricular septal defect.

†If dynamic RV obstruction operative, limit tachycardia.

‡Occasionally, right-to-left shunt (hypoplastic left heart).

§Recommendations for coarctation of the aorta and aortic stenosis are the same except where indicated (HR and ↑ SVR recommendations apply to aortic stenosis).

Mitral stenosis (MS) is another valvular lesion with specific implications for choice of anesthesia induction drug. Patients with MS have a dilated left atrium and an under-filled but physiologically normal left ventricle. Patients with baseline normal sinus rhythm can manifest acute congestive heart failure if they lapse into atrial fibrillation. Thus such patients should not be made anxious during airway manipulations. Hemodynamic goals for MS include reducing the heart rate, thus allowing time for blood to flow from the dilated volume-overloaded left atrium through the stenotic mitral valve and into the relatively empty left ventricle. Normal sinus rhythm should be maintained (if the patient is in this rhythm). Left ventricular preload must be kept as elevated as possible without causing pulmonary edema.

Mitral regurgitation (MR) is the final valvular lesion with significant hemodynamic considerations for induction of anesthesia for emergency airway management. Patients with this lesion have left ventricular volume overload physiology. The heart rate should be maintained in the higher range, and left ventricular preload should be elevated during anesthesia induction. The SVR should be kept low, however, to help the left ventricle to empty blood in a forward direction rather than retrograde through regurgitant mitral valves. Contractility should be

maintained. Pharmacologic methods of increasing the heart rate (with atropine, epinephrine, isoproterenol) should be available in case the rate decreases with the manipulations used to control the airway.

Asthma

Patients with reactive airways disease are frequently encountered in the CICU. The asthmatic patient presents several difficult problems that simultaneously impinge on emergency airway management. These patients may be very distressed and agitated, may be moving very little air, and may have wide swings in blood pressure owing to the effects of the transmitted pleural and intra-abdominal pressures on the cardiovascular system. Furthermore, a very significant problem for the anesthesiologist or airway expert is the specter of unrecognized esophageal intubation resulting from the difficulty of hearing breath sounds in asthmatic patients during an acute attack. Therefore, a rigid direct laryngoscopic technique is recommended in the asthmatic patient. Visualization of the cords is superior to a blind technique because not only is it difficult to hear breath sounds transmitted, but also the chest wall excursions may be so minimal that the airway expert may not hear much flow in and out of the ETT during the blind technique.

Table 49–9. Anesthesia Induction Considerations for Patients with Valvular Heart Disease*

	Aortic Stenosis	Aortic Insufficiency	Mitral Stenosis	Mitral Regurgitation
<i>Pathophysiology</i>	Concentric hypertrophy	Dilated LV, volume overloaded Stroke volume and ejection fraction maintained with preload reserve	Dilated LA, ↑PAP, empty and protected LV May manifest as dyspnea, may be secondary to increased cardiac output (pregnancy or sepsis)	Dilated LA and LV, volume overloaded LV failure may be underdiagnosed because of regurgitant flow to LA despite severely decreased forward stroke volume
<i>Hemodynamic goals</i>				
Heart rate	↓↓	↑	↓↓	↑
Rhythm	NSR	—	Frequently in AF But, NSR→AF = ↓ BP	—
LV Preload	↑	↑	↑	↑
SVR	↑	↓	↔	↓
PVR	↔	↔	↓	↓
			(these patients may have severe PA HTN)	
Contractility	↔↑	↔↑	↔	↔↑
<i>Induction considerations</i>	Avoid myocardial depression, maintain CA perfusion, pressure (↑SVR, ↑BP) Be prepared to perform cardioversion if an arrhythmia occurs (CPR is futile) Treat hypotension with phenylephrine (Etomidate is good induction choice)	Minimize myocardial depression and keep the patient fast, full, and vasodilated. A PAC is useful to measure filling pressures and cardiac output. Dobutamine is a reasonable support drug at anesthesia induction.	Avoid tachycardia (No pavulon, etc. Conduction through the AV node may dramatically increase ventricular HR) Do not decrease contractility Inadequate sedation can precipitate extreme anxiety and tachycardia Consider esmolol to treat tachycardia	Isolated MR rare. Usually secondary to papillary muscle dysfunction or RHD. MVP is most common cause of <i>trivial</i> isolated MR. Keep the patient fast, full, and vasodilated Have several ways on hand to increase heart rate

AI, aortic insufficiency; AV, atrioventricular; BP, blood pressure; CA, coronary artery; CHF, congestive heart failure; CPR, cardiopulmonary resuscitation; HR, heart rate; HTN, hypertension; LA, left atrium; LV, left ventricle; MR, mitral regurgitation; MVP, mitral valve prolapse; NSR, normal sinus rhythm; PAC, pulmonary artery catheter; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance; RF, rheumatic fever; SBE, subacute bacterial endocarditis; SVR, systemic vascular resistance; ↑, slightly increased; ↑↑, significantly increased; ↓, slightly decreased; ↓↓, significantly decreased; ↔, maintained stable without need for increase or decrease.

If a rigid, direct laryngoscopic technique is selected, ketamine is the ideal induction drug, because it provides some hemodynamic stability and, most importantly, bronchial dilation.⁴³ If the asthmatic patient also has a difficult airway, fiberoptic bronchoscope intubation should be used.

Airway Management for Cardioversion

Direct-current cardioversion is commonly employed in the CICU setting. Synchronized cardioversion is used to convert supraventricular and ventricle arrhythmias to sinus rhythm. When the patient is hemodynamically stable and has an arrhythmia of long duration that does not respond to drug therapy, cardioversion can be performed electively.

Cardioversion is painful, and thus, a light general anesthesia is required to allow the patient to undergo the procedure without remembering it or experiencing the pain. Thiopental,

methohexital, propofol, etomidate, and midazolam have all been used successfully for cardioversion.^{44–46} When cardioversion is performed electively, the patient should have fasted 8 hours before the procedure and should be monitored with pulse oximetry, blood pressure, and ECG.

Anesthesia should not be induced until the cardiologist is ready to administer the countershock. At this time, the patient is preoxygenated and given small, incremental doses of anesthetic drug until no longer responsive. Gail and colleagues⁴⁶ have demonstrated that a continuous slow injection of anesthetic drugs is superior to intermittent injections and that patients tend to require less drug and to suffer fewer hemodynamic effects with this technique. Both propofol and methohexital are superior to midazolam in their ability to provide rapid anesthesia onset and rapid recovery. Most authorities recommend removal of the mask immediately before countershock, so that no one is

touching the patient. However, in patients with significant right-to-left shunting the airway expert can keep the mask on the patient's mouth by holding only the plastic mask with one gloved hand, thereby keeping the rest of his or her body completely away from the patient. This technique ensures that the patient will not breathe any room air during the application of the countershock.

Often, more than one shock is required for restoration of normal sinus rhythm, and additional doses of intravenous medication may be required. Following the production of normal sinus rhythm, the patient is allowed to resume spontaneous ventilation, and the mask should be held in place until the patient awakens and has control of the airway and gag response. No muscle relaxants should be used, and intubation is not required unless the patient is prone to aspiration or has a full stomach.

If the cardioversion is performed on an emergent basis, it must be remembered that the patient has not fasted, and intubation of the trachea may be appropriate. Furthermore, in hemodynamically unstable patients, a drug devoid of myocardial depressor or vasodilator effects, such as etomidate, is superior to thiopental, propofol, or midazolam.

Conclusion

Emergency airway management in patients in the CICU is fraught with danger for the patients, because on average they tend to be sicker than patients in elective cases and because proper equipment and expert help may be difficult to obtain in a timely manner.

The morbidity and mortality of emergency airway manipulation in these settings can be decreased by carefully preparing the patient and physician for the planned manipulation, and by developing alternative plans before the initiation of airway management. Thinking ahead helps one avoid the four major complications of emergency airway management: failed intubation/lost airway, unrecognized esophageal intubation, aspiration of gastric contents, and hemodynamic compromise. A common theme developed throughout this chapter and supported by the literature is to maintain spontaneous ventilation and to use an awake intubation technique in any patient recognized to have a difficult airway.

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Mechanical Ventilation in the Cardiac Care Unit

Daniel Baram, Paul Richman

CHAPTER 50

Introduction
Impact of Positive Pleural Pressure on Hemodynamics
Indications for Mechanical Ventilation
Managing Gas Exchange and Oxygen Delivery

Delivery of Mechanical Ventilation
Complications of Mechanical Ventilation
Ventilation of ARDS and Obstructive Airways Disease

Introduction

Mechanical ventilation is a common indication for intensive care unit (ICU) admission. This chapter will provide an overview of mechanical ventilation: its indications, basic physiology, ventilator settings, and issues that arise in caring for patients on mechanical ventilation.

Understanding mechanical ventilation requires a review of normal breathing. Ventilation occurs when fresh gas enters the alveolus, carbon dioxide diffuses from the blood across the alveolar-capillary membrane, and the carbon dioxide is exhaled. Oxygenation occurs simultaneously as oxygen diffuses from the inhaled gas into capillary blood. Total ventilation is divided into alveolar ventilation, that portion which participates in gas exchange, and dead-space ventilation, that portion that does not reach a functioning alveolar unit and is exhaled unchanged.

The functional residual capacity (FRC) is the resting volume at which the elastic recoil pressure of the lung inward equals the elastic recoil pressure of the chest wall outward, alveolar and mouth pressure are both zero, and there is no airflow. FRC increases with low lung elastic recoil pressure (such as in emphysema) and decreases when lung recoil pressure is high (such as in pulmonary edema or fibrosis).

Inspiratory muscles lower pleural pressure, generating a negative alveolar pressure while mouth pressure remains constant. Gas follows the pressure gradient and enters the lung. Expiration occurs when the lung returns to FRC with the relaxation of the inspiratory muscles although expiratory muscles can be used to speed the flow of gas out of the lung or to reduce lung volume below FRC down to residual volume.

Tidal volume is the volume of gas entering and leaving the lung during a respiratory cycle. It is determined by the pressure gradient from airway to alveolus and the mechanical properties of the lung and airways. Modern ICU ventilators deliver tidal volume by applying positive pressure to the airway. Negative pressure devices that lower the pressure outside of the chest wall, akin to the iron lung of historical note, are still used for some patients with chronic respiratory failure, but these devices are rarely used in the acute setting.

The history of mechanical ventilation is replete with famous figures in pulmonary physiology, anesthesia, and surgery.¹ Ventilators have been used in the operating room since the end of

the 1900s, but widespread use in respiratory failure began in the 1950s treating patients with paralysis from polio. Advances in oxygen delivery and blood gas analysis allowed the treatment of patients with increasingly complex pulmonary and chest wall diseases over the next decade. Modern ventilators continue to advance with improvements in reliability and responsiveness and increasing ability to control all phases of the inspiratory cycle.

Impact of Positive Pleural Pressure on Hemodynamics

The complex interactions between the cardiac and pulmonary systems are well known to the cardiologist. Lowering of alveolar and pleural pressure during normal spontaneous breathing augments venous return, explaining the varying split of the S₂ heart sounds and the variation in right ventricular murmurs with inspiration. Analogously, the Valsalva maneuver, sustained forced expiration against a closed glottis raising pleural pressure, lowers cardiac output and left ventricular size accentuating the murmur of hypertrophic cardiomyopathy; release of the Valsalva restores venous return accentuating right-sided murmurs.

Transitioning from negative pressure in the pleura to positive has important hemodynamic consequences affecting both the right- and left-sided cardiac circulations.² A complete review of this topic is beyond the scope of this chapter, but understanding basic cardiopulmonary interactions allows the reader to predict the impact of positive pressure breathing on a given patient's condition.^{3,4}

Positive alveolar pressure affects blood circulation in two important ways:

1. A portion of the alveolar pressure is transmitted to the pulmonary capillaries and veins, as increasing alveolar volume compresses the pulmonary capillary. The extent of transmission is dependent on lung elastance; more compliant lungs distend more easily, increasing stretch of the alveolar wall and increasing transmission of pressure. Increased capillary pressure has two net effects. Blood already within the capillary and pulmonary veins is ejected forward into the left atrium, increasing left ventricular preload acutely. The increased pressure acts as increased afterload for the right ventricle, decreasing left ventricular preload during the next cardiac cycle.

2. Rise in alveolar pressure distends the lung raising pleural pressure. Using the analogy of a balloon being inflated within a box, pleural pressure reflects distention of the lung up against the chest wall. The extent of transmission of alveolar pressure to the pleura is dependent on both chest wall and lung compliance; index of transmission = (lung compliance)/(lung compliance) + (chest wall compliance) defines this relationship. The lower the chest wall compliance compared to lung compliance, the more pressure is transmitted. Patients with stiff lungs and a normal chest wall have smaller increases in lung volume and therefore pleural pressure changes little; conversely, patients with normal lungs and stiff chest walls have lungs that push against the stiff chest wall, raising pleural pressure more steeply.⁵⁻⁷

A rise in pleural pressure directly affects right ventricular preload and left ventricular afterload. Venous return is affected by central venous pressure as described by Guyton, and this determines right ventricular preload. Blood drains from the systemic veins down the pressure gradient from the mean systemic pressure down to central venous pressure; any increase in central venous pressure reduces the gradient, lowering venous return. Pleural pressure is also a determinant of left ventricular afterload. Increased intrathoracic pressure ejects blood out of the thoracic aorta; this decreases afterload and facilitates left ventricular emptying. This can also be expressed as decreased myocardial work, which is determined in large part by transmural pressure.

Decrease in preload and afterload can occur cyclically during inspiration or can be continuous. For instance, patients ventilated with positive pressure breathing with positive end-expiratory pressure (PEEP) of zero have the normal negative pleural pressure at end-expiration that becomes positive during inspiration. Patients treated with continuous positive airway pressure (CPAP) continue to breathe unassisted spontaneously (i.e., lower their pleural pressure with each breath), but the baseline pressure is shifted upwards resulting in a continual hemodynamic effect. Often patients on mechanical ventilation receive positive inspiratory pressure on top of PEEP, thereby having cyclic decreases in preload on top of an already reduced baseline.

Manipulation of pleural pressure offers therapeutic options when patients are in the cardiac care unit, and it is important to remember these hemodynamic effects when initiating or withdrawing mechanical ventilation or adjusting settings. Patients who are preload dependent frequently develop hypotension after intubation, for instance those with hypovolemia, right ventricular infarction, pulmonary hypertension, or aortic stenosis; great care should be taken when initiating mechanical ventilation in patients with pericardial tamponade because deterioration in to pulseless activity (PEA) has been documented. Alternatively, the decrease in preload and afterload from intubation is beneficial for patients with congestive heart failure.

The interplay of breathing and hemodynamics offers an opportunity to determine preload responsiveness in critically ill patients. Combining the models of Guyton and Starling, Magder and colleagues showed that careful interpretation of the central venous pressure waveform during spontaneous breathing can differentiate those patients who are on the ascending portion of their Starling filling curves, thereby correctly predicting which patients will increase their cardiac output with a fluid challenge.^{8,9} Similarly patients with large swings in arterial blood

pressure with positive intrathoracic pressure are preload dependent and likely responsive to fluid.¹⁰ A thorough review of this topic has been published.¹¹

Indications for Mechanical Ventilation

The most common reason for mechanical ventilation in the cardiac care unit (CCU) is cardiogenic pulmonary edema. The underlying cardiac pathology may be a cardiomyopathy, valvular disease, or tachyarrhythmia. Whatever the cause, the resulting respiratory insult is the same: increased left atrial pressure and imbalance in Frank-Starling forces across the lung capillary membrane. This results in transudation of fluid into the lung interstitium and flooding of the alveoli. The lungs become stiff, and gas exchange is impaired across the thickened capillary membrane. In addition, the bronchi become edematous, so that airway narrowing may complicate the picture. All this leads to ventilation-perfusion ($\dot{V}/\dot{Q}$) mismatch causing severe hypoxemia, and increased work of breathing causing ventilatory failure and CO₂ retention. Excess work of breathing increases the oxygen demand by the diaphragm, further stressing the heart. In this state, the goals of mechanical ventilation are to improve gas exchange and reduce the patient's work of breathing. Settings for mechanical ventilation should reflect these dual goals.

Other indications for mechanical ventilation in the CCU include:

- Loss of upper airway reflexes and/or aspiration pneumonia. This may be due to cardiac arrest, cardiogenic shock, or the need for heavy procedural sedation
- Acute and/or chronic pulmonary disease
- Concomitant neuromuscular disease

Finally, nosocomial and iatrogenic complications in the CCU may result in respiratory failure and the need for mechanical ventilation. These include pulmonary embolism, hospital-acquired pneumonia, critical illness polyneuropathy, and pneumothorax after placement of a central venous catheter.

Managing Gas Exchange and Oxygen Delivery

Oxygenation

The paramount goal of mechanical ventilation is to assure an adequate PaO₂ (arterial pO₂), such that hemoglobin saturation (SaO₂) is comfortably above 90%. It is important to recognize however that SaO₂ is only one of three factors whose product determines O₂ delivery to the tissues, the other two being cardiac output and the concentration of hemoglobin, as described by the equation:

$$O_2 \text{ delivery} = SaO_2 \times C.O. \times [Hgb] \times \text{constant}$$

From this it is clear that an increase in cardiac output from 5.0 to 6.0 liters/min or a rise in hemoglobin from 8 to 10 mg% will have a greater impact on O₂ delivery than a rise in O₂-hemoglobin saturation (SaO₂) from 92% to 98%. Further, once SaO₂ is >92%, the patient is on the "flat portion" of the hemoglobin-O₂ saturation curve, such that small changes in PaO₂ will not greatly affect the SaO₂. For both of these reasons, keeping SaO₂ in the range of 92-95% is a reasonable goal when adjusting ventilator settings.

Importantly, the 3 factors in the equation above can interact with each other; for example increasing the intensity of

mechanical ventilation to improve SaO_2 may over-pressurize the thorax, reduce venous inflow to the right ventricle and impair cardiac output. Excessive red blood cell transfusion to achieve a “normal” hemoglobin concentration is also ill advised, as it will increase blood viscosity and may impair C.O. Careful attention to these interactions will guide the clinician in choosing interventions to improve O_2 delivery to tissues.

The measurement of O_2 saturation by pulse oximetry (SpO_2) is a good estimate of SaO_2 in most situations, though it also records carboxyhemoglobin. When blood concentration of carbon monoxide is high (in heavy smokers or smoke-inhalation victims) the SpO_2 overestimates SaO_2 .

In the mechanically ventilated patient, the two main parameters that affect the PaO_2 are the FiO_2 (fraction of O_2 in inspired air) and the mean airway pressure. A moderate increase in FiO_2 is often adequate to improve the PaO_2 in patients with respiratory failure due to mismatching of ventilation and perfusion in the lung (V/Q mismatch). This situation occurs commonly in patients with inhomogeneous airway diameter due to obstructive lung disease or early interstitial lung edema in patients with CHF.

Severe hypoxemia however may be refractory to increases in FiO_2 when it is due to pulmonary “shunting” in which a significant fraction of the cardiac output passes through a lung capillary bed that is not aerated (not exposed to gas). This commonly occurs in patients with consolidated pneumonia, massive pulmonary edema or atelectasis due to airway obstruction or compression of lung tissue. In these scenarios, even FiO_2 levels approaching 100% will be unsuccessful in treating the cyanosis, just as in patients with an intra-cardiac shunt. Fortunately, there are alveoli at the margins of consolidated or atelectatic lung regions that can be “recruited” to function as gas exchange units if a high distending pressure is maintained. These higher airway pressures are commonly achieved by applying positive end-expiratory pressure (PEEP), which exerts its beneficial effect on PaO_2 by preventing the collapse of recruitable lung units during exhalation. The effect of PEEP on cardiac output is complex, as it reduces both RV preload and LV afterload. The result may be either beneficial or deleterious, depending on the patient's volume status and lung compliance.^{12,13} This is detailed in the preceding section.

Ventilation

Alveolar ventilation is the process by which the lungs excrete CO_2 , and is thus inversely proportional to PaCO_2 . So called “minute ventilation” (Ve) is the total volume of air exhaled per minute, and is the sum of alveolar ventilation (Va) and ventilation of the pulmonary “dead space” (Vd), which is the volume of exhaled air that did not participate in gas exchange at the alveolar membrane:

$$\text{Ve} = \text{Va} + \text{Vd}$$

Elevated dead space may be present chronically, as in patients with emphysema, or acutely as in a patient who has suffered a pulmonary embolism. In either case however, if dead space is stable over time, control of minute ventilation will control alveolar ventilation and thus will regulate PaCO_2 . Ve is measured as the product of respiratory rate (RR) and tidal volume (TV). Thus adjusting these two ventilator parameters will regulate PaCO_2 . An important caveat to this is that patients on mechanical ventilation regulate their own RR via respiratory drive mechanisms, unless heavily sedated or paralyzed; therefore raising or

lowering the ventilator “set” rate will not necessarily change the patient's actual RR or alter PaCO_2 .

The chief reason to control alveolar ventilation or PaCO_2 is to regulate pH. Marked acidosis can impair cardiac contractility and responsiveness to vasopressors^{14,15}; marked alkalosis reduces the threshold for ventricular arrhythmias in susceptible patients.¹⁶ However mild derangements in pH (0.10 to 0.15 units either way) are generally harmless. Thus strict control of pH by adjusting Ve is often unnecessary, particularly if it requires harmful increases in the intensity of alveolar ventilation (see section on ARDS, below). Inadequate levels of Ve will however cause respiratory acidosis (low pH, high PaCO_2), stimulating the patient's respiratory drive; in experimental studies this may divert up to 30% of cardiac output to the respiratory muscles.¹⁷ Conversely, excessive Ve causes respiratory alkalosis (high pH, low PaCO_2) which suppresses respiratory drive and can cause a patient to be apneic during a weaning trial, thereby prolonging the use of mechanical ventilation.

Delivery of Mechanical Ventilation

There is a rapidly expanding menu of options when delivering mechanical ventilation. Terminology is complicated by proprietary names entering bedside usage and by the retention of historical abbreviations that were nonideal. Although nomenclature standardization has been proposed, it has not reached universal usage, causing confusion at the bedside.^{18,19} Another source of confusion is that different ventilators may require entry of a setting in different ways; for example, inspiratory time may be entered in seconds (e.g., 1.5 seconds) or as a percentage of cycle time (e.g., 25% of 6 seconds) or a ratio of inspiration to expiration (e.g., 1:3 of 6 seconds).

Despite the rapid increase in options, there are little randomized controlled data showing a benefit to a particular style of ventilation. There are significant differences in comfort and muscle unloading depending on the mode selected, but no mode has been shown superior in regards to patient outcome.^{20,21} Ventilator setting in most ICUs remains dependent on local expertise and the model of mechanical ventilator available. Improved understanding of the available modes allows finer control over ventilation and a better understanding of how a change in patient status will affect the setting. Most important to the patient is whether ventilation is assured, the respiratory muscles are effectively unloaded, and whether the tidal volume and end-expiratory volume are appropriate for the disease.

Mechanical ventilators allow manipulation of nearly every aspect of inspiration; expiration however, is not controlled except for airway pressure (PEEP). Usually discussed first is the pattern of breathing, or mode. A mode will allow different types of breath: each with its own name, options, and settings. These issues will be introduced in this chapter but full discussion requires a textbook and is beyond the scope of this chapter.²²

Most breaths on mechanical ventilation can be classified as either mandatory or spontaneous. The ventilator exerts more control during mandatory breaths; settings include when to start the breath, what to control during the breath, and when the breath ends. Common mandatory breaths include: volume control, pressure control, and demand-flow volume control.

A hallmark of mandatory breaths is the required setting of inspiratory time. During spontaneous breathing, the ventilator does not control inspiratory time but rather supports the inspiratory efforts. Common spontaneous breaths include pressure support and unsupported.

Some ventilators allow breaths that are not easily classified as mandatory or spontaneous. One example is volume-assured pressure support, which is a hybrid with spontaneous breathing that converts to mandatory if a tidal volume target is not reached.²³ Another example is biphasic positive airway pressure (BIPAP) in which there are two asynchronous cycles as the ventilator maintains a background pattern of varying positive pressure breathing interspersed with patient effort.²⁴

Mode

Generally the first decision in ventilator setting is the mode. The most common modes are continuous mandatory ventilation (CMV), intermittent mandatory ventilation (IMV), and spontaneous ventilation (CPAP).¹⁸ CPAP, standing for continuous positive airway pressure, describes a mode which is continuously spontaneous and therefore never mandatory. The name is intrinsically confusing, as the acronym CPAP also signifies a therapy for sleep apnea, a type of mask, and delivery of positive airway pressure. It is also inaccurate as airway pressure is not constant (when used in conjunction with pressure support) or necessarily positive as CPAP can be set to zero. Despite attempts at renaming, CPAP remains entrenched in bedside and ventilator manufacturer usage.

CMV allows only mandatory breaths, the shape and size is determined by the settings described below. There is a minimum set rate. Patients can increase ventilation by “triggering” additional breaths; the ventilator senses either a drop in airway pressure across a closed inspiratory valve or inspiratory flow from a bias flow circuit. Regardless if the breath is time-triggered (i.e., at the minimum set rate) or patient-triggered (i.e., above the minimum set rate), every breath is mandatory and largely controlled by the ventilator.

CPAP allows only spontaneous breaths. There is no minimum set rate; each breath is started and stopped by the patient, and the patient breathes at the tidal volume and respiratory rate determined by their drive and respiratory mechanics. The ventilator can mimic unassisted breathing or can provide “support” during each breath; the level of support can vary from minimal support, to low levels of support to overcome the inherent added work of the ventilator, to higher levels of support that can actually be sufficient to essentially take over the entire work of breathing except for the initial trigger. It is important to remember that the ventilator is adjusting the inspiratory flow continuously over the breath to allow a spontaneous breath; it is not that the ventilator is just standing by passively. The ability of the ventilator to mimic unsupported breathing has improved significantly over the last decade; prior ventilators had high levels of imposed work that are much lower today.

IMV delivers a set number of mandatory breaths delivered per minute. Patient triggering above this set rate delivers spontaneous breaths. As such, IMV requires setting of two distinct parameters: a full description of the mandatory breaths and the level of support to deliver during spontaneous breaths. Careful attention to both the mandatory and spontaneous breaths is needed to appropriately adjust the amount of ventilatory support delivered to the patient. Most ventilators attempt

to synchronize the mandatory breaths with patient effort so a patient trigger may yield a mandatory or a spontaneous breath. This can lead to instability in the respiratory center as identical phrenic nerve output results in different tidal volumes. During IMV, patients may be performing more work during the mandatory breaths than during the spontaneous ones.²⁵

Mandatory Breaths

Volume Control

Volume control is a mandatory breath in which the ventilator delivers a preset flow rate over a set time to generate the set tidal volume. Some ventilator manufacturers use the term “volume control” to include breaths with demand flow; in this chapter these breaths will be discussed after pressure control as they are akin to pressure control than volume control.

Flow is predetermined and set during these breaths. Some ventilators require inspiratory flow to be constant (“square”); others allow different shapes such as decelerating (“ramp”). After normalization for inspiratory time, the impact of changing shape is likely small.^{26,27} Although certain ventilators appear to have different setting requirements, delivery of a volume control breath includes these presets: flow, volume, and time. Inspiratory time is determined by the time required to deliver the set volume at the set flow rate and shape.

It is easiest to understand volume control by first imagining the patient as being totally relaxed. Flow is delivered through the airway into the lung. A tidal volume of 500 mL in a normal-sized adult should result in a rise of airway pressure of 10 cm H₂O. A component of this pressure is related to resistance; a component is related to elastance (or stretch of the chest wall and lung). Other forces such as inertia are generally not clinically relevant. Patients with high resistance (such as asthma or an obstructed endotracheal tube) or low elastance (such as congestive heart failure or pneumonia) require a larger change in pressure to deliver the set tidal volume.

Maintaining an inspiratory hold, or “plateau,” at the end of the breath allows partitioning of the airway pressure. There is no inspiratory flow during the plateau so resistive forces fall to zero; airway pressure now reflects only the elastic recoil force of the lung and chest wall. This allows bedside analysis of an elevated airway pressure.

The plateau pressure reflects end-inspiratory stretch of the alveolus; this is always lower than the peak airway pressure because this includes the pressure required to overcome resistance. In patients where the resistance is predominantly in the large airways or endotracheal tube, the alveoli are protected from the peak airway pressure; in diseases where the resistance is heterogeneously distributed into smaller airways, alveoli at the ends of low resistance bronchi are likely exposed to nearly the peak airway pressure shown on the ventilatory screen.

If the patient breathes during volume control, this lowers airway pressure. As the flow during the breath is set, effort from the patient generates some inspiratory flow and the ventilator needs to push less hard. The stronger the patient effort, the closer to zero the pressure curve becomes. If the patient effort would have generated a higher flow than that set, the ventilator in effect becomes a brake limiting flow, resulting in negative airway pressure. Attempts to lower airway pressure by lowering inspiratory flow often lead to increasing patient effort and dyssynchrony.

It should be clear that volume control requires careful attention to flow rate settings. Settings need to satisfy the patient's

need for airflow and maintain an appropriate inspiratory time to allow expiration. Practitioners at the bedside need to readjust flow settings to changing patient effort such as occurs during awakening from sedation.

Pressure Control

Pressure control describes a mandatory breath in which the ventilator maintains the set airway pressure for a given inspiratory time. Maintaining positive airway pressure inflates the lung. Analogous to volume control, the pressure volume relationship is determined by the mechanics; therefore in patients with normal mechanics a low inspiratory pressure will generate an adequate tidal volume, but patients with poor mechanics will require a higher pressure.

Adjustment of tidal volume during pressure control requires careful attention to the inspiratory flow-time curve. If inspiratory flow is continuing at the end of the breath, prolonging inspiratory time will increase tidal volume; if flow has stopped, alveolar pressure equals airway pressure, resulting in an inspiratory plateau, and an increase in inspiratory pressure is needed to increase tidal volume. Patients with low resistance and low compliance have very short time constants and therefore tolerate short inspiratory times.

Pressure control will generally have a lower peak airway pressure than volume control because flow rate decreases over time, making the gradient from peak to plateau smaller. For a given tidal volume, pressure control and volume control yield the same alveolar pressures. As noted under volume control, limiting peak pressure is not as crucial as limiting alveolar pressure unless there is marked heterogeneity in airway resistance.

A more important difference between pressure control and volume control is how it adapts to varying patient effort. Patient effort generates inspiratory flow, which the ventilator must meet and exceed to raise airway pressure to the target; increasing effort requires increasing flow and results in increasing tidal volume. Whereas patient effort during volume control results in the patient doing work the ventilator would have done, during pressure control any patient work is additive to ventilator work.

One caveat to pressure control is that volume is not assured so a rapid worsening in mechanics will lead to an abrupt rise in Paco_2 . As all ventilators have alarms that monitor low exhaled tidal volume, this concern is perhaps overstated.

Demand-Flow Volume Control

This mandatory setting is available under various trade names on newer ventilators. It combines the assurance of a set tidal volume with the comfort and responsiveness of pressure control. The ventilator delivers pressure-controlled breaths, slowly titrating the inspiratory pressure to achieve the set tidal volume.

Settings are tidal volume and inspiratory time. Demand-flow volume control adjusts to patient effort. Increasing patient effort will result in larger tidal volumes for a given airway pressure. Although there is a set tidal volume target, the actual tidal volume on a given breath varies based on the inspiratory pressure, mechanics, and patient effort.

Over time, the ventilator adjusts the pressure to the target. For example, a patient with pneumonia will require lower inspiratory pressures to maintain the desired tidal volume as the lung improves. If the patient had been receiving the set tidal volume and now has increasing effort, the ventilator will gradually reduce the inspiratory pressure on subsequent breaths to

re-establish the desired tidal volume. Provided stable respiratory drive, the patient and ventilator will interact and establish an equilibrium sharing the respiratory work.

This option for ventilatory support is increasingly replacing traditional volume control. Demand-flow, improved patient interaction, and avoiding the need to preset flow rate are significant advantages.

Spontaneous Breaths

Unsupported

On IMV and CPAP, the ventilator can adjust inspiratory flow to match the effort of the patient. The target is to maintain a constant airway pressure during the inspiratory and expiratory phase. As the ventilator is using feedback to adjust flow, there is inherent delay and the resulting breath is not exactly like a patient breathing atmospheric pressure. There is an imposed work from the cumulative delays in pressure sensing and flow controllers present primarily at the initiation of inspiration and expiration. Improvements in ventilator design have significantly reduced this imposed work, such that breathing on CPAP is now much easier on a modern ventilator than one built 10 to 20 years ago.

Pressure Support

During spontaneous breathing, the ventilator can raise the target airway pressure during the inspiratory cycle, delivering "pressure support." The ventilator transitions from PEEP to a higher inspiratory target when patient effort is detected; this higher pressure is maintained until a predetermined signal that the breath is ending. This signal is typically defined as a reduction in inspiratory flow.

Initially designed as a means to overcome the imposed work of the ventilator and the endotracheal tube, pressure support can be titrated from zero (i.e., unsupported) to that sufficient to deliver full support, referred to as PSVmax. Pressure support allows precise titration of the support provided, although it is important to remember that the percentage of support given varies with the total amount of work required. Therefore a pressure support level of 10 may be full ventilatory support for a patient with normal lungs, but may only provide a small percentage of support for a patient with stiff lungs who required inspiratory pressures of 30 to deliver a tidal volume on volume control.

Patient ventilator interactions on pressure support vary depending on patient mechanics. In patients with low static compliance, lowering pressure support below PSVmax results in increasing patient work to maintain tidal volume; raising support above PSVmax results in increased tidal volume and continued minimal work. In patients with obstruction, raising pressure support increases tidal volume and decreases respiratory drive; these often contribute to diminished ability for the ventilator to sense patient effort, so-called failed triggers.

Initial Ventilator Settings

Any attempt to provide a simple algorithm to properly set a ventilator is doomed to failure because there are such a multitude of variables. Rather this section will highlight some considerations in selecting initial settings. The patient should then be carefully reassessed and each setting titrated.

1. **Oxygenation:** it is customary in many centers to deliver 100% oxygen in the first moments of ventilation until the ABCs of resuscitation are ensured. Provided the endotracheal is in place and secure and ventilation is occurring, most patients

can be rapidly titrated downward. FiO_2 above 60% is toxic, though generally 50% is considered safe. Though many patients are hypoxemic at time of intubation, most will tolerate reduced FiO_2 as their hypoxemia reflects ventilatory failure that should improve with mechanical ventilation.

- Patients who remain hypoxemic on 100% FiO_2 are manifesting shunt. Those with bilateral infiltrates may benefit from rapid titration upward of PEEP to decrease intrapulmonary shunt.²⁸ Patients with intracardiac shunt will not respond to ventilation and need manipulation of hemodynamics to minimize right-to-left shunting. Patients with unilateral infiltrate and pulmonary shunting are difficult to oxygenate; options may include nitric oxide inhalation or use of gravity to increase blood flow to the better ventilated lung.
2. Minute ventilation: at time of intubation many patients are deeply sedated or paralyzed and are unable to set their respiratory rate or control their minute ventilation. Patients with severe metabolic acidosis or with high dead space will require a high minute ventilation to maintain pH. Though normal minute ventilation is 5 to 6 L/min, some patients require a fourfold increase or more. Another indication for initial high minute ventilation includes tricyclic and salicylate overdose. Hypercapnic patients due to respiratory depression, such as narcotic overdose, do not require increased minute ventilation because carbon dioxide rapidly corrects after initiation of normal ventilation.
 3. Tidal volume: mean initial tidal volume settings have fallen from the historical 15 mL/kg/IBW to below 10 mL/kg/IBW.²⁹ Patients with small, fibrotic, diffusely infiltrated or compressed lungs may require a lower tidal volume. As discussed below, a tidal volume of 6 mL/kg/IBW reduces mortality in patients with ARDS.
 4. Respiratory rate: selection of minute ventilation and tidal volume will typically determine the set rate. Patients who will remain paralyzed or deeply sedated require the clinician to precisely titrate rate; otherwise selecting a low backup rate may avoid diaphragmatic atrophy by requiring patient trigger.³⁰
 5. Mode: Patients with acute respiratory failure or hemodynamic instability benefit from full ventilatory support. This can be delivered as mandatory breathing, high level pressure support³¹ or both. This is little data showing an advantage of CMV versus IMV as an initial setting.³²

Non-Invasive Ventilation

Acute decompensation of two chronic conditions, CHF and COPD, may result in critical hypoxemia or intolerable work of breathing that is reversible over the course of hours. In these situations, gas exchange and work of breathing may be temporarily assisted by means of so-called non-invasive positive-pressure ventilation (NPPV) without the use of mechanical ventilation via an endotracheal tube.³³⁻³⁵ The patient interface for NPPV is most commonly a mask with a silicone rim strapped to the patient's head to provide a tight seal over the nose and mouth; occasionally a nasal mask or nasal cushions covering the nares may be sufficient. NPPV can be applied in a variety of ways: the airflow generator may be a standard ventilator with separate inspiratory and expiratory tubing, or a simpler pressure generator that provides controlled airflow to a set pressure via a single tube (in this case a "bias flow" allows exhaled gas to be flushed out through an opening near the mask).

The simplest form of NPPV is constant positive airway pressure (CPAP) whereby a steady supra-atmospheric pressure is applied to the airway to recruit collapsed alveoli and improve oxygenation. This is most often successful in rescuing patients with pulmonary edema and a normal PaCO_2 . More commonly, the NPPV machine algorithm delivers variable flow to achieve a higher airway pressure in inspiration than in exhalation, termed "bilevel" pressure ventilation. This non-invasive mode provides mechanical assistance to a patient who cannot perform enough alveolar ventilation to excrete CO_2 , due to COPD or neuromuscular weakness for example. In such patients with impending respiratory failure due to a reversible condition, NPPV can provide a "bridge" of mechanical assistance and improved oxygenation until the acute decompensation is corrected. This may allow the patient to avoid the morbidity associated with intubation and mechanical ventilation. Prospective trials have demonstrated that judicious use of NPPV prevents the need for mechanical ventilation in up to 75% of acute COPD exacerbations and 50% of acute CHF decompensations.³⁶⁻³⁹

Because NPPV mask ventilation cannot reliably provide controlled alveolar ventilation it should not be used in patients with florid respiratory failure. In fact it is contraindicated in this circumstance, as it may lull the provider into a false sense of security while the dyspneic patient deteriorates with a mask covering his face. In addition, the mask interface applies pressure not only to the airway, but also the esophagus, which may result in gastric distension, vomiting inside a closed mask and a disastrous aspiration. Patients with impaired mental status are particularly at risk. Obtundation is a therefore a relative contraindication to NPPV; its use should be restricted to patients who are fairly alert and can protect their airway. Another important caveat is that a hemodynamically compromised patient on NPPV may deteriorate to point of cardiac arrest with an unprotected airway, converting a planned intubation into an emergent "code" situation.^{40,41}

Monitoring should include visual observation of their work of breathing, and an ABG performed 1-2 hours after initiating NPPV to ensure that CO_2 retention is not occurring. It has been recommended that patients who do not improve in the first 2-4 hours should be considered for prompt endotracheal intubation.⁴²

Discontinuing Mechanical Ventilation

The term "weaning" from mechanical ventilation implies a gradual process. In general, this is not necessary, as mechanical ventilation can be stopped promptly when the cause of respiratory failure has improved. Use of the word "weaning" has thus declined in favor of the term "liberation" from the ventilator. Ironically, in fact, it is often the physician who must be "weaned" from the belief that a patient still requires mechanical ventilation. An important recent finding is that a protocol mandating daily tests of the patient's ability to breathe off the ventilator will shorten the mean duration of mechanical ventilation by 1 to 2 days. This is significant, since the risk of nosocomial pneumonia, with its attendant 20% to 50% mortality, increases with the duration of ventilation.

Historically, physicians in the CCU have been concerned that a "weaning" trial may increase the O_2 demand by the respiratory muscles (by 15% to 25%), increase cardiac afterload and lead to a catecholamine release, which together may precipitate ischemia in patients with unstable coronary disease.^{43,44} It is thus

conventional to keep a ventilated patient sedated to avoid stress and the potential risk of hypoxemia, until ischemia has resolved or revascularization accomplished. Of note, however, studies in mixed MICU-CCU patients have found that acute troponin I elevation or ST segment deviation occurs only rarely during ventilator liberation trials.⁴⁵

Once the CCU patient's condition has stabilized, the process of liberation from the ventilator requires the few brief assessments. First, the patient must be reasonably awake, able to clear secretions, and protect the airway. This may be a problem in obese patients who have received continuous sedative infusions. It has been shown that the pharmacokinetics of the short-term sedatives, such as midazolam and propofol, change after 48 hours of continuous infusion in such patients; clearance of the drug from adipose stores in the body is slow. It is often a distressing surprise to stop the sedative infusion before a liberation trial, only to find the patient remains deeply sedated for greater than 24 hours.

Secondly, the patient must be able to oxygenate at moderate settings for FiO_2 and PEEP. A general rule of thumb is that the oxygen saturation should be above 92% on an FiO_2 less than 50% with a PEEP 5 cm H_2O or less. Thirdly, the patient should be hemodynamically stable.

Once these conditions have been met, many clinicians use "weaning parameters" to predict whether extubation will be successful before removing the endotracheal tube. Multiple parameters have been studied; the most common method is to place the patient on spontaneous unassisted ventilation (CPAP) for 30 to 60 minutes and record the ratio of respiratory rate to tidal volume (f/TV). A cutoff value less than 105 yields an 86% positive predictive value and 82% negative predictive value for extubation success.⁴⁶ However, a recent study showed that when the f/TV ratio is incorporated into a weaning protocol, the time to extubation is delayed.⁴⁷ Though controversial, "weaning parameters" such as the f/TV ratio may be useful parameters to guide clinical judgment about when to extubate a patient.^{48,49,50}

A number of ventilator settings have been used to wean patients from mechanical ventilation, including CPAP with pressure support titration, SIMV titration, and single or multiple daily trials of spontaneous breathing via a T-tube or CPAP. The latter has been consistently associated with a shorter duration of mechanical ventilation in multiple studies, and is the method most often used in modern ventilator liberation protocols.

Since it is not possible to predict extubation success with 100% accuracy, some patients (approximately 10% to 15%) will require reintubation for recurrent respiratory failure in the first 24 hours after extubation. Therefore close observation for 12 to 24 hours after extubation is essential. This should include frequent monitoring of vital signs and arterial O_2 saturation and physical examination. The latter may reveal postextubation stridor, indicating laryngeal and subglottic edema. In the pediatric population, this has been successfully treated with nebulized dexamethasone, an approach which has been extrapolated to adults. Factors such as traumatic intubation, a history of self-extubation, and a prolonged period of ventilation predispose patients to postextubation stridor. Patients at risk of this complication can be identified by measuring the magnitude of tidal volume "leak" after deflating the endotracheal tube cuff. Treatment with prophylactic IV corticosteroids may reduce the incidence of this complication in a high-risk population.

Monitoring of Patients on Mechanical Ventilation

Radiology

It has been routine to obtain daily portable chest radiographs for patients intubated on mechanical ventilation, though some studies suggest that it may be safe and cost-efficient to change this practice.⁵¹⁻⁵⁴ Chest radiographs have utility in monitoring fluid status, evaluating for ventilator-associated pneumonia, and confirming the proper location of a patient's tubes and lines.⁵⁵ However, portable films are limited and differ from routine chest radiographs. Standard radiographs are taken in the standing position, shot from posterior to anterior, and can be obtained with higher energy because such analysis of a portable chest radiograph requires recalibration.

Radiographs should be carefully inspected in regard to indwelling lines and catheters; in fact, these account for most of the new diagnoses in most studies. Endotracheal tubes (ETT) should be located approximately 2 cm from the carina. Remember that the tip of the ETT changes with head position: in orally intubated patients, the ETT tip moves up when the head is flexed and vice versa; in nasally intubated patients the opposite occurs. If inserted too far, typically the ETT will move into the right mainstem where it may occlude the right upper lobe bronchus; therefore atelectasis of the left lung or right upper lobe should prompt careful inspection of the ETT location. Correct location of venous catheters and aortic balloon pumps should be ascertained on every film. Additionally, care should be taken to ensure there are no retained guide wires or other foreign bodies within the chest.

Fluid status can be assessed on a chest radiograph. Bilateral effusions and bilateral infiltrates suggest pulmonary edema; additional signs include cardiomegaly and width of the vascular pedicle.⁵⁶ Vascular redistribution and Kerley B lines are less specific on portable films as many are taken in a supine or semi-recumbent position.

Chest radiographs are less sensitive and specific for pneumonia as classic findings of lobar consolidation are uncommon in ventilator-associated pneumonia. Consolidation and atelectasis are difficult to distinguish, especially on a single film. Persistent opacities, especially in the right clinical context, are more likely to be infectious. Left lower lobe atelectasis, recognized as a triangular density behind the heart, is extremely common in patients who are obese or with cardiomegaly.

It is important for clinicians to be aware of the differences in detecting pneumothorax in the ICU.⁵⁷ Though even a small pneumothorax is readily detected on an upright film, moderate and large pneumothoraces can be easily overlooked on a portable chest x-ray. Air will collect in the most superior aspect of the chest; in a supine patient this is at the anterior costophrenic angle. A "deep sulcus" sign signifies air pushing the diaphragm downward. Lung marking may still be present as the lung will be seen posterior to the air collection. Useful findings for pneumothorax include subcutaneous air, mediastinal shift, and abnormal sharpness in the margins of the heart, aorta, or mediastinum. In the case of suspected pneumothorax, obtaining a truly upright or decubitus film may be useful. Similarly, pleural effusions can be quite large before they become evident; posterior layering effusion appears as a general graying over the lung that usually becomes less evident at the apex. Bedside ultrasound allows localization of pleural effusion and facilitates drainage procedures.^{58,59}

Though transportation to the scanner can be challenging and at times impossible, computed tomography (CT) scan is extremely useful to visualize the lung, pleura, and mediastinum.^{60,61}

Pneumothorax can be definitively diagnosed and the chest tube placement facilitated. Effusions can be evaluated for loculations, pleural enhancement, and size. CT imaging of acute respiratory distress syndrome (ARDS) has significantly advanced our understanding of the physiology of this disease.⁶¹ Many patients will demonstrate unexpected pulmonary infiltrates, though this can lead to difficulty when trying to evaluate for pneumonia. CT scanning is very useful in evaluating for pulmonary embolism because ventilation-perfusion scanning is extremely challenging to interpret in the mechanically ventilated patient.

Ventilator Alarms and Waveform analysis

Careful monitoring of airway pressure and flow provides invaluable information during mechanical ventilation. These monitors are essentially continuous pulmonary function tests and will provide assessment of mechanics, be early warning signs of complications, and allow tracking of a patient's course.

The most basic monitor is airway pressure. It is continuously monitored and displayed on most ventilators, and alarms are set to monitor for both high and low pressure. Loss in airway pressure suggests a leak, commonly signifying a ventilator circuit disconnect or patient extubation. Other potential causes include a rupture in the balloon cuff of the endotracheal tube, poor mask seal during noninvasive ventilation, or incorrectly set tidal volume.

Sudden rise in airway pressure implies a change in airway resistance or compliance. Airway resistance may signify an obstructed endotracheal tube, patient biting of the tube, airway secretions, or blockage along the ventilator circuit, such as a clogged heat-moisture exchanger. Sudden drop in pulmonary compliance may indicate a tension pneumothorax or advancement of the endotracheal tube down the right mainstem bronchus, or "air trapping" from dynamic hyperinflation.

Many ventilators now provide graphic displays that provide more information than simple readout of peak airway pressure. Common waveforms that are monitored include airway pressure versus time and airflow versus time; other options include pressure-volume and flow-volume curves. Full analysis of these curves is beyond the scope of this chapter, but these graphs are invaluable in determining the physiologic cause of a patient's respiratory failure or while troubleshooting an acute problem.

During standard volume control, airflow is preset, so little is gained analyzing the inspiratory phase of the flow-time curve. Similarly, during pressure control the inspiratory pressure waveform is preset. Expiratory flow-time curves are useful regardless of the ventilatory settings because they reflect patient expiration. Patients should have a nearly linear expiratory flow curve; scooping or decelerating curves indicate airway resistance. Patients who continue to show exhalatory airflow as the next breath is initiated are likely air-trapping.

Work of Breathing

Assessment of the work of breathing is crucial in evaluating a patient. Patients with high workload are more likely to require mechanical ventilation until mechanics improve. Patients in respiratory failure with a normal workload should be evaluated for neuromuscular weakness or excessive sedation because the respiratory failure is not explained by mechanics.

Ventilator work is defined as the change in airway pressure related to tidal volume or $\int P \, dv$. Work is expressed as joules per liter, though it may also be useful to express joules per breath

or joules per minute. Low compliance, high airway resistance, and high minute ventilation all result in increased work. When patients are relaxed, ventilator work is the change in airway pressure during the tidal volume. Patient work is more difficult to measure. Monitoring of esophageal pressure only captures work performed across the lung and does not include work across the chest wall. Expiratory work is even more difficult to calculate; patients with obstructive airway disease perform significant expiratory work because the ventilator only assists in inspiration.

Most patients are not fully relaxed during mechanical ventilation, and many patients continue to work during a mandatory breath. In fact, many patients "resting" on the ventilator are working harder breathing than the physicians caring for them. Simply triggering a ventilator can require significant work, especially in patients with airway obstruction.

Though patient work may be difficult to quantify, bedside clinical examination can identify patients performing significant work. Signs of high work include agitation, tachypnea, hypertension, tachycardia, nasal flaring, accessory muscle use, and intercostal retractions, just as in patients who are not intubated. Signs of respiratory distress in ventilated patients are commonly attributed to anxiety and treated with benzodiazepines. Care must be taken to fully evaluate the cause of the distress. Often adjustment of the ventilator settings can relieve this distress, reducing the need for sedation.

Complications of Ventilation

- Sedation/delirium: Causes, Treatment, Complication, Daily wake-ups
- VAP: diagnosis, prevention, treatment
- Prolonged mechanical ventilation
- Tracheotomy

Complications of Mechanical Ventilation

Ventilator-Associated Pneumonia (VAP)

Attributable mortality from VAP may be as high as 30%.^{62,63} This feared complication is the main rationale for trying to limit the duration of ventilation. Risk factors include advanced age, severity of illness, immunosuppression, the use of heavy sedation, colonization of the upper airway by pathogens and long duration of ventilation. Recently an association has been recognized with the presence of an infected "biofilm" inside the endotracheal tube, which is now the target of preventative interventions.^{64,65} The reader is referred to excellent recent reviews of this topic.⁶⁶⁻⁶⁸

Barotrauma and "Volutrauma"

Expiratory airflow in the diseased lung is non-homogeneous leading to focal air-trapping. The parenchyma may rupture, allowing air to track medially along the bronchovascular sheath, leading to pneumomediastinum and ultimately free rupture into the pleural space. Tension pneumothorax may occur when rapid accumulation of air pressurizes one hemithorax and compresses the central veins, causing shock. This is evident at the bedside: a patient who develops sudden shock, absent air entry and distension on one side and contralateral shift of the trachea should undergo prompt needle decompression, even before a confirmatory chest x-ray.

Many experts prefer the term "volutrauma," since it is now understood that ventilation with large tidal volumes causes

sequential inflation-deflation cycles in regions of atelectatic lung, resulting in shear injury and contributing to the lung pathology (see “ARDS” below)

Hemodynamic Compromise

This occurs most commonly at the initiation of mechanical ventilation in a volume-depleted or otherwise pre-load dependent patient, as detailed elsewhere in this chapter

Oversedation

As noted above, this complication is due to the well-intentioned use of rapid-acting sedatives by continuous infusion. After 24-48 hours, these drugs demonstrate prolonged elimination times, especially in the obese patient, which delays weaning. It is preventable by a brief daily interruption all continuous sedative infusions.^{69,70}

Respiratory Muscle Weakness

This problem, though rare in patients ventilated for <72 hours, is more common when patients are paralyzed or heavily sedated for long periods. Suppression of respiratory drive leads to alterations in diaphragmatic muscle fibers that are associated with respiratory muscle weakness.⁷¹ The problem may be compounded by malnutrition and the use of medications that cause myopathy such as corticosteroids and aminoglycosides.

Airway injury/stenosis: The incidence of clinically important laryngeal injury and subglottic stenosis is <2% with the use of modern low-pressure endotracheal tubes cuffs. However, re-intubation, shock and hyperactivity in the ventilated patient place the patient at risk. Careful monitoring to keep endotracheal tube cuff pressure <30 cmH₂O is recommended to avoid this complication⁶⁷

Ventilation of ARDS and Obstructive Airways Disease

Acute Respiratory Distress Syndrome

The acute respiratory distress syndrome (ARDS) was first described in 1967 and is now recognized as the development of non-cardiogenic pulmonary edema as a response to either a pulmonary or nonpulmonary injury.^{72,73} Disruption of the alveolar capillary membrane leads to surfactant inactivation, hyaline membrane formation, and alveolar flooding. Frequently seen in the setting of multiorgan failure and sepsis, it can also present as a single organ system failure.

Diagnostic criteria from an international consensus require (1) acute onset in the proper clinical setting, (2) arterial hypoxemia, (3) bilateral radiographic infiltrates, and (4) that it is not explained by increased hydrostatic pressure (e.g., heart failure).^{74,75} Though these criteria have been proven useful in designing clinical trials, there are significant issues regarding sensitivity and specificity.⁷⁶⁻⁷⁸

Problematic in the CCU is the exclusion of patients with elevated left atrial wedge pressure. ARDS has been well described after myocardial infarction.⁷⁹ If ARDS occurs after a large myocardial infarction and the patient then develops acute heart failure, ARDS is still present. Though patients with uncomplicated congestive heart failure often respond fully to diuretics, patients who develop pulmonary edema during acute illness may remain tachypneic and hypoxemic despite

maximum diuresis, suggesting a “noncardiogenic” component to their edema.

Increasingly, it is recognized that ventilatory strategies play an important role in the development of ARDS, prompting the term “ventilator-induced lung injury.” Animal models have clearly demonstrated that ventilation of normal lungs with high tidal volume leads to lungs with histopathologic changes identical to ARDS; ventilation of injured lungs with a normal tidal volume yields the same results. During ARDS much of the lung does not participate in ventilation, such that delivering what would generally be considered a normal tidal volume is too large and contributes to lung injury. Large randomized studies have proved the importance of reducing tidal volume and current recommendations are for selecting a tidal volume of 6 mL/kg/IBW.⁸⁰ In mild ARDS, increasing respiratory rate can compensate for the reduced tidal volume, but in severe cases, quite extreme hypercapnia and acidemia may need to be tolerated. It is crucial to allow this “permissive hypercapnia,” because there is a mortality benefit to reducing tidal volume; there is no proven benefit to maintaining a normal pH.⁸¹

Initially ARDS was considered a “stiff lung” that showed reduced static compliance, poor oxygenation, and abnormal x-rays. In fact, an ARDS lung that is forced open under high pressure will function normally and appear normal on a CT scan; if allowed to collapse fully, it again becomes stiff and oxygenates poorly.⁸² This cycling between airless (or derecruited) and ventilated (or recruited) is thought to contribute to ventilator-induced lung injury. ARDS is perhaps better considered an abnormally derecruitable lung, and most patients with ARDS will improve their oxygenation with raised airway pressure because applying high airway pressure will recruit collapsed lung units.^{61,82,83}

Open-lung strategies have been developed that capitalize on the concept that the lung functions more normally when aerated. The lung will continue to function well provided airway pressure does not fall below a critical closing pressure. Lungs that have been recruited in this manner will oxygenate well; several strategies have been devised for ventilation (i.e., carbon dioxide removal) while maintaining an open lung.⁸⁴

Maintaining high PEEP throughout the cycle will optimize arterial oxygenation; care must be taken to carefully follow tidal volume and peak inspiratory pressure as the lung is already quite full even before inspiration begins. Controlled studies have shown high PEEP strategies to be safe but did not reduce mortality over more conservative PEEP approaches.⁸⁵

High frequency oscillators (HFO) or jet ventilators offer a means to excrete carbon dioxide with extremely small tidal volumes.⁸⁶ Using this approach requires (1) opening the lung through the application of high airway pressure and (2) delivering rapid breaths often at a rate of 180 to 300 (3 to 5 Hertz) with a controlled I:E ratio. Tidal volumes of just 100 to 200 mL at 3 to 5 Hertz can maintain adequate arterial blood gases through a variety of physiologic mechanisms. Once the lung is fully opened, gradual reductions in airway pressure are tolerated. This mode requires dedicated ventilators, deep patient sedation, and careful monitoring. Studies suggest improved patient outcome, but larger randomized studies are required to prove mortality benefit.⁸⁷⁻⁸⁹

Another open-lung approach is airway pressure release ventilation (APRV).^{90,91} Two separate dyssynchronous actions contribute to ventilation. First, there are brief intermittent

decompressions that allow carbon dioxide removal; the expiratory time is kept very short (often 0.5 second) to prevent alveolar derecruitment. Second, the patient is allowed to spontaneously ventilate; lung compliance is improved as the lung is recruited and the patient is able to maintain an acceptable tidal volume. A major advantage of APRV is the avoidance of the deep sedation commonly required with HFO, but there is no proven mortality benefit over conventional ventilation.^{84,92}

It is important to identify patients with ARDS. Studies have shown high variability in diagnosing it across ICUs and across hospitals.^{74,78,93} Patients with bilateral infiltrates who are hypoxemic should be evaluated. Patients with shock are likely to have a component of ARDS, even if they also have cardiogenic pulmonary edema. Once ARDS is identified, ventilatory strategy dictates reducing the tidal volume to 6 cc/kg/IBW and titrating PEEP to improve oxygenation; another option is to transition to an open-lung strategy.⁸⁰ The clinician must understand that the patient may remain in respiratory failure for several days, requiring heightened awareness regarding nutrition, minimizing nosocomial complications, attention to patient comfort and sedation, and discussion with the family.

COPD and Asthma

Many patients with cardiac disease have coexistent asthma and chronic obstructive pulmonary disease (COPD). Patients with severe chronic disease and those with acute exacerbations require careful attention while on mechanical ventilation. The clinician must be aware that increasing flow into the lung is only beneficial provided the air can get back out. Obstructive airways manifest primarily during expiration and mechanical ventilators assist inspiration. Patients are at risk for hyperinflation with attendant risks of reduced preload and pneumothorax.⁹⁴ Most dramatic are patients with status asthmaticus; though management is similar to that of COPD, severe status is a true emergency that may benefit from consultation with a pulmonologist.⁹⁵

Patients with airway obstruction require attention to expiratory time. Unfortunately, ventilators do not display this important parameter. Though normally a patient can exhale a standard tidal volume in under 2 seconds, patients with COPD require longer. For example, a patient with severe COPD with an FEV₁ of 0.6 L can only exhale 600 mL in 1 second; when sedated on a ventilator, expiratory flows are lower. If this patient is given a tidal volume of 800 mL with an expiratory time of 2 seconds, it is predictable that the patient will not return to FRC and develop hyperinflation. Breath stacking or “dynamic hyperinflation” increases elastic recoil pressure such that the patient may reach an equilibrium that permits expiration of 800 mL in 2 seconds, but at the expense of increased intrathoracic pressure or “auto-PEEP.” If equilibrium is not reached, either the ventilator will stop delivering tidal volume due to reaching the high pressure limit or pneumothorax develops.

Hemodynamically, autoPEEP acts identical to PEEP, decreasing preload and venous return. AutoPEEP is also similar to set PEEP in that hyperinflation increased inspiratory work because the respiratory system is less compliant as it nears total lung capacity. AutoPEEP differs from PEEP in that alveolar pressure is above airway pressure at the beginning of inspiration; this results in an imposed work of trigger that needs to be overcome with each inspiratory effort.^{96,97}

Though expiratory time is not reported, many ventilators do report inspiratory time to expiratory time ratios (I:E). Simple

arithmetic shows the limitation of exclusively focusing on I:E ratio. A patient breathing at 10 breaths/min (i.e., each breath lasts 6 seconds) with an I:E ratio of 1:2 has an inspiratory time of 2 seconds and expiratory time of 4 seconds. A patient breathing at a rate of 20 breaths/min (i.e., each breath lasts 3 seconds) cannot have 4 seconds to exhale, even with an I:E ratio of 1:100.

Optimizing expiratory time requires control of the respiratory rate and short inspiratory time. Inspiratory time during mandatory breaths (i.e., CMV and IMV) is set. During standard volume control, inspiratory time is determined by tidal volume and air-flow and increasing flow rate will shorten inspiratory time. In pressure settings, generally the I-time can be set in seconds. If a patient has a set rate of 12/min and the I:E ratio is deemed appropriate, the ventilator will not shorten the inspiratory time if the patient begins to breathe more rapidly; therefore the I:E ratio will become inappropriately high (with insufficient exhalatory time) even if the ventilator allows “setting of the I:E ratio.”

Patients with obstructive airways often receive bronchodilators, such as inhaled β_2 -agonists and anticholinergics.⁹⁸ These medications can be delivered from a meter-dosed inhaler with an adapter or from a nebulizer.^{99,100} Both of these delivery systems are inefficient at times, delivering less than 10% of the expected dose with much of the drug depositing in the ventilator circuit or endotracheal tube. As bronchodilators are generally safe and inexpensive, the dose is commonly increased. There remains significant uncertainty regarding how much, if any, drug is actually delivered. Careful attention to aerosol delivery can significantly increase drug delivery; factors to consider include bypassing the humidifier, distance of the nebulizer from the Y connector, and ventilator settings.^{101,102} These issues take on greater significance when delivering drugs with a narrow therapeutic window or high cost.

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Emergency Dialysis and Ultrafiltration

Nand K. Wadhwa

CHAPTER 51

Indications for Renal Replacement Therapy
Principles and Technical Aspects of Renal Replacement Therapy

CRRT Compared with IHD
Ultrafiltration for Decompensated Heart Failure
Conclusion

MANAGEMENT OF critically ill patients with acute kidney injury (AKI) in the intensive care unit (ICU) often necessitates emergency dialysis for optimization of volume and metabolic status.¹ AKI often develops as one of the manifestations of multiple organ failure¹⁻⁴ and is an independent risk factor for mortality.⁵⁻⁷ Despite technological advances in renal replacement therapy (RRT) and improved delivery methods, the in-hospital mortality rate associated with AKI ranges from 35% to 80% in critically ill patients.^{1-5,8-11} This may be in part explained by the fact that presently no effective pharmacologic therapy exists for AKI and that RRT is only a supportive therapy for AKI. However, timing of initiation and dose and modality of RRT may affect the outcomes.¹²⁻¹³ This chapter describes the different modalities of RRT and addresses the basic principles regarding selection of different RRT for management of patients with renal failure and/or volume overload in the cardiac intensive care unit (CICU).

Indications for Renal Replacement Therapy

In a multinational study, the prevalence of AKI requiring RRT in the ICU was reported at 5.7%.¹ More importantly, there is an increasing need for dialysis in the CICU as highlighted in a recent study from the ADHERE registry stating that 91% of the patients hospitalized for acute decompensated heart failure (ADHF) had some degree of renal failure, with 64% having at least moderate renal failure and that 14% of them required initiation of RRT.¹⁴

The basic goals for management of patients with AKI are maintenance of fluid and electrolyte balance, avoidance of nephrotoxic agents (i.e., aminoglycosides, radiocontrast agents, etc.), maintenance of adequate nutrition, and appropriate dosing of medications according to the renal function.¹⁵ When conservative therapy fails to achieve optimal fluid and metabolic control, dialysis is initiated. The most widely accepted indications for RRT in patients with AKI are: (1) fluid overload refractory to diuretics; (2) hyperkalemia (usually serum potassium >6.5 mEq/L); (3) severe metabolic acidosis (arterial pH <7.1); (4) signs of uremia, such as pericarditis, neuropathy, or unexplained altered mental status. However, there is a wide disparity among nephrologists regarding the timing of initiation of dialysis based on concentrations of blood urea nitrogen (BUN) or serum creatinine and/or urine output in the ICU.¹⁶⁻¹⁹

Principles and Technical Aspects of Renal Replacement Therapy

There are multiple modalities of dialysis that are included under RRT and are summarized in Table 51-1. The comparison of solute removal and main features of various techniques are summarized in Table 51-2. These modalities mainly differ in the principles of solute removal and rate of solute removal. Solute removal during dialysis occurs by three mechanisms: (1) passive diffusion of solutes between the plasma and the dialysis fluid along their concentration gradient; (2) convection (i.e., dragging of the solutes along with the plasma water across the filter membrane); and (3) adsorption of solutes to the filter membrane. Each modality will be discussed in the following sections.

Table 51-1. Modalities of Renal Replacement Therapy

Intermittent Therapies	Hybrid Therapies	Continuous Therapies
Hemodialysis (HD)	Sustained	Slow continuous
Peritoneal dialysis (PD)	low-efficiency dialysis (SLED)	ultrafiltration (SCUF)
Ultrafiltration (UF)	Extended daily dialysis (EDD)	Continuous hemofiltration: (CHF) - CAVH, CVVH
Hemofiltration (HF)		Continuous hemodialysis: (CHD) - CAVHD, CVVHD
		Continuous hemodiafiltration: (CHDF) - CAVHDF, CVVHDF
		Continuous cyclical peritoneal dialysis (CCPD)

CAVHD, Continuous arteriovenous hemodialysis; CVVHDF, Continuous venovenous hemodialysis; CAVHF, Continuous arteriovenous hemofiltration; CVVHF, Continuous venovenous hemofiltration; CAVHDF, Continuous arteriovenous hemodiafiltration; CVVHDF, Continuous venovenous hemodiafiltration.

Table 51–2. Comparison of Solute Removal and Main Features of Renal Replacement Therapies

	IHD	SLED/EDD	SIUF/SCUF	C-HF/CVVHF	C-HD/ CVVHD	C-HDF CVVHDF	CCPD
Duration hr	3-4	8-12	8- Continuous	Continuous	Continuous	Continuous	Continuous
Access	Blood access	Blood access	Blood access	Blood access	Blood access	Blood access	Peritoneal access
Solute removal	Diffusion	Diffusion	Convection	Convection	Diffusion	Both	Diffusion
Blood flow rate mL/min	250-400	100-200	50-100	100-300	100-200	100-300	—
Dialysate flow rate mL/min	500-800	100	0	0	9-34	9-34	2 L every 2 hr exchange
Replacement fluid L/day	0	0	0	24-96	0	24-48	0
Fluid removal L/day	0-4	0-4	0-5	0-4	0-4	0-4	0-4
Effluent L/day	—	—	0-5	24-100	12-52	36-100	24-28
Effluent saturation %	15-40	60-70	100	85-100	100	85-100	60-70
Urea clearance mL/min	180-240	75-90	3.5	14-69	8-36	21-69	10-14

Data from Daugirdas JT, Blake PG, Ing TS: Handbook of Dialysis, 4th ed. Philadelphia, Lippincott Williams & Wilkins, 2007.

IHD, Intermittent hemodialysis; SLED, slow sustained extended dialysis; EDD, extended daily dialysis; SIUF, slow intermittent ultrafiltration; SCUF, slow continuous ultrafiltration; C-HF, continuous hemofiltration; CVVHF, continuous venovenous hemofiltration; C-HD, continuous hemodialysis; CVVHD, continuous venovenous hemodialysis; C-HDF, continuous hemodiafiltration; CVVHDF, continuous venovenous hemodiafiltration; CCPD, continuous cyclical peritoneal dialysis.

Intermittent Hemodialysis (IHD)

IHD is the dialytic modality of choice in hemodynamically stable patients with AKI needing RRT. Typically it is performed 3 days a week, but may increase to daily if necessary, with each session lasting for 3 to 4 hours. Solute is removed primarily by passive diffusion of small solutes such as urea and creatinine from the plasma into the dialysate, down their favorable concentration gradient. In contrast, bicarbonate diffuses from the dialysate into the plasma during metabolic acidosis. Blood (250 to 400 mL/min) and dialysate (500 to 800 mL/min) flow at high rates through the dialyzer in a countercurrent fashion, thus removing small solutes at a substantial rate (180 to 240 mL/min for blood urea nitrogen). The constant flow of new blood with high solute concentration and new dialysate with low solute concentration maximizes the rate of diffusive loss by maintaining a high concentration gradient between the two compartments. The net effect is that the loss of small solutes is much greater than that of fluid. On an average, up to 4 L of fluid are removed during each session of HD, thus limiting convective removal of solutes, with diffusion being the main mechanism for solute removal during IHD.

Slow Low-Efficiency Dialysis or Extended Daily Dialysis (SLED/EDD)

Solute removal during SLED/EDD also occurs mainly by diffusion. In comparison to IHD, blood flow rates (100 to 200 mL/min) and dialysate flow rates (100 mL/min) are much lower in SLED/EDD, with each session lasting for 8 to 12 hours. Hence, the rate of solute removal is much slower in SLED/EDD compared with IHD, which minimizes hemodynamic instability due

to the dialysis procedure itself. However, fluid removal during SLED/EDD is similar to IHD, but can be increased depending upon the volume status and hemodynamic stability of the patient.

Peritoneal Dialysis (PD)

PD uses a highly permeable natural peritoneal membrane for dialysis. This modality is mainly used as continuous cyclical PD (CCPD) in the ICU setting but can also be used on intermittent (IPD) basis. Solute removal during PD also occurs mainly by diffusion, driven by the osmotic gradient. Solute clearance depends upon the exchange volume and the dwell time (the time during which the fluid is present in the peritoneal cavity). For example, with an exchange time of 2 hours (which includes fill time of 5 to 10 minutes, dwell time of 90 minutes, and drain time of approximately 20 to 30 minutes) and an exchange volume of 2 L, approximately 24 L of fluid will be exchanged daily. If the daily net fluid removal is 4 L, total daily drained dialysate will be 28 L (24 L + 4 L). Given the urea concentration in the drained dialysate is about 60% to 70% of that in the plasma in a patient with average peritoneal membrane transport, the urea clearance would be approximately in the range of 16.8 to 19.6 L/day (0.6 to 0.7×28 L). This clearance is somewhat lower and may not be sufficient in a critically ill, catabolic patient.

Continuous Renal Replacement Therapies (CRRT)

The concept of continuous dialysis was introduced in the 1960s, but only recently has this modality become well established in the ICU.²⁰ Solute removal is achieved either by convection,

diffusion, adsorption, or a combination of these methods depending upon the prescription. It is the therapy of choice in critically ill patients who are hemodynamically unstable and are in need of dialysis. The therapy is intended to run 24 hours a day. Depending on the mechanism of solute removal, CRRT are sub-classified into continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD), continuous venovenous hemodiafiltration (CVVHDF), and slow continuous ultrafiltration (SCUF).

CVVH uses convection for solute removal with ultrafiltration rates (fluid removal rate) on an average of 1 to 4 L/hr. Fluid balance is achieved by replacing the ultrafiltrate with a physiologic electrolyte-based replacement solution, which can be infused either before or after the dialyzer. Solute removal in CVVH is regulated by the characteristics of the membrane and on the site of replacement solution administration, either predialyzer (predilution hemofiltration) or postdialyzer (postdilution hemofiltration). For the same effluent flow rate, clearance in predilution hemofiltration mode is less than that in postdilution hemofiltration. However, because of the dilution of blood by the replacement fluid before entering the dialyzer, much higher filtration fractions (larger effluent flow rate and replacement fluid rate) are feasible in predilution hemofiltration.²¹ By contrast, CVVHD uses only dialysate and hence, removes solute by diffusion. The dialysate flow rates (9 to 34 mL/min)²² in this modality are significantly lower than the dialysate flow rates in IHD and SLED/EDD. CVVHDF, as the name implies, uses both dialysate and replacement fluid and thus uses both diffusive and convective clearance.²³ Finally, SCUF does not use either dialysate or replacement fluid and is primarily used for optimization of volume status in patients that are hemodynamically unstable. Hence, CRRT techniques differ in the mechanism of solute removal. Despite the difference in the mechanism of solute clearance to achieve metabolic control, no study to date has clearly demonstrated improved clinical outcomes based on the different modality of CRRT.

The CRRT modalities can be performed using either an arteriovenous or venovenous circuit. Pump-driven venovenous circuits are better because they allow for higher solute clearance and also eliminate the need for arterial cannulation.²⁴ A prospective study comparing two consecutive groups of patients with AKI treated with either CVVHD (25 patients) or CAVHD (continuous arteriovenous hemodialysis, 28 patients) revealed a greater amount of hourly ultrafiltrate (mean, 590 mL versus 424 mL; $P < 0.001$) with CVVHD, but urea and creatinine clearances were not significantly different between the two groups. The major advantage of CVVHD was the substantial decrease in the number of access-related complications (2 versus 10; $P < 0.025$). Therefore the use of venovenous circuit is preferred over arteriovenous circuit.²⁴

CRRT Compared with IHD

CRRT is superior to IHD for the management of patients with AKI, particularly in patients that are hemodynamically unstable. The gradual removal of fluid and solute during CRRT enhances hemodynamic stability, which allows for increased salt and water removal and aggressive nutritional support. Furthermore, enhanced clearance of inflammatory mediators, particularly with hemofiltration in patients with concomitant sepsis, might provide additional benefits.²⁵⁻²⁷

However, to date no study has shown a survival benefit with CRRT when compared with IHD. This might be in part explained by the fact that most of the studies comparing IHD and CRRT have been nonrandomized observational studies or retrospective case series in which analysis was confounded by variations in disease severity among treatment groups.²⁸⁻³² In a multicenter study, conducted at four academic medical centers in Southern California, Mehta and colleagues³³ randomized 166 patients with AKI to IHD or CRRT. In the primary intention-to-treat analysis, 28-day all-cause mortality was 59.5% in patients that were randomized to CRRT compared with 41.5% in patients randomized to IHD ($P < 0.02$). However, unbalanced randomization had resulted in more patients with significantly higher APACHE III scores and a higher prevalence of liver failure in the CRRT group, both of which are associated with increased mortality. Adjustment for this imbalance in randomization using multivariate techniques yielded an adjusted odds of death associated with CRRT of 1.58 (95% CI 0.7 to 3.3). Similarly, Swartz and colleagues³⁴ used multivariate regression to adjust for severity of illness in 349 patients and reported that the adjusted risk of death associated with CRRT was 1.09 (95% CI 0.67 to 1.80) compared with IHD, which suggests neither a benefit nor a hazard associated with modality of dialysis. Since then, two meta-analyses^{35,36} comparing CRRT and IHD have shown improved outcomes with CRRT, but these results have not been supported by any of the randomized trials. In aggregate, after randomization of more than 700 patients, no survival benefit can be ascribed to modality of dialysis therapy.

Several studies³⁷⁻³⁹ have reported that despite the absence of a survival benefit, CRRT is associated with improved recovery of renal function compared with IHD. The analyses used in these studies, however, only considered recovery of renal function in surviving patients, and did not adjust for differences in mortality between the treatment groups. Reanalyzing the data using an end point that combines both mortality and nonrecovery of renal function demonstrated no apparent difference in outcome between groups.⁴⁰ Similarly, no difference in recovery of renal function was observed in three recent randomized trials.⁴¹⁻⁴³ Thus current data do not suggest improved recovery of renal function with CRRT. Although SLED has similar hemodynamic effects and metabolic control as CRRT,⁴⁴ currently no study has compared outcomes between SLED and other modalities.

In summary, current data suggest that survival and recovery of renal function are similar with both IHD and CRRT. In the majority of patients, selection of modality should therefore be based upon local expertise and available resources. In selected patients, CRRT may provide enhanced hemodynamic stability, and better management of volume status and nutritional requirements. It also provides for better preservation of cerebral perfusion in patients with brain injury or fulminant liver failure.⁴⁵

Optimal Timing for Initiation of RRT

In its early use, IHD was initiated only once advanced signs and symptoms of uremia and volume overload had set in.⁴⁶⁻⁴⁷ Despite control of these symptoms, no reduction in mortality was demonstrated. This led to the concept of "prophylactic" IHD.⁴⁸ Three retrospective studies reported that early (defined as BUN less than 93 to 150 mg/dL) versus late initiation of dialysis (BUN greater than 160 to 200 mg/dL) was associated with improved survival (43% to 75% for early dialysis versus 12% to 58% for late dialysis).^{49,50} Another prospective study of 18 patients reported

better survival (69% versus 20%) with early initiation of dialysis (BUN <60 versus 150 mg/dL).⁵¹ Similarly, using the Program to Improve Care in Acute Renal Disease (PICARD) database, a multicenter observational study for AKI, Liu and colleagues¹³ reported that patients in the “high” BUN group at time of initiation of dialysis had slightly lower survival rates at 14 and 28 days despite having a reduced burden of organ failure when compared with patients in the “low” BUN group. This result was not confirmed by another prospective study of 34 patients with AKI, which showed no difference in mortality among patients who started dialysis at BUN of 60 mg/dL or later at 100 mg/dL.⁵²

In relation to the timing of CRRT and clinical outcomes, three nonrandomized studies have reported improved outcomes, including improved survival with early versus late initiation of therapy.^{13,53–55} In a retrospective study of 100 consecutive patients treated with CVVH in a single shock trauma unit, survival was 39% among patients who were initiated on CVVH with BUN less than 60 mg/dL compared with 20% in patients with BUN greater than 60 mg/dL at the time of initiation of RRT.⁵³ Similarly, two other studies involving patients who developed AKI following cardiac surgery demonstrated higher survival rates in patients in whom CVVH was initiated when urine output was less than 100 mL within 8 hours after surgery, despite diuretic administration, compared with patients in whom therapy was withheld until objective laboratory criteria for dialysis, such as higher levels of serum creatinine, BUN, and potassium, were present.^{54–55}

In summary, no recommendations on the timing of initiation of RRT are possible beyond those defined by the conventional criteria for usual indications for RRT. General clinical practice is to start RRT when the BUN reaches 80 to 100 mg/dL, even though no consensus exists and practice patterns vary widely. The optimal timing for initiation of RRT in patients with AKI will require an adequately powered prospective randomized trial.

Optimal Dose of RRT in the ICU

Currently, no evidence-based recommendations exist regarding the optimal dialysis dose in AKI. Two components that affect the dosing of IHD include (1) the dose delivered during each treatment and (2) the frequency of treatment. No prospective studies have evaluated the impact of the dose of IHD per treatment on a fixed treatment schedule (e.g., three times per week). One retrospective study, evaluating the outcome of 844 critically ill patients with AKI requiring RRT,⁹ showed no correlation between delivered dose of dialysis and outcomes in patients with either very low or very high severity scores of illness. However, in patients with intermediate severity of illness, improved survival was observed in patients in whom the delivered dose of dialysis was above the median Kt/V_{urea} (K is the dialyzer urea clearance in mL/min, T is the duration of dialysis treatment in minutes, and V is the total body water in liters) of more than one. Similarly, Schiffl and colleagues evaluated the impact of the frequency of IHD on outcomes in 160 patients with AKI who were assigned to either daily or every other day IHD.⁵ Compared with alternate day dialysis, daily dialysis was associated with a significant reduction in all-cause mortality 14 days after the last hemodialysis session (from 46% to 28% [$P = 0.01$]). In addition, fewer hypotensive episodes were observed with daily hemodialysis and more rapid resolution of AKI (mean 9 days versus 16 days) was seen. However, the delivered dose in the alternate day dialysis group was significantly lower than the “acceptable and adequate dose” of dialysis. Thus, rather than

comparing an “adequate” with an “enhanced” dosing strategy, the increased mortality in the every-other-day group might have resulted from “inadequate” therapy.

Similarly, the relationship between patient outcomes and dosing of CRRT has been assessed in three randomized controlled trials.^{12,56,57} In the first study, 425 patients with AKI were randomly assigned to receive CVVH with ultrafiltration rates of 20, 35, or 45 mL/kg/hr.¹² Using an intention to treat analysis, survival 15 days after discontinuation of CVVH was 41% in the lowest dose arm compared with 57% and 58% in the intermediate and highest dose arms, respectively ($P < 0.001$). In the second trial, 106 oliguric patients were randomly assigned to early high-volume CVVH, early low-volume CVVH, or late low-volume CVVH.⁵⁶ At 28 days, survival was similar for all three groups (74%, 69%, and 75%, respectively). In the third study, 206 patients from a single center were randomly assigned to either CVVH (with a hemofiltration rate of 25 ± 5 mL/kg/hr) or CVVHDF (with a hemofiltration rate of 24 ± 6 mL/kg/hr plus 18 ± 5 mL/kg/hr of dialysate flow).⁵⁷ Survival after 28 days was 39% in the CVVH group and 59% in the CVVHDF groups ($P = 0.03$).

The Veterans Affairs/National Institutes of Health Acute Renal Failure Trial Network study which was designed as a multicenter study evaluating the effect of dialysis intensity on patient outcome comparing IHD in hemodynamically stable patients with either CVVHDF or SLED in hemodynamically unstable patients. The two dosing regimens were: 1) intensive therapy: hemodialysis and SLED were administered six times per week with a target Kt/V of 1.2 to 1.4 per treatment, while CRRT was provided with an effluent flow rate of 35 mL/kg per hour; 2) less intensive therapy: hemodialysis and SLED were given three times per week, while CRRT was provided with an effluent flow rate of 20 mL/kg per hour.⁵⁸ The rate of death from any cause by day 60 was 53.6% with intensive therapy and 51.5% with the less intensive therapy (odds ratio, 1.09; 95% confidence interval, 0.86 to 1.40; $P = 0.47$). Furthermore no significant differences occurred in in-hospital mortality, duration of RRT or recovery of renal function. The Randomized Evaluation of Normal versus Augmented Level of RRT (RENAL) conducted in Australia and New Zealand was designed to randomly assign patients with severe acute kidney injury who required intensive care to CVVHDF at a total effluent flow rate of either 25 or 40 mL/kg per hour.⁵⁹ In both treatment groups, 44.7% of patients died in the first 90 days after randomization (odds ratio, 1.00; 95% confidence interval, 0.81 to 1.23; $P = 0.99$). Overall, similar rates of recovery of kidney function were observed in both groups.

In summary, we can conclude from these studies that at least a delivered dose of Kt/V urea of 1.2 to 1.4 per IHD treatment session should be provided when given three days a week in a stable patient. The goal of therapy for CRRT should be to provide a total effluent flow rate of at least 20–25 mL/kg per hour in patients who requires intensive care.

Goals of RRT/Monitoring Parameters

The basic goals of management of patients admitted to CICU are the maintenance of fluid and electrolyte balance and hemodynamic stability in the presence of compromised heart performance. Hemodynamic instability has a marked effect on kidney function irrespective of the etiology and type of heart failure, and often results in AKI or worsening of preexisting kidney disease.

When IHD is initiated, initial treatment should be aimed to decrease BUN slowly, with a target urea reduction ratio of

less than 40%, especially if the predialysis BUN is greater than 125 mg/dL. This is done since rapid removal of solutes in the acute setting may result in dialysis dysequilibrium syndrome, causing altered mental status, seizures, and/or coma.⁶⁰⁻⁶² The patient should initially be hemodialyzed daily for 3 days with a gradual increase in the dose of HD. Subsequent HD sessions should provide a goal Kt/V of at least 1.2 per session. Adequacy of dialysis can also be assessed by urea reduction rate (URR) of at least 65% after each HD treatment. Dialysis should be continued as long as clinically necessary. One does not need to start CRRT or PD slowly, since they do not cause dialysis dysequilibrium syndrome because both modalities lead to slower removal of solutes when compared with IHD.

RRT for ESRD Patients in the ICU

End-stage renal disease (ESRD) patients on chronic maintenance dialysis are often admitted to the CICU for cardiac complications including acute coronary events. Most of these patients can usually tolerate IHD even in the presence of some hemodynamic instability with concomitant use of appropriate vasopressors. Daily dialysis may be needed in some patients to provide optimal metabolic and volume control. However, for patients who are hypercatabolic and hemodynamically unstable, CRRT is the modality of choice. Before initiation of CRRT in patients with ESRD, most of the centers place an acute dialysis catheter in the internal jugular vein or the femoral vein, even in patients with a functioning permanent arteriovenous access, such as an arteriovenous fistula or graft, due to safety issues. However, at Stony Brook, we regularly use the permanent AV access by using an angiocath⁶³ since temporary vascular access is associated with thrombosis of the cannulated vein and catheter-related infections.^{64,65} ESRD patients receiving continuous ambulatory peritoneal dialysis (CAPD) are usually switched to continuous cycler peritoneal dialysis (CCPD) in the ICU. If a patient on PD develops communication between the pleural cavity and the peritoneal cavity following cardiac surgery or develops compromised respiratory status requiring mechanical ventilation, IHD or CRRT should be considered. In addition, in a hypercatabolic patient, IHD or CRRT are preferred to PD due to better fluid and metabolic control.

Ultrafiltration for Decompensated Heart Failure

Heart failure (HF) affects approximately 4.9 million people in the United States and accounts for an estimated 1 million hospital admissions each year and remains the single most common admitting diagnosis in the United States for patients older than 65 years.⁶⁶ Hospitalizations for acutely decompensated heart failure (ADHF) have increased from 399,000 in 1979 to 1,100,000 in 2005, just in the United States.⁶⁷ An estimated \$12.7 billion is spent each year on inpatient management of ADHF. Despite advances in treatment, the number of deaths due to heart failure has steadily increased and an estimated 300,000 patients die of heart failure each year.⁶⁸

Heart failure involves impairment in the ability of the heart, particularly the left ventricle, to fill with or eject blood in amounts adequate to meet the body's metabolic needs. Decreased cardiac output leads to renal hypoperfusion, which causes activation of the renin-angiotensin-aldosterone system (RAAS) that further leads to increased fluid retention. This vicious cycle, if allowed

to continue, results in an approximately 50% risk of death at 1 year following initial hospitalization for HF. Clearly, removal of the excess volume is associated with improved prognosis. In one study, patients with New York Heart Association (NYHA) class IV heart failure and evidence of volume overload had improved survival with optimization of volume status.⁶⁹

Diuretics are currently the mainstay of therapy aimed at acutely reducing pulmonary capillary wedge pressure and leading to a negative fluid balance. All loop diuretics reduce sodium chloride reabsorption in the thick ascending limb of the loop of Henle.⁷⁰ The efficacy of the loop diuretics is dose-dependent and is determined largely by the rate at which the diuretic is delivered to its site of action. Loop diuretics are highly protein-bound and therefore enter the urine primarily by tubular secretion in the proximal tubule rather than by glomerular filtration.⁷⁰

Patients with HF respond less effectively to a given dose of diuretic than normal subjects. This is due to decreased delivery of the diuretics to the kidney since renal blood flow is reduced and also due to increased renal sodium reabsorption via RAAS. In addition, intestinal absorption of the diuretic may also be delayed.⁷¹ Moreover, in patients on chronic loop diuretics, distal tubular hyperplasia may inhibit diuresis via increase in the activity and number of Na⁺/Cl⁻ cotransporters.⁷² Besides questions regarding optimal dosing, dosing intervals, goal of diuresis, and the potential toxicities of these drugs have not been studied in placebo-controlled randomized clinical trials. This is particularly relevant since, although useful, diuretics have many undesirable side effects including promotion of potassium and magnesium wasting that may provoke arrhythmias, exacerbation of glucose intolerance, and the activation of the RAAS. In addition, overdiuresis can induce renal dysfunction, which has been associated with poor long-term outcomes.⁷³⁻⁷⁵ More importantly, poor response to diuretics may contribute to high rates of readmission for HF as observed in the Acute Decompensated Heart Failure National Registry (ADHERE). Despite the use of intravenous diuretics in almost 90% of the patients admitted with ADHF, 42% of patients were discharged home with unresolved symptoms, which might have contributed to the high rates of readmission for HF.⁷⁶

In an attempt to find better treatment for HF, studies have been performed to compare the efficacy of ultrafiltration with diuretic therapy in the treatment of ADHF. UF is a safe and reliable means for removing excess fluid. It removes water and non-protein-bound small- and medium-sized solutes through a semipermeable membrane.⁷⁷ In the RAPID-CHF study, 40 patients admitted with acute decompensated heart failure were either randomized to the usual care or usual care and UF. In the UF group, patients received 8 hours of UF treatment in addition to the usual care, resulting in greater average volume removal and weight loss at 24 and 48 hours.⁷⁸ In the study by Costanzo and colleagues, UF was initiated early on (within hours of admission) in 20 patients with ADHF who had clinical evidence of volume overload along with either diuretic resistance or presence of renal insufficiency. UF was continued until the patients' congestive symptoms were relieved, resulting in aggressive fluid elimination (approximately 8.6 L) and improvement in clinical signs and symptoms that lasted for 90 days following UF treatment.⁷⁹ Similarly in the UNLOAD study, a prospective clinical trial, 200 heart failure patients with at least two signs of volume overload were randomized to either UF therapy or intravenous diuretics. At 48 hours, the UF group demonstrated a significantly greater amount of weight loss (5 kg versus 3.1 kg; $P = 0.001$) and

larger net fluid loss (4.6 L versus 3.3 L; $P = 0.001$), compared with the diuretic group. More importantly, at 90 days, UF resulted in lower readmission rates for HF (18% versus 32%; $P = 0.037$), decreased length of hospital stay among patients that required readmission (1.4 days versus 3.8 days; $P = 0.022$), and lower rates of unscheduled visits (21% versus 44%; $P = 0.009$). However, no differences were observed in serum creatinine between the two groups.⁸⁰ Similarly, Marenzi and colleagues removed 4880 ± 896 mL (range 4300 to 7000 mL over 9+3 hours) by UF in 24 patients with NYHA class IV refractory heart failure and reported a significant increase in the cardiac output and stroke volume at the end of UF and also reported continued improvement even 24 hours after UF.⁸¹ Moreover, both right and left heart pressure decreased in equal ratio with UF.⁸²⁻⁸⁵ Additionally, UF has been shown to improve exercise tolerance and mechanical lung function, and also has been shown to reset the neurohumoral activation, thereby restoring response to diuretics.^{81,86-89} The improvement in both exercise tolerance and pulmonary function with UF has been reported to persist even 6 months after treatment.^{84,90}

In conclusion, studies have shown that ultrafiltration is an effective method of fluid removal in patients with ADHF, with advantages that include adjustable rate of fluid removal, predictable UF volume, and no major effect on serum electrolytes. In addition, it might also decrease the neurohormonal activity, thus inhibiting the vicious cycle of fluid and salt retention. It is not clear whether UF provides an additional advantage in patients who respond adequately to standard intravenous diuretics. In addition, given the relatively small body of data, it is not possible to assess the safety of ultrafiltration in terms of catheter-related infections, thrombosis of veins, and long-term outcomes.

At our center, we perform UF in patients with ADHF who are diuretic-resistant. We perform UF using the PRISMA M100 set with AN69 hemofilter (Gambro) (Fig. 51-1). The vascular access consists of a double-lumen catheter placed in the internal jugular vein or an angiocath placed in peripheral vein. We prefer to use the internal jugular vein in these patients because most of these patients have underlying chronic renal dysfunction¹⁴ and preservation of the peripheral veins is essential for future placement of permanent dialysis access. The blood flow rates are maintained at 50 to 100 mL/min. The ultrafiltration rate is

usually maintained between 300 to 800 mL/hr while maintaining systolic blood pressure at least greater than 80 mm Hg. Anticoagulation includes continuous heparin infusion at 500 units/hr. We allow for a maximum of 5 L of fluid removal over a period of 8 hours in a day. Blood pressure and heart rate are recorded every 30 minutes. The patient undergoes daily ultrafiltration for 8 hr/day until the patient becomes clinically euvolemic.

Conclusion

In the CICU, dialysis is needed for management of patients with ESRD, AKI, and/or acute decompensated heart failure. Patient survival and recovery of renal function are not affected by IHD or CRRT. However, CRRT is the modality of choice in hemodynamically unstable patients since it allows for better management of volume status and nutritional needs. Management of AKI is different from that of ESRD, and the RRT prescription should incorporate the unique characteristics of each patient. The close collaboration among nephrologists, cardiologists, and intensivists would allow for better management of patients in the ICU and may improve outcomes.

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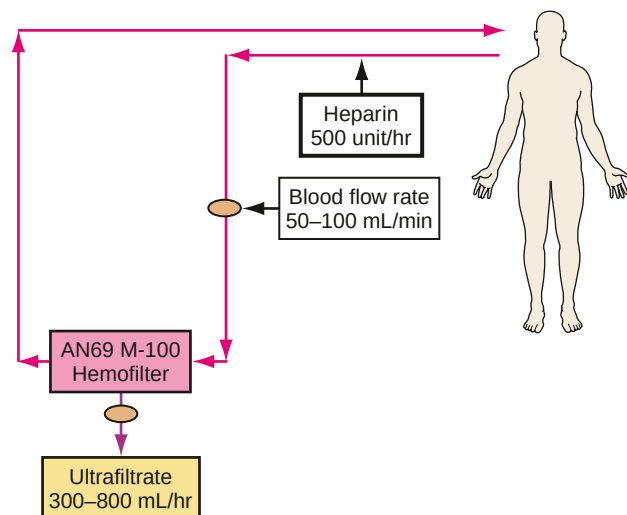


Figure 51-1. Ultrafiltration circuit with AN69 M-100 hemofilter using the Gambro Prisma machine. (Lakewood, Colorado, USA).

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Cardiocerebral Resuscitation, Defibrillation, and Cardioversion

Gordon A. Ewy



Etiology of Ventricular Arrhythmias	Mechanical Devices for Resuscitation
Three Phases of Ventricular Fibrillation	Postresuscitation Dysfunction
Defibrillation	Postresuscitation Care
Cardiocerebral Resuscitation for Cardiac Arrest	Ending Resuscitative Efforts
Bystander Responder Critical	Techniques of Defibrillation
Hemodynamics of Cardiac Arrest	Electrical Cardioversion of Atrial Arrhythmias
Cardiopulmonary Resuscitation	Conclusion
Considerations in Resuscitation Research	

SUDDEN DEATH is a leading cause of mortality in developed countries and accordingly an important public health problem.^{1,2} Although out-of-hospital cardiac arrest is the major cause of sudden death, in-hospital cardiac arrest is also a significant concern. Fortunately, the incidence of ventricular fibrillation (VF) occurring in hospitalized patients with and after an acute coronary syndrome is decreasing because of more aggressive revascularization that decreases ischemia and limits infarct size, the use of β -adrenergic blockers that reduce ischemia, and the correction of hypomagnesemia and hypokalemia—electrolyte abnormalities that predispose to ventricular arrhythmias.² Despite this trend, ventricular fibrillation is still one of the many medical emergencies that the physician must be able to manage.

Although ventricular arrhythmias are always secondary to some abnormality, they are classified as *primary* because of the sudden onset of ventricular fibrillation or pulseless ventricular tachycardia and *secondary* when the cardiac arrest follows prolonged hypotension from cardiogenic, septic, or hemorrhagic shock or from respiratory arrest. This chapter addresses primary cardiac arrest.

The approach to the therapy of ventricular fibrillation both in and out of hospital depends upon its duration. Therefore this chapter begins by reviewing this important and relatively new concept, delineating the electrical, circulatory, and metabolic phases of untreated ventricular fibrillation.³

A major portion of this chapter will deal with cardiocerebral resuscitation (CCR), a more effective approach to the therapy of unexpected or primary cardiac arrest that is so new that many of its tenets have yet to be incorporated into national and international guidelines.⁴⁻⁸ A review of national and international guidelines for cardiopulmonary resuscitation (CPR) and advanced cardiac life support (ACLS) for primary cardiac arrest is not appropriate because significant portions of even the 2005 guidelines are currently out of date.⁹ Traditional CPR should be

reserved for respiratory arrest—a review of which is beyond the scope of this chapter.

Etiology of Ventricular Arrhythmias

The most common causes of ventricular tachycardia and fibrillation are acute myocardial infarction, chronic ischemic heart disease with decreased ventricular function, valvular heart disease that results in significant myocardial dysfunction, and cardiomyopathies (dilated, hypertrophic, arrhythmogenic right ventricular dysplasia [ARVD], and neuromuscular disorders).² Other causes include myocarditis, infiltrative cardiomyopathies, end-stage chronic kidney disease, and congenital heart disease in adults who had postoperative correction of their defect(s). Normal ventricular function does not rule out a cardiac cause of near syncope, frank syncope, or cardiac arrest because there are a number of arrhythmias that can produce such symptoms. Genetic identification is now possible for some conditions that predispose to serious cardiac arrhythmias, such as long QT syndrome, short QT syndrome, Brugada syndrome, and idiopathic ventricular tachycardia. Other conditions such as electrolyte disturbances and toxic agents that can cause ventricular tachycardia, VF, and sudden death must be identified clinically. Stress cardiomyopathy is a newly recognized entity of myocardial dysfunction that occurs predominantly in women following severe emotional stress that may result in ventricular dysfunction, hypotension, shock, and even ventricular fibrillation—an explanation for emotionally induced sudden death.

Three Phases of Ventricular Fibrillation

Some of the recent changes in the approach to the therapy of ventricular fibrillation (VF) are based on the three-phase, time-sensitive model of untreated VF articulated by Weisfeldt and

Becker.³ This model helps to explain why some of the previous approaches to and recommendations for the therapy of VF are ineffective.

The first, or electrical phase (Fig. 52-1) of untreated VF, lasts for 4 or 5 minutes. During this time the most important therapeutic intervention is prompt defibrillation. Although the heart is fibrillating, the myocardium has neither used up all of its energy stores nor undergone serious cellular damage and is therefore able to respond to the electrical defibrillation and generate a perfusing rhythm. This is why implantable cardioverter-defibrillators (ICDs) are so effective and why automated external defibrillators (AEDs) have been employed successfully in patients with out-of-hospital cardiac arrest in airplanes and airports, casinos, and in communities where prompt defibrillation was possible.¹⁰⁻¹² However, even in the electrical phase of VF, the earlier the defibrillation, the greater the chance that it will result in a perfusing rhythm and therefore survival.

The second or circulatory phase (see Fig. 52-1) of untreated VF lasts for a variable period of time, originally estimated to be from about minute 5 to about minute 10 of untreated VF (but probably extends from minute 5 to about minute 15). During this circulatory phase of ventricular fibrillation, the continued lack of myocardial perfusion during the continued uncoordinated myocyte contractions of untreated VF results in declining amplitude and frequency spectrum of the electrocardiographic fibrillation waveforms, declining myocardial energy stores, and the accumulation of toxic metabolites.^{13,14} Defibrillating during this circulatory phase without first improving myocardial perfusion by chest compressions usually results in pulseless electrical activity (PEA) or asystole. A critical intervention during this second or circulatory phase of VF cardiac arrest is restoring myocardial blood flow by the generation of adequate coronary perfusion pressure with chest compressions not only before but also immediately after direct current shocks.⁴ Chest compressions during the circulatory phase of VF increase the amplitude and the frequency spectrum of the fibrillation waveforms and improve the chances of restoring a perfusing rhythm following defibrillation. Chest compression immediately after the electrical shock provides perfusion to the energy-starved poorly contracting myocardium, increasing its chance of recovery and allowing it to develop enough strength or force of contraction to generate a perfusing rhythm. The third or metabolic phase (see Fig. 52-1) of VF follows the circulatory phase. Survival in this phase, in the absence of hypothermia, is unusual.

Electrical phase Minute 0 to minute 4 or 5
Circulatory phase Minute 4 or 5 to minutes 10 to 15
Metabolic phase After minutes 10 to 15

Figure 52-1. Three-phase, time-sensitive model of untreated ventricular fibrillation. During the electrical phase, the most important intervention is prompt defibrillation. During the circulatory phase, the fibrillating heart has used up much of its energy stores, and defibrillation in this phase usually results in asystole or pulseless electrical activity, unless the heart is first perfused by chest compressions. During the metabolic phase, newer approaches are needed because resuscitation during this phase is usually impossible.

In summary, during the electrical phase (the first 4 to 5 minutes) of untreated ventricular fibrillation arrest, the most important therapy is early defibrillation. During the circulatory phase (from approximately minute 5 to about minute 15) of previously untreated VF, the provision of myocardial perfusion by chest compressions before and immediately after the electrical shock is essential to allow the ventricular myocardium to produce a postdefibrillation perfusing rhythm. Importantly, the duration of both the electrical and circulatory phase of VF can be prolonged by adequate perfusion of the fibrillating heart, such as with prompt effective chest compressions.

Defibrillation

Within minutes, untreated ventricular fibrillation (VF) is fatal. Accordingly, few therapies in medicine are more dramatic or more crucial to the patient's outcome than urgent electrical defibrillation. Defibrillation has been variously defined but practically speaking, *defibrillation* means the termination of ventricular fibrillation irrespective of the resulting rhythm.

Mechanical Defibrillation (Precordial Thump)

A blow to the chest with a clenched fist, referred to as a “precordial thump,” was first reported in the 1960s.¹⁵ Precordial thump delivered soon after the onset of VF was found to be capable of defibrillating ventricular fibrillation and converting ventricular tachycardia to normal sinus rhythm. A precordial thump is the easiest, though least effective form of defibrillation. A precordial thump defibrillates less than 2% of patients with VF and does so only in those with a very recent onset of ventricular fibrillation.¹⁵ The response of ventricular tachycardia to a precordial thump is more effective but is less predictable. A blow to the chest has been estimated to convert about one third of patients with ventricular tachycardia (VT) into sinus rhythm. In another third, a precordial thump has no effect, and in the final third VT is converted to VF. Because of this observation, monitored VT in a patient without cardiac arrest should not be treated with precordial thump unless a defibrillator is present.¹⁶ Nevertheless one might consider a precordial thump as the initial therapeutic approach in an unresponsive patient with witnessed collapse and abnormal breathing because of its rapidity and ease of delivery.

Electrical Defibrillation

During the first 4 to 5 minutes or the electrical phase of ventricular fibrillation, the most important intervention is prompt electrical defibrillation. There are rare instances of spontaneous reversion of ventricular fibrillation, but many of these are in fact instances of polymorphic ventricular tachycardia incorrectly assumed to be VF. The shorter the duration of VF before electrical defibrillation, the more likely it will result in successful resuscitation. Experience with modern implantable cardioverter-defibrillators (ICDs) is that if the electrical shock is applied within seconds, nearly 100% can be defibrillated.¹⁷ Kouwenhoven's experimental studies of over a half century ago found that if the defibrillation shock was delivered within 30 seconds of the onset of ventricular fibrillation, 98% of the animals survived; if the shock was delayed just 2 minutes, only 27% lived. More recent reviews estimate that the chances of successful defibrillation decrease about 10% for each minute of untreated VF.

The technique, physics, and hemodynamics of defibrillation in cardiac arrest are addressed later in this chapter.

Ventricular Tachycardia or Fibrillation Storm

Frequently recurring episodes of ventricular tachycardia (VT) degenerating into VF requiring multiple defibrillations has been termed “VT storm.”² In such patients, in addition to appropriate defibrillations, intravenous β -blockade and/or urgent cardiac catheterization should be considered, for if ischemia is the initiating factor and it is still present, every effort needs to be directed at decreasing the ischemic burden.² Amiodarone, often in combination with β -blockers, can be useful for patients with left ventricular (LV) dysfunction because of prior myocardial infarction (MI) and recurrent VT.² If the VT storm is from polymorphic VT, intravenous β -blockade is the single most effective therapy.² All too often VT storm is secondary to the administration of multiple antiarrhythmic drugs.

Cardiocerebral Resuscitation for Cardiac Arrest

Why CCR for cardiac arrest? Although CPR has been in existence for almost a half century, in the absence of early defibrillation in patients with primary cardiac arrest, the survival rates are poor and have remained essentially unchanged for decades.^{4,5} It is now apparent that a major reason for the heretofore abysmal survival rates of patients with out-of-hospital cardiac arrest (OHCA) is that the previous guidelines were far from optimal and the current (2005) guidelines, while improved, leave much to be desired.

One reason for the poor survival is the lack of bystander-initiated CPR. This is in part due to the recommendation for mouth-to-mouth ventilation or so called “rescue breathing.”⁴ It is well known that this recommendation is a major reason individuals are not willing to perform bystander CPR on a stranger. And with the current universal precautions in hospitals, mouth-to-mouth ventilations are rarely performed in hospitals anymore. And for OHCA, if one calls 911 and does nothing until the paramedics arrive, the patient is not likely to survive. Or in large hospitals, if the cardiac arrest team is activated but bystander resuscitation efforts are not initiated until the team arrives, the chance of survival is greatly diminished. Any chain is only as strong as its weakest link, the weakest link in the chain of survival for cardiac arrest is the first link—bystander CPR. The solution to this problem is bystander continuous chest compressions or chest-compression-only CPR.

This approach is called “cardiocerebral resuscitation” or CCR.^{4,5} The major tenets of CCR are based on the fact that during resuscitation for cardiac arrest, the cardiac output or forward blood flow is so marginal that any interruption in continuous chest compressions is deleterious, and that during out-of-hospital cardiac arrest, the paramedics arrive not during the first or electrical phase of VF arrest but during the circulatory phase. And during this phase chest compression before and after defibrillation is necessary for optimal survival.⁴

Circulatory Phase of Untreated Ventricular Fibrillation

Although prompt defibrillation is often effective in the electrical phase of VF, direct current shocks, especially sequential or so-called stacked shocks are not only not effective, but are harmful during the circulatory phase of untreated VF because they interrupt or delay chest compressions during the critical circulatory phase of ventricular fibrillation.^{4,18} This concept led

to an important change in the 2005 guidelines for ACLS.⁹ These guidelines no longer recommend stacked shocks but a single shock followed by the immediate application of 200 continuous chest compressions before rhythm and pulse analysis. These recommendations have been a part of CCR since 2003.^{4,19,20}

Cardiocerebral Resuscitation—A New Approach for Cardiac Arrest

If a monitored patient develops ventricular fibrillation, the optimal approach is rapid defibrillation—a major advantage of the coronary and intensive care units. However, the majority of OHCA and some in-hospital cardiac arrests occur in a location that takes the emergency response services (EMS) several minutes to arrive. In this situation, CCR, a new approach to patients with OHCA that dramatically improves survival, is recommended.^{4,5} Why a new approach to cardiac arrest? Despite standards published in 1974, standards and guidelines published in 1980, guidelines in 1992, and updates of guidelines in 2000,²¹⁻²⁴ the survival rate of patients with OHCA has not improved, and in the absence of early defibrillation is so poor it is near that described as medical futility.²⁵ Accordingly in 2003, our University of Arizona Sarver Heart Center Resuscitation Research Group, based on more than 3 decades of defibrillation and resuscitation research and our interpretation of the literature, could no longer in good conscience follow the guidelines, and developed the CCR approach.^{4,5,19,26} This approach has now been shown to dramatically improve survival over the previous approach for patients with OHCA.^{5,26}

CCR has three components (Fig. 52-2). For bystanders, continuous chest compression (CCC-CPR) or chest-compression-only is recommended because it has been shown that patients with cardiac arrest are more likely to be in VF when the EMS arrives if a bystander initiates resuscitation efforts (or bystander CPR) and bystanders are more likely to initiate bystander resuscitation efforts if mouth-to-mouth or so called “rescue breathing” is not required.²⁷ Chest compression only, as will be described later, also results in better survival because it does not result in excessive interruptions of the marginal forward blood flow existent during traditional resuscitation efforts for cardiac arrest.^{28,29}

The second and major component of CCR is a new approach to advanced cardiac life support (e.g., the approach of medical personnel who arrive with a defibrillator, but who did not

- | CARDIOCEREBRAL RESUSCITATION |
|---|
| 1. Continuous chest compression CPR for first responders |
| 2. New algorithm for advanced cardiac life support |
| 3. Postresuscitation in-hospital care that includes urgent cardiac catheterization and mild hypothermia |

Figure 52-2. Three components of cardiocerebral resuscitation. The first component is continuous chest compressions (CCC) without assisted ventilation for bystanders and first responders (CCC-CPR). The second component is a new approach to advanced cardiac life support (the details of which are shown in Fig. 52-3). The third component includes an aggressive approach to cardiac catheterization and intervention when appropriate and therapeutic hypothermia for patients who are comatose after resuscitation. CPR, cardiopulmonary resuscitation.

witness the arrest, and thus arrive most often after the electrical phase of the patient's cardiac arrest [Fig. 52-3]). If adequate continuous chest compressions are not being done by the bystander, CCR advocates an initial 200 continuous chest compressions with special attention to appropriate technique.⁴ The appropriate technique of chest compressions for cardiac arrest includes forceful chest compressions of adequate depth (1½ to 2 inches) at a rate of 100 compressions a minute, each followed by removal of the heel of the hand from the sternum to allow full chest wall recoil. This compression technique is essential during the circulatory phase of VF arrest, both before and after a single defibrillation shock.

CCR eliminates any intervention that delays or interrupts continuous chest compressions, or provides positive pressure ventilation. The reason for limiting interruptions of chest compressions is that during compressions for cardiac arrest, the forward blood flow is so marginal that any delay or interruption of chest compression significantly decreases cerebral blood flow and decreases the chance for neurologically intact survival.⁴ The use of automated external defibrillators (AEDs) while effective during the electrical phase of VF arrest is detrimental during the circulatory phase of cardiac arrest if they significantly delay and interrupt chest compressions.⁴ Thus after the shock is delivered by an AED, the verbal instructions of AED presently must be ignored. Two hundred postshock chest compressions are to be immediately instituted (see Fig. 52-3). The reason for this recommendation is that in our experimental laboratory model of OHCA, defibrillation during the circulatory phase of VF arrest

usually results in very low pressure pulses that increase with assistance of continuous chest compressions.^{4,30}

Another important component of CCR is the elimination of positive pressure ventilations (see Fig. 52-3). The reasons for the elimination of positive pressure ventilations are twofold: First, intubation results in a significant delay in chest compressions during the circulatory phase of VF arrest. Secondly, during chest compressions for cardiac arrest, the forward blood flow is so marginal that any increase in intrathoracic pressure decreases venous return and subsequent cerebral blood flow.^{4,6,29}

The prevention of positive pressure ventilations and hyperventilation (very common during the excitement of a cardiac arrest) is accomplished by using passive oxygen insufflation^{5,31} (see Fig. 52-3). Passive oxygen insufflation is applied by a second rescuer, and is accomplished by placing an oral pharyngeal airway and nonrebreather mask and high flow oxygen. Another advantage of this approach is that this frees the second rescuer to perform other critically important functions such as starting an intravenous line for epinephrine administration.⁵

Cardiocerebral Resuscitation Improves Survival of Patients with Out-of-Hospital Cardiac Arrest

It has been shown that the application of CCR dramatically improved survival of patients with OHCA compared to that existent in the same (EMS) systems that used the Guidelines for Cardiopulmonary Resuscitation and Advanced Cardiac Life Support (ACLS) hereafter referred to as "Guidelines 2000." The first report was from two rural counties in Wisconsin, where

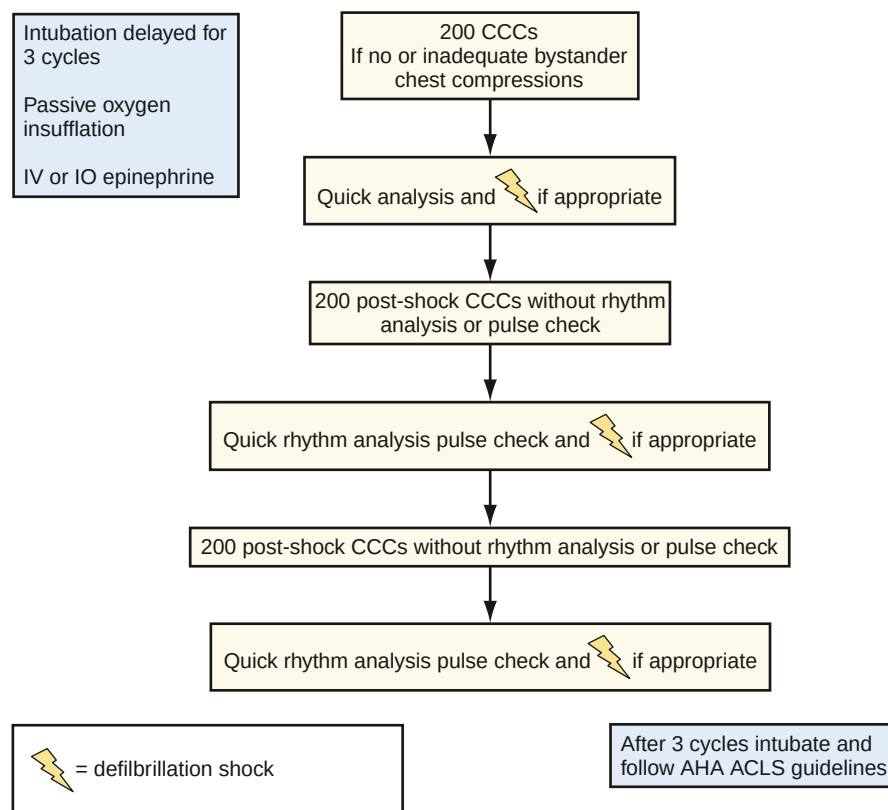


Figure 52-3. Cardiocerebral resuscitation (CCR) approach to advanced cardiac life support (ACLS). Passive oxygen insufflation consists of placing an oropharyngeal airway, a nonrebreather mask, and high-flow (10 to 15 L/min) oxygen. AHA, American Heart Association; CCC, continuous chest compressions; IO, intraosseous; IV, intravenous.

CCR was initiated in early 2004.⁵ In the 3 years (2002 to 2005) when the Guidelines 2000 approach was used, in this report, there were 93 witnessed out-of-hospital adult cardiac arrests with an initially shockable rhythm. Nineteen patients survived and 14 of 92 (15%) were neurologically normal at hospital discharge. During the first year that CCR was instituted, the neurologically normal survival was 16 of 33 (48%).⁵ This study clearly supported the new approach of cardiocerebral resuscitation but was not definitive because of the small number of patients treated by CCR and because of a potential Hawthorne effect—that is improved performance of individuals who knew they were being studied. Longer duration of study was needed to address these concerns. Longer follow-up has been completed. During the 3 years of CCR follow-up, from 2005–2007, there were 91 patients with witnessed cardiac arrest who had a shockable rhythm on arrival of the EMS personnel. Forty-four survived (48%) and 37 (40%) were neurologically normal at hospital discharge ($P = 0.001$). The institution of CCR tripled neurologically intact survival of patients with witnessed OHCA and a shockable rhythm on arrival of the emergency medical system. One could conclude that there was some Hawthorne effect in the initial report because the second report with longer follow-up found a 250% increase in survival rather than the initial report of a 300% increase in survival (Fig. 52-4).

CCR was then instituted in two large municipal fire departments in the Phoenix metropolitan area in 2005. Survival to hospital discharge and other data were collected from these two large fire departments when Guidelines 2000 CPR and ACLS were used, and then following training of the emergency medical services (EMS) firefighters in CCR. Among the 713 cardiac arrests in these two fire departments, survival improved from 1.8% ($n = 2/219$) pretraining to 6.5% ($n = 32/494$) posttraining. In the subgroup with witnessed arrest and ventricular fibrillation on arrival of the EMS, survival to hospital discharge improved from 5% ($n = 2/43$) pretraining to 25% ($n = 22/89$) posttraining.²⁶ The results of these initial observations on the application of CCR are shown in Figure 52-5. Application of CCR for witnessed OHCA worldwide would result in the saving of innumerable lives.

Guidelines 2005 did make some changes in recommendations for ACLS that have been shown to improve survival. The change from

multiple or stacked defibrillator shocks to a single shock followed by 200 chest compressions before pulse check or rhythm analysis, part of the tenets of CCR that we instituted in 2003, has also resulted in improved survival of patients with out-of-hospital cardiac arrest.¹⁸

Proper Technique of Chest Compressions

As noted previously, during cardiac arrest and resuscitation efforts, the perfusion pressures and forward blood flow generated by chest compressions are marginal at best. Accordingly, any interruption of chest compressions has an adverse effect on cerebral and myocardial perfusion and dramatically decreases the chance of neurologically intact survival. The delivery of near continuous, appropriate chest compressions is therefore another fundamental tenet of CCR.⁴

The emphasis on limiting interruptions of chest compressions is based upon research that showed that the major determinant of neurologically intact survival from prolonged cardiac arrest because of VF is the perfusion pressures generated by chest compressions rather than the blood gas composition, acid-base balance, or the frequency or strength of defibrillation shocks.^{32–34} During resuscitation efforts, any interruptions of chest compressions immediately curtail blood flow to the heart and the brain and resumption of chest compressions may take several compressions to restore good perfusion pressures.^{32,35,36} CCR advocates near continuous chest compressions and limits assisted ventilations until after three rounds of chest compressions, shock when indicated, and chest compressions (see Fig. 52-3). There should be no interruptions of chest compressions for anything but post-chest compression defibrillation until the return of spontaneous circulation or the termination of the resuscitation effort. Pulse checks are to be done only during pauses in chest compression for rhythm analysis after the 200 postdefibrillation chest compressions.⁵

The third component of CCR is postresuscitation care. If the patient is unconscious postresuscitation, mild hypothermia (32°C to 34°C) has been shown to improve neurologically normal survival.^{37–39} Most patients should be taken to the cardiac catheterization laboratory because some will have acute coronary occlusion without ST-segment deviation on their electrocardiogram. Attention to glucose control and electrolyte balance is also an important part of postresuscitation care.

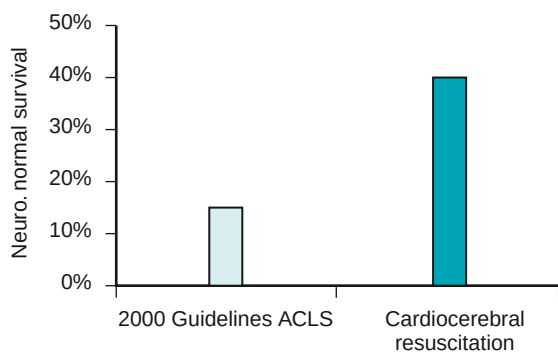


Figure 52-4. Percent of neurologically normal survival in patients with witnessed out-of-hospital cardiac arrest and a shockable rhythm during a 3-year period when 2000 American Heart Association advanced cardiac life support (ACLS) was used (2000 Guidelines ACLS) and during the next 3 years after instituting cardiopulmonary resuscitation in the same two small counties in Wisconsin.

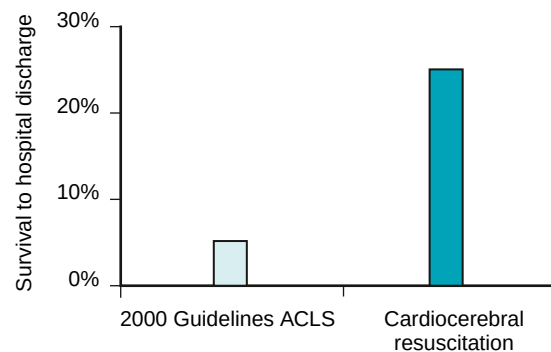


Figure 52-5. Percent of survivors to hospital discharge of patients with witnessed out-of-hospital cardiac arrest and a shockable rhythm during a period when 2000 American Heart Association advanced cardiac life support (ACLS) was used (2000 Guidelines ACLS) and during the time after cardiopulmonary resuscitation was introduced in two large metropolitan fire departments in Arizona.

Bystander Responder Critical

Role of Continuous Chest Compressions or Chest-Compression-Only CPR

Several studies have found that survival of patients with OHCA who receive chest compression alone without mouth-to-mouth ventilations by bystanders are not statistically different from survival of such patients who receive chest compression plus so-called “rescue breathing.”⁴⁰⁻⁴² Nevertheless, the technique of chest compressions without rescue breathing has not been recommended by the guidelines unless the bystander is unable or unwilling to perform mouth-to-mouth ventilation.^{9,24} The rationale for this recommendation is that the guidelines’ authors evidently did not want lay individuals to have to decide if the patient has a cardiac arrest or a respiratory arrest. As will be noted later, this author thinks that this is not only possible but essential because many more individuals have OHCA and respiratory arrest. In Tucson, Ariz., it has been estimated that there are about 100 out-of-hospital cardiac arrests for every drowning death. In Seattle, the reported incidence of cardiac arrest to respiratory arrest is 20 to 1.⁴² In certain cultures, for example in those with a high incidence of drug abuse, the incidence is probably higher. In other cultures the incidence of respiratory to cardiac arrests is probably lower.

Studies by Kern and associates, in realistic swine models of OHCA, found that the provision of chest-compression-only CPR was more effective than the provision of standard 2:15 CPR, when each set of 15 chest compressions was interrupted for a realistic 16 seconds, to simulate the duration without chest compressions reported for a single rescuer to deliver the recommended “two quick breaths” and resume chest compressions.³⁶ In 2007, similar findings were reported in humans.²⁸ The survey of survivors (SOS) KANTO study reported that the overall survival of patients with OHCA was 2.2% for those who had not received bystander CPR when the EMS arrived, 4.2% for those who were receiving chest compressions plus mouth-to-mouth ventilation, and 6.2% for those receiving chest-compression-only by bystanders.²⁸ More importantly, these investigators reported that in the subset of patients with the greatest chance of survival—those with witnessed arrest and a shockable ventricular arrhythmia upon arrival of the EMS personnel, the survival was nearly twice as great (11% versus 19%, $P = 0.05$) in those who had received bystander chest compression alone than in those who received chest compression plus mouth-to-mouth ventilation.²⁸

Following the publication of this important study, the guidelines were not changed despite a call for urgent changes.⁴³ The reason was that this observational study was done during a time when the recommended ventilation to chest compression ratio was still 2:15. The 2005 Guidelines of the American Heart Association (AHA), the European Resuscitation Council, and the International Liaison Committee for Resuscitation (ILCOR) changed their recommendations in the 2005 guidelines for ventilations to chest compression ratio to 2:30.⁹ The change in the 2005 guidelines from 2:15 to 2:30 was based in part on the findings of Abella and colleagues.⁴⁴ In a prospective observational study of in-hospital cardiac arrest in three hospitals during 2000-2003, those patients who had a return of spontaneous circulation (ROSC) received a greater number of chest compressions per minute than those who did not. The average number of chest compressions per minute was 90 ± 17 in those who had ROSC compared with 79 ± 18 in those who did not have ROSC.⁴⁴ In their analysis, it seemed that a compression rate of at

least 89 compressions per minute was necessary for higher rates of ROSC. Of note is the fact that the survival of patients with in-hospital cardiac arrest in these three academic hospitals was so poor that it was not reported.⁴⁴

Animal studies showed that ROSC was better with a 2:30 ventilation to compression ratio than with the previous standard of 2:15.⁴⁵ Thus there was no long-term (24-hour) survival evidence that the change to the recommended 2:30 ventilation to compression ratio would improve survival. The recommendation was based on consensus.⁹ One could argue that observational studies in man were needed before guideline changes could be made. We argue that our swine models of OHCA, showing that continuous chest compressions were better than 2:15 when a realistic 16-second interruption was used to provide the two ventilations, predicted the results found in man.^{28,43}

In subsequent studies using the same swine model of OHCA, Ewy and colleagues found that when simulated bystander resuscitation was initiated 4 to 6 minutes after the onset of VF arrest, and defibrillated after 12 minutes of VF, chest-compression-only CPR (CCC-CPR) resulted in a greater number of neurologically normal 24-hour survivors than did 2:30 ventilations to compressions.⁴⁶ Neurologically normal survival was found in 16 of 24 (64%) of the swine who received continuous chest compression compared with 6 of 23 (26%) receiving two ventilations for every 30 chest compressions before defibrillation.⁴⁶

Teaching Bystander “Chest-Compression-Only CPR”

The lay component of CCR emphasizes calling the emergency medical system (911 in the United States) followed by continuous chest compressions without mouth-to-mouth ventilation. This activity is only to be interrupted if an AED is available.⁴

We think it is important that bystanders be told that it is not necessary to remove any of the patient's clothing because this act alone prevents many bystanders from initiating bystander CPR. Bystanders are to place the fallen individual on his or her back on a hard surface or on the floor, to place the heel of one hand in the center of the patient's chest (on the sternum, usually between the nipples), with the heel of the other hand on top of the first. They are to lock the elbows so the arms are straight, and with the shoulders above the center of the patient's chest, to fall so the weight of their upper body compresses the patient's chest. Few if any are strong enough to do adequate chest compressions using just the muscles of their upper extremities. The compression rate should be 100/min. Lifting the hands or the heel of the bottom hand completely off the chest after each compression is necessary to allow full chest recoil and is specifically emphasized (see later discussion).⁴⁷ This is an important issue and one reason that external chest compressions should not be referred to as external cardiac massage. Massage implies continuing pressure and continuing pressure or any lean on the chest during the release phase of chest compression decreases forward blood flow and survival. If more than one rescuer is present, they are to trade off doing chest compressions after each 100 or 200 compressions because, properly done, continuous chest compressions at 100/min is very tiring, especially for older individuals.

Full Chest Wall Recoil Following Chest Compressions is Essential

Full chest wall recoil during the release phase of each chest compression is extremely important.⁴⁷ During the release phase of chest compression, a small negative pressure is created within

the chest as the chest wall recoils back to its resting position.⁴⁷ This draws venous blood back into the right heart from the systemic veins and may draw air into the airways. Incomplete chest recoil compromises perfusion because it interferes with the generation of this negative pressure in the chest, and thus decreases venous blood return to the heart. As a consequence, cardiac output and perfusion pressures are reduced. Incomplete chest recoil has been reported in 46% of simulated resuscitations performed by paramedics.⁴⁷ Furthermore, when incomplete chest recoil was combined with excessive ventilations, perfusion was severely compromised.⁴⁷

Placement of any device between the heel of the hand and chest wall is detrimental because one cannot allow full chest wall recoil because one is making sure the device does not fall off. In our early animal studies, we were criticized by journal reviewers because we did not report the force that we were using for chest compression. We then placed a force transducer between the heel of the hand and the anterior chest wall. Continuous pressure had to be exerted to keep the device from slipping off the chest wall. Survival of our experimental animals with this technique was markedly decreased. At the time we had no idea why, but we had to discontinue the measurement because of decreased survival compared with that present when we used only our bare hands. In retrospect, the device had to be maintained on the chest wall, so that the chest wall was never allowed to fully recoil.

There are newer thin devices that stick on the chest that are being evaluated to provide instant feedback to paramedic/firefighters doing chest compressions to ensure optimal technique. Such devices may be helpful in training.

Dispatch-Directed Chest-Compression-Only CPR Generally Accepted

A part of the first component of CCR consists of new recommendations for dispatch-directed bystander resuscitation.⁴² Continuous chest compression CPR or chest-compression-only bystander resuscitation instructions are given by phone from EMS dispatch centers. This approach is now generally followed in most metropolitan cities in the United States.

What Is the Role of Gasping or Agonal Respirations?

Gasping or agonal respirations are common early on following cardiac arrest. Clark, Eisenberg, and associates reported gasping in 56% of patients with OHCA on arrival of paramedics.⁴⁸ Gasping or agonal breathing is probably more common soon after cardiac arrest and is more common in individuals who receive bystander CPR. When these forms of abnormal breathing occur in patients with cardiac arrest, it is both unfortunate and fortunate. It is unfortunate because gasping or agonal breathing may be interpreted by uninformed lay individuals as an indication that the person who collapsed is still breathing and therefore delay initiating bystander resuscitation and the activation of the emergency medical services. However, gasping is fortunate because if recognized for what it is (e.g., agonal breathing), and chest compressions are promptly initiated, the subject is likely to continue to gasp and provide physiologic self-ventilations. And if continuous chest compressions are initiated, the nongasping subject is more likely to begin gasping. The longer the duration of untreated VF before the initiation of resuscitation efforts, the longer the duration of bystander CPR efforts before gasping resumes.

Clark and associates also reported that gasping or agonal breathing was highly correlated with survival.⁴⁸ We have found similar results in our swine model of OHCA laboratory. Animal research laboratories that use paralysis as part of the protocol when studying CPR eliminate this physiologically important reflex. It is our opinion that results in paralyzed animals cannot be applied to humans who are not paralyzed when they have cardiac arrest.

Recently we evaluated the role of gasping and type of bystander CPR on 24-hour neurologically normal survival. Using our swine model of OHCA, we found that subjects treated with CCC-CPR were more likely to gasp and to survive than those treated with a 30:2 chest compression ventilation ratio when each 30 chest compressions were interrupted by a realistic 16 seconds to simulate a lay bystander delivering two mouth-to-mouth breaths. In addition, we found that the longer the duration of arrest before the initiation of bystander initiated resuscitation efforts, the longer it took for the animals to resume gasping once bystander CPR was initiated.

Assisted Ventilations Should Not Be Done, Even If More Than One Qualified Person is Present

The question is frequently asked if someone should do assisted ventilations if two qualified persons respond to the arrest. The answer is no. First, properly performed continuous chest compressions are very tiring and therefore the two rescuers should spell each other after 100 or 200 continuous chest compressions. Second, as will be noted later, during cardiac arrest and chest compressions the forward blood flow is so marginal that increasing intrathoracic pressure by positive pressure decreases venous return to the chest and therefore forward blood flow. This point will be expanded upon later because it is also one of the reasons positive pressure ventilations should be limited by medical and EMS personnel as well.

Emergency Medical Services Components of Cardiocerebral Resuscitation

The first component of CCR is continuous chest compression CPR for bystanders.⁴ The second component of CCR consists of a new algorithm for ACLS (see Fig. 52-2).⁵ Law officers and other EMS rescuers who are equipped with AEDs are to defibrillate immediately only if they personally witness the collapse or if good continuous chest compression CPR is being provided by a bystander when they arrive.⁵ Otherwise, they are to bare the chest and attach the defibrillator pads if using an AED or hand-held defibrillation electrodes and promptly perform forceful uninterrupted chest compressions at 100 compressions per minute for 2 minutes (200 compressions) before quick rhythm analysis and prompt defibrillation if indicated (see Fig. 52-3).

If two rescuers are available, one begins chest compressions while the other attaches the defibrillator pads. If after 200 chest compressions, a shockable rhythm is present, a single defibrillation shock is delivered followed immediately by an additional 200 chest compressions before any rhythm and pulse analysis. The reason for the 200 immediate postshock chest compressions is that during the circulatory phase of VF arrest, the shock often defibrillates the patient into a nonperfusing rhythm, and if one delays the resumption of chest compression to try to find a pulse, the nonperfused ventricles often fibrillate again. In our experimental laboratory, where the swine are continuously monitored, we see the nonperfusing rhythm and note that

with the resumption of chest compression the arterial pressure gradually increases until there is a perfusion rhythm. Therefore, if AEDs are being used by EMS personnel, many of the voice instructions on the currently available AEDs are inappropriate for the new CCR and must be ignored.

Is the Patient in the Electrical or Circulatory Phase of VF?

Because of the difficulty in ascertaining an accurate downtime in emergency circumstances, unless the collapse is witnessed, it is difficult to determine if the victim is in the electrical or the circulatory phase of VF arrest. Although AEDs are being developed to determine the phase of VF via analysis of the VF waveforms, we think this is unnecessary and this analysis will only delay or interrupt essential chest compressions. Previous reports by Cobb and Wik and associates in humans not only demonstrated the beneficial effects of chest compression before defibrillation in the circulatory phase (after the first 4 to 5 minutes) of VF arrest (Fig. 52-6), but equally important, they did not find a detrimental effect of performing chest compressions before defibrillation during the electrical phase (first 4 to 5 minutes) of VF arrest (e.g., 90 seconds of chest compressions before defibrillation in the report of Cobb and associates⁴⁹ or 3 minutes of chest compression before defibrillation in the report of Wik and associates).

CCR simplifies the decision-making process of the EMS person arriving on the scene by advocating an initial 2 minutes of chest compressions—not deleterious in the electrical phase and improves survival in the circulatory phase of VF arrest. The recommendation of 200 chest compressions (2 minutes at 100 compressions per minute) is a compromise between the 1 and 1½ minutes used by Cobb and the 3 minutes used by Wik. Using 200 compressions has the added benefit that the EMS personnel do not have to check their watch to time the duration of

continuous chest compressions before defibrillation. They just count the number of continuous chest compressions.

Minimal Interruptions of Chest Compressions for Defibrillation Is Essential

CCR also emphasizes minimizing the time between cessation of chest compressions, the delivery of the defibrillating shock, and the resumption of chest compressions.

Three sequential shocks of increasing energy are not advocated and are no longer recommended in Guidelines 2005.^{4,9} For years, so-called stacked or three sequential shocks were recommended. The reasons were twofold: first was the conviction that defibrillation was the highest priority for everyone in VF and therefore one should do several shocks as soon as possible. We now know that in the circulatory phase of VF arrest, this approach can be deadly.

Weaver and associates reported that high energy (360 J) shocks from monophasic wave defibrillators resulted in a higher incidence of postdefibrillation heart block.⁵⁰ Accordingly, previous guidelines recommended repeated or stacked shocks of escalating energy. Heart block is rare with monophasic defibrillators and we are not aware of its being reported when biphasic defibrillators are used. And as noted previously, repeated defibrillation shocks without chest compressions in the circulatory phase of VF arrest are harmful because of the long delays and/or interruptions of cerebral perfusion during the critical circulatory phase of VF arrest.

Continuous Chest Compression Immediately After Defibrillation

Why 200 chest compressions immediately after the defibrillator shock (see Fig. 52-3)? In animal models of prolonged VF arrest (e.g., the circulatory phase of VF arrest), a direct current shock often defibrillates the subject into a nonperfusing rhythm—PEA.⁵¹ In the experimental laboratory, the low perfusion pressure following defibrillation for prolonged VF is obvious on the monitor screen and immediately resuming chest compressions increases the arterial pressures, thereby restoring coronary perfusion pressures. The initially weak contraction generated by the recently defibrillated heart gradually becomes stronger, and the low blood pressure gradually becomes higher because the PEA is converted into a perfusing rhythm.⁵¹

Observational studies in humans by paramedic units found that a pulse was rarely if ever present immediately after the initial defibrillation shock and therefore immediate postshock chest compressions without pulse or rhythm analysis are now also recommended by the 2005 guidelines.⁹ This change, instituted by our group in 2003, became part of the 2005 guidelines. This change was also instituted in 2004 by resuscitation researchers in Seattle and was reported by Rea and associates to improve survival of their patients with OHCA.¹⁸

Positive Pressure Ventilations Eliminated or Delayed

Another major difference between CCR and CPR is in the recommendations for ventilation. The three CCR recommendations concerning airway management and ventilations in cardiac arrest can be summarized as follows: (1) Bystander or first responders are to perform continuous chest compressions without ventilations or without so-called rescue breathing; (2) initial EMS airway management is limited to ensuring an open airway with a nasopharyngeal airway and administration of high flow

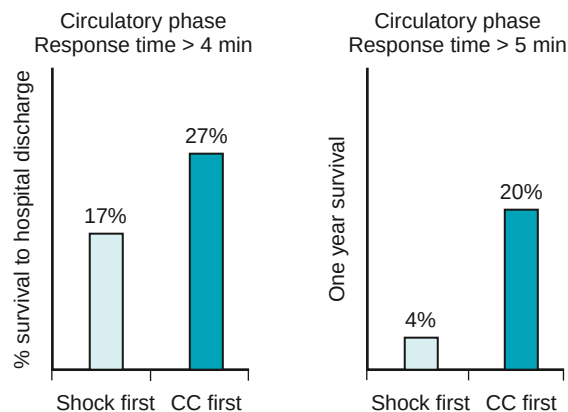


Figure 52-6. Percent of survivors to hospital discharge in Seattle (left) and Norway (right) with standard advanced cardiac life support (ACLS) “shock first” before and “CC (chest compressions) first” before delivering the first defibrillation shock. In the study by Cobb and associates,⁴⁹ 90 seconds of chest compressions was delivered first. In the study by Wik and associates, 3 minutes of chest compressions was delivered before delivering the first defibrillation shock. In the study by Cobb and associates, the circulatory phase of ventricular fibrillation (VF) arrest was taken as greater than 4 minutes of untreated VF. In the report by Wik and associates, the circulatory phase of VF was taken as greater than 5 minutes of untreated VF.

supplemental oxygen via a nonrebreather mask; (3) advanced airway management (intubation or bag-valve mouth ventilation) is initiated only after return of spontaneous circulation (ROSC) in those who are in a coma and need it or in those without ROSC after three sequences of defibrillation and 200 chest compressions (see Fig. 52-3).

Each of these three recommendations represents a marked deviation from the CPR and ACLS guidelines and each is counterintuitive to the “ABCs” that have been taught for decades. CCR does not advocate the elimination of ventilations; instead, it emphasizes the beneficial effects of negative intrathoracic pressure respiration (e.g., gasping or agonal breathing) and the possible “high frequency ventilation” effects afforded by rapid chest compressions. CCR does decry the interruptions of chest compressions for ventilations and the adverse effects of positive pressure ventilations during cardiac arrest and resuscitation.^{5,52}

Intubation and Positive Pressure Ventilations Eliminated or Delayed

There are three major problems with endotracheal intubation during the resuscitation efforts of cardiac arrest. The first is that intubation is often difficult, necessitating prolonged interruption of chest compressions to establish an airway. The resulting interruptions of chest compressions, during the critical circulatory phase of VF arrest, contribute to decreased survival. But even if intubation is done within seconds, positive pressure ventilations are detrimental during cardiac arrest and resuscitation efforts because positive pressure ventilations increase intrathoracic pressure, impede venous return to the chest, and thereby reduce cerebral and myocardial perfusion despite continued chest compressions. And thirdly, to make matters worse, rapid ventilation and hyperventilation are common during resuscitation efforts for cardiac arrest. Aufderheide and colleagues found that “there is an inversely proportional relationship between mean intrathoracic pressure, coronary perfusion pressure, and survival from cardiac arrest.”^{53,54} Observations of hospital-based responders to cardiac arrest and those of paramedics found that both professionals almost always performed assisted ventilation at excessively high rates. Two separate studies observed that both delivered an average of 37 ventilations per minute rather than the 10 to 12 per minute recommended; even after retraining, paramedics were observed to ventilate at 22 times per minute.^{52,55}

CCR protocols minimize these adverse effects of positive pressure and excessive ventilations by advocating passive oxygen insufflation during the initial phases of resuscitation (see Fig. 52-3). Passive oxygen insufflation consists of the placement of an oropharyngeal airway, a nonrebreather mask, and oxygenation with high flow (10 to 15 L of oxygen per minute).^{5,6} As noted above, this approach has another major benefit; it frees a professional for other critically important duties during cardiac arrest, such as obtaining vascular access for intravenous therapies and/or spelling the person doing chest compressions. Intubation or positive pressure ventilation with bag-valve-mask ventilation is delayed until after ROSC or if the patient is not awake after three single shocks, each followed by 200 chest compressions (see Fig. 52-3).⁵

Why isn't more ventilation or oxygenation necessary? Gasping, for sure, and perhaps high frequency ventilations from rapid chest compressions and/or chest wall recoil provide some oxygenation. During cardiac arrest and resuscitation, the forward blood flow is so marginal that there is not a large

ventilation-perfusion mismatch. And continuous forward blood flow is more important than interrupted flow, even if the interruptions result in better oxygenation of the blood.

Chandra and associates have shown, in an animal model of cardiac arrest, that even after 8 minutes of cardiac arrest with chest compressions but without assisted ventilations, the arterial oxygen saturation was still 75%.⁵⁶ Some of the values may be due to gasping, but it is also possible that with cardiac arrest, there are immediate cellular changes that decrease their oxygen uptake. However, the point of continuous perfusion is that blood contains many essential nutrients in addition to oxygen. With cardiac arrest, many microvascular beds close, perhaps decreasing the total amount of oxygen consumed by organs other than the heart and the brain. Although many of these explanations are speculation, the fact remains that fully oxygenated blood is not necessary for resuscitation, and interventions directed at assuring fully oxygenated blood have decreased survival of patients with OHCA.

Hemodynamics of Cardiac Arrest

Ventricular fibrillation results in totally uncoordinated contractile activity of the ventricular myocytes, resulting in almost immediate cessation of effective ventricular pump function. However, antegrade blood flow continues after cardiac arrest until the pressure gradient between the arterial and venous pressures is completely dissipated, and the pressures in the arterial and venous systems equalize at the “mean circulatory filling pressure” of Guyton.⁵⁷ Because of a variety of compensatory mechanisms, including increased sympathetic activity and the fact that some microvascular beds close, the equilibrium between the arterial and venous systems does not occur until after about 5 minutes of VF in animal models.⁵⁸

One result of the shift of blood from the arterial to the venous circuits is prompt distention of the right ventricle. Magnetic resonance imaging of the closed chest animal models of VF show a rapid increase in right ventricular volume, but not a dramatic decrease in left ventricular volume until the development of “stone heart” (extreme myocardial contraction) significantly later.⁵⁹

The changes in coronary blood flow and carotid blood flow in response to ventricular fibrillation are different. Carotid blood flow declines exponentially to zero over approximately 4 minutes but coronary blood flow rapidly declines to zero by 1 minute.⁵⁸

The Mechanisms of Blood Flow During Cardiac Arrest and Closed-Chest Compression

Closed-chest compressions during cardiac arrest result in phasic forward blood flow. The mechanisms responsible for forward blood flow during closed-chest compressions are variable and depend upon several factors. Of the factors identified, perhaps the most important is the duration between the onset of ventricular fibrillation arrest and initiation of chest compressions. Cardiac compressions as the mechanism of forward blood flow are more likely early during resuscitation and the so-called thoracic pump mechanism is more likely late in resuscitation when the heart begins to develop stone heart. Another important determinant is the patient's chest wall configuration. If the patient has a large anterior-posterior chest diameter, it is probable that cardiac compression is not likely.

According to the cardiac compression theory, direct compression of the ventricles between the sternum and the vertebral column closes the mitral and tricuspid valves and ejects blood forward out of the ventricles. The ventricles then refill during the decompression phase.

When closed-chest cardiac massage was introduced in the 1960s, it was assumed that the mechanism of blood flow was much the same as with open-chest cardiac massage, wherein the heart was grasped in the hand and the flow was produced by squeezing the fibrillating left ventricle. This was the presumed operative mechanism of forward blood flow during CPR until a study was done in humans by researchers at Johns Hopkins published in 1980.⁶⁰ Their data suggested that the mechanism of blood flow during chest compression was the “thoracic pump” mechanism: external chest compression increases intrathoracic pressure, forcing blood to flow from the thorax. A pressure gradient for cerebral flow is maintained by the jugular venous valves at the thoracic outlet. According to this paradigm, the heart acts merely as a passive conduit without having a pump function.

However, the Johns Hopkins study, while performed in humans, was performed very late in cardiac arrest, after the house staff had decided that resuscitation was not likely.⁶⁰ Thus these hemodynamic measurements were made after prolonged cardiac arrest when one would expect the onset of myocardial stiffness and swelling that progress to stone heart.⁵⁹ Thus when the thoracic pump is the mechanism of blood flow during chest compressions, resuscitation and survival are less likely.

Transesophageal echocardiography evaluations in humans during cardiac arrest and resuscitation attempts have shown both mechanisms—cardiac compression in some and the thoracic pump in others. However, the cardiac compression mechanism was more likely to be seen in patients studied early after arrest and the thoracic pump mechanism when cardiac arrest patients were studied later.⁶¹ And in one such study, survival only occurred among those studied early; there were no survivors among those who demonstrated the thoracic pump mechanism.⁶¹

It is probable that in younger individuals with compliant chest walls and/or narrow anterior posterior chest dimensions, the cardiac pump is the predominant mechanism and that they are more likely to be resuscitated. In patients with severe emphysema and a “barrel chest” the mechanism of blood flow is likely due to the thoracic pump mechanism, but these patients are also not likely to be revived by closed chest compressions.

The actual mechanism of forward blood flow during resuscitation is of great import because previous guidelines for CPR have been altered dramatically, depending upon the alleged or accepted operative mechanism. Based on the thoracic pump theory, the 1980 AHA guidelines recommended a chest compression rate of 60/min and noted that “compression should be sustained for 0.5 second, with relaxation given for an equal period.”²² In hindsight this recommendation was incorrect because it resulted in too few compressions per minute.⁴⁴

This recommendation of 60 compressions per minute was not accepted by many clinicians who had years of experience with successful resuscitations using much faster chest compression rates. Accordingly, investigators from our group at The University of Arizona and in cooperation with investigators at Duke Medical School initiated animal studies that found that the optimal chest compression rates for survival from VF arrest were 80 to 120/min.⁶² Because a chest compression rate of 120/min

was thought to be too fatiguing for the general public, the 1992 AHA guidelines compromised and recommended rates of 80 to 100/min.²³ The Guidelines 2005 recommend a compression rate of 80 to 100/min. However, as noted above, a compression rate of 80/min is probably not adequate and the target rate should be 100/min.

Cardiopulmonary Resuscitation

Cardiopulmonary resuscitation has been defined as chest compression and assisted ventilations. CPR is indicated for respiratory arrest and appears to be critical in subjects after the complete loss of arterial pressure secondary to asphyxial cardiac arrest.⁶³ Ventilations or “rescue breathing” is considered important in cardiac arrest secondary to respiratory arrest where a respiratory problem initiated hypotension that caused the cardiac arrest and where VF or asystole is a relatively late event.⁶³

Unlike primary cardiac arrest due to sudden onset of VF or pulseless VT, cardiac arrest secondary to hypoxia is associated with severely abnormal arterial blood gases. The typical sequence for untreated respiratory arrest is hypoxia followed in several minutes of hypotension leading to hypoxic ischemia and finally cardiac arrest.⁶³

Treated early in this sequence, before hypotension ensues, the only intervention that is usually necessary is relieving the cause of the hypoxia. An example of asphyxial arrest is the so-called “café coronary,” where aspiration of a large piece of food obstructs the trachea. The Heimlich maneuver, or similar maneuver, to abruptly increase the intrathoracic pressure and cause a forceful expulsion of air from the lungs may be all that is needed to relieve an obstruction. Assisted ventilation may be all that is necessary in a patient with respiratory depression or respiratory arrest secondary to drug overdose or other causes of severe hypoxia before cardiac arrest has ensued.

Considerations in Resuscitation Research

Return of spontaneous circulation (ROSC), being alive at hospital admission, or being alive at some later designated time were all used previously as criteria for survival for out-of-hospital cardiac arrest. Most such “survivors” ultimately died before being discharged from the hospital, making these definitions objectionable. In addition, different definitions of survival made comparisons of different approaches to CPR difficult.

A more clinically relevant definition of “survival” has been introduced: neurologically normal survival at hospital discharge or at a specified time after discharge for humans, or neurologically intact survival at 24 or 48 hours for experimental animals. When definitions of survival such as neurologically normal or near normal are used, it is clear that survival rates for OHCA with cardiopulmonary resuscitation have been very low and, with the exceptions of early application of an AED, have remained stagnant over the last few decades.^{4,5}

Most survivors of OHCA are found in the subset of patients with a bystander-witnessed arrest and a shockable rhythm on arrival of EMS with a defibrillator. In this subset of patients, survival in 2002 in Los Angeles was 6%, survival from 1992 to 2002 in Tucson, Ariz., averaged 10%, survival in Tokyo was 11%, while in Rock and Walworth counties in Wisconsin during 2001-2004

it was 20%.^{5,20,28,64} These survival differences probably reflect differences in EMS response times.

Chest Compression Rates Correlate with Survival

Abella and associates reported that suboptimal compression rates during in-hospital cardiac arrest correlated with the poor ROSC.⁴⁴ Although survival rates were not reported, there would be no survival in those without ROSC. In this study, ROSC was significantly higher for patients receiving more than 87 compressions per minute than those receiving fewer than 72 compressions per minute.⁴⁴ In this in-hospital study, ventilations were given quickly by a second rescuer. In the out-of-hospital situation, where a single bystander is performing CPR, if every set of 15 compressions is interrupted for 14 to 16 seconds to deliver the recommended two ventilations, the individual will not receive enough chest compressions for ROSC. In fact, if every set of 30 compressions is interrupted 14 to 16 seconds for single bystander CPR, the delivered chest compressions would still fall short of the near 90 compressions needed for ROSC in this in-hospital population.

Mechanical Devices for Resuscitation

Mechanical Devices for Chest Compression

The major theoretical advantage of mechanical devices is that they should improve the quality of prolonged chest compression over manual techniques because manual resuscitation is susceptible to fatigue of the would-be rescuer. However, there are both real and theoretical disadvantages of these devices. The major disadvantage is the interruption of chest compressions necessary to place the device. Any significant interruption of chest compression during the circulatory phase of cardiac arrest is deleterious. Theoretical disadvantages include cost, additional interruptions of chest compression, and the possible tendency of EMS personnel to focus on the machine rather than the patient, and the potential adverse effects related to the type of chest compression. Finally, in the absence of active decompression, mechanical devices, like poorly controlled mechanical chest compressions, have the potential of limiting chest wall recoil. It is unclear to us whether such devices, in the absence of active decompression, optimally facilitate chest wall recoil.

Our view is that mechanical devices should not be used early in resuscitation efforts because they all delay or interrupt continuous chest compression, which is essential to optimal resuscitation. Like endotracheal intubation for assisted ventilation, with or without devices that decrease intrathoracic pressures with positive pressure ventilations, they may be indicated in patients who do not respond to the initial resuscitation attempts, but in whom there is a reasonable chance of survival with more prolonged aggressive therapy. However, more study is needed with these devices before they can be recommended.

Patients Often “Awake” With Good Resuscitation

In some cases of optimal CPR, either manual or with mechanical devices, the forward blood flow is so good that the patient awakes and sedation is necessary. This needs emphasis, as all too often when the patient begins moving, manual chest compressions are stopped until the patient becomes unresponsive—a procedure that should be deplored.

Postresuscitation Dysfunction

The major concern of aggressive management of a patient with cardiac arrest has always been that the patient will survive in a vegetative state with severe neurologic impairment from the global ischemia.

The best prognostic sign in cardiac arrest patients after ROSC is rapid regaining of consciousness. Often regaining of consciousness is a gradual process that may take days to evolve. There are, at present, no clinically relevant, reliable predictive tools that can be used in recently resuscitated, comatose patients to distinguish who will or will not wake up and be neurologically intact.

Although neurologic function after prolonged cardiac arrest is of major concern, there is almost always other organ dysfunction as well, a syndrome referred to as “postresuscitation disease.” This is a multiorgan pathophysiologic state that affects almost all body systems, but especially the cardiovascular, nervous, pulmonary, renal, and metabolic systems.⁶⁵ Postresuscitation disease has been postulated to consist of four different pathophysiologic mechanisms: (1) Perfusion failure consisting of multifocal no-reflow phenomenon; (2) reperfusion injuries from oxygen free radicals, invasion of inflammatory cells, defects in injured mitochondria, and trigger programmed cell death; (3) postanoxic viscera damage and dysfunction; and (4) blood derangement from stasis during the arrest.⁶⁵

Myocardial dysfunction after resuscitation from cardiac arrest has been described in both clinical studies and animal models. In a study of 165 patients who had ROSC after OHCA, 55% had hemodynamic instability requiring vasoactive drugs during the first 72 hours following resuscitation.⁶⁶ The left ventricular ejection fraction was found to be depressed in all patients. Of clinical import is the observation that hemodynamic instability was not predictive of neurologic outcome and myocardial dysfunction appeared to be reversed by 72 hours.⁶⁶

In animal models, the myocardial dysfunction has been shown to be related to the duration of arrest and resuscitation. Kern and associates noted progressive systolic and diastolic progressive dysfunction, but if the animals survived, these abnormalities spontaneously recovered.⁶⁷ In these animals, myocardial function could be improved with dobutamine but not with intra-aortic balloon counterpulsation.⁶⁷

Postresuscitation Care

Postresuscitation care includes therapeutic hypothermia, aggressive approach to performing percutaneous coronary intervention (PCI) even in the absence of ST segment changes on the electrocardiogram, and optimal management of hemodynamics, glucose and electrolytes, and ventilation (Fig. 52-7)

- Therapeutic hypothermia
- Aggressive PCI when indicated
- Hemodynamic control
- Ventilation control
- Glucose control

Figure 52-7. Formalized approach to postresuscitation hospital care. PCI, percutaneous coronary intervention.

Hypothermia Therapy

The most promising approach to resuscitated cardiac arrest patients in a coma is hypothermia.^{37,38} Hypothermia activates shivering, and in comatose patients post-cardiac arrest, shivering-produced thermogenesis is potentially deleterious. Uncontrolled hypothermia results in catecholamine release and vasoconstriction. Many of the early studies using moderate (28° C to 32° C) or severe (<28° C) hypothermia for cerebral protection had worse survival than normothermic controls. In contrast, therapeutic, controlled mild hypothermia (32° C to 34° C) has been shown to be beneficial for preserving cerebral function.

The modern era of postarrest hypothermia was ushered in by Peter Safer's group, which focused on mild hypothermia, (32° C to 34° C).⁶⁸ These studies set the stage for major clinical trials.

The International Liaison Committee on Resuscitation (ILCOR) issued an advisory statement in 2003 recommending "Unconscious adult patients with spontaneous circulation after OHCA should be cooled to 32° C to 34° C for 12 to 24 hours when the initial rhythm was ventricular fibrillation (VF). Such cooling may be beneficial for other rhythms or in-hospital cardiac arrest." Similar recommendations were echoed in the 2005 guidelines and by ILCOR.^{9,69}

The mechanism of action of hypothermia is unknown, but is thought to be related to its inhibitory effect on adverse enzymatic and chemical reactions that are initiated by the global ischemia. It is well known that cooling slows chemical reactions. It is therefore logical to assume that the sooner therapeutic cooling is begun the better.

There is evidence that cooling should be started by the paramedics in the field. Bernard and colleagues began cooling measures in 22 comatose patients following resuscitation from OHCA by a rapid infusion of 30 mL/kg of 4° C Ringer's lactate solution over 30 minutes.^{70,71} The Seattle CPR research group used a similar approach but used 4° C normal saline. Rapid infusion of 2 L of 4° C cold normal saline (20 to 30 minutes into a peripheral vein with a high-pressure bag) resulted in a mean temperature drop of 1.4° C 30 minutes after the initiation of the infusion.⁷² The rapid infusion of cold saline was not associated with clinically important changes in vital signs, electrolytes, arterial blood gases, or coagulation parameters. The initial mean left ventricular ejection fraction was 34%, and the infusion did not affect ejection fraction or increase central venous, pulmonary, or left atrial filling pressures as assessed by echocardiography.⁷² Following the infusion, passive cooling (fans, directed on the uncovered patient) was compared with active cooling (cooling blankets, neuromuscular blockade) to maintain mild hypothermia. This study showed that active cooling was necessary.⁷²

Because the management of such patients with hypothermia is complex, a team approach is essential. Hospitals with this interest and proven ability might rightfully be designated as "Cardiac Arrest Centers" much the same way that "Trauma Centers" are presently designated in the United States. There are efforts in Arizona to designate certain hospitals as "cardiac arrest hospitals."

Therapeutic hypothermia may be associated with hyperglycemia. Although control of blood glucose in the range of 80 to 110 mg/dL has not been specifically studied in postcardiac arrest patients, studies of patients with stroke or other serious cardiovascular conditions suggest that control of blood glucose is another important therapeutic goal. Attention to other details,

such as raising the head of the bed of the intubated comatose patient to decrease aspiration is important.

Ending Resuscitative Efforts

It is essential to determine and document the patient's resuscitation status soon after admission to the hospital. The cost of providing emergency medical service to victims in an OHCA is considerable. Given this fact, the cost benefit ratio might be examined. At one end of the spectrum of patients with OHCA are those in whom the arrest was not witnessed, or in whom the arrest was witnessed but no bystander resuscitation efforts were made, or for whom the arrival of those delivering emergency medical services was delayed. This subset of patients has little chance of survival. Studies have found that, if in addition, a defibrillator shock is not delivered or advised and there is no ROSC, almost no one lives. It has therefore been acknowledged by expert groups that there are some patients with little or no chance of survival for whom continued efforts at resuscitation in the field are perhaps not merited.

The AHA 2005 guidelines state that resuscitation efforts should be continued until "reliable criteria indicating irreversible death are present."⁹ This position leaves considerable latitude for the judgment of the medical personnel involved but is more difficult to apply uniformly in practice.

Techniques of Defibrillation

Contraindications

Defibrillation is contraindicated when the patient's desire not to be resuscitated has been clearly documented in the patient's medical record or other legal document, when continued resuscitation is determined to be futile by the treating physician, or in the extremely rare situation where there is danger to the rescuers because of the patient's location or environment.

Ventricular Fibrillation

Ventricular fibrillation results from the chaotic electrical excitation of the ventricles. Ventricular fibrillation is best explained by re-entrant depolarization initially in larger waves that then take circuitous routes and then often degenerate into smaller re-entry circuits. The hemodynamic consequence is the loss of coordinated contractions of the myocytes, resulting in the loss of the rhythmic contractile function of the ventricles so essential to life.

The larger the heart and the more diseased, the easier it is to fibrillate. Small hearts are difficult to fibrillate. It is difficult to kill a rodent by ventricular fibrillation because once the 60 Hz current is removed, the heart often returns to sinus rhythm. If a fibrillating heart of a larger animal is cut in two, both halves continue to fibrillate, but when cut again and again fibrillation stops when the remaining ventricular muscle size is too small to sustain the re-entrant circuits of ventricular fibrillation. These observations have immense clinical importance because cardiac arrest in neonates and children is most commonly due to asystole from respiratory arrest or prolonged periods of inadequate myocardial perfusion and not because of ventricular fibrillation. In contrast, the diseased, dilated, or hypertrophied adult heart is prone to ventricular fibrillation.

The electrocardiographic reflection of ventricular fibrillation is characteristically a chaotic irregular pattern that frequently



Figure 52-8. ECG tracing of ventricular fibrillation.

passes through but spends no time at the isoelectric point (Fig. 52-8). Although ventricular fibrillation is easy to recognize, in some subjects, in some leads, ventricular fibrillation can appear as a very fine ventricular fibrillation or even as a straight line.⁷³

Ventricular fibrillation is usually short-lived because the resulting fall in blood pressure and lack of myocardial perfusion causes the myocardium to use up its energy stores. The electrocardiographic VF wave form decreases in amplitude and becomes finer. However, if myocardial perfusion is maintained by the precordial compressions, VF duration is prolonged. The longest duration of ventricular fibrillation that we observed is 10 days. The patient was in our intensive care unit with an implanted left ventricular assist device when he developed VF. Several attempts at defibrillation were not successful, so the patient was left in ventricular fibrillation, his blood pressure being maintained by the left ventricular assist device. The patient could be seen in a chair reading the paper, with the electrocardiographic monitor showing ventricular fibrillation. His blood pressure was being maintained by the left ventricular assist device.

This observation is important because continuous chest compression in patients with ventricular fibrillation results in prolongation of VF, increasing the patient's chance of survival.

Electrical Defibrillation

Electrical defibrillation is accomplished by passing an adequate current density of appropriate waveform through the fibrillating myocardium. Since it takes a critical mass of muscle to sustain fibrillation, it is not necessary to defibrillate every myofibril. However it appears that most of the myocardial mass must be defibrillated.⁷⁴ This requires among other things appropriate electrode size and placement. The electrodes cannot be placed just anywhere on the chest. If the electrodes are too close together, the current tends to shunt between the electrodes and will not depolarize enough of the left ventricular mass (Fig. 52-9). For most emergency defibrillation, the recommended electrode position is anterior-apical. One paddle electrode is placed under the right clavicle just to the right of the sternum and the other just below the level of the left of the nipple in the anterior axillary line (Fig. 52-10).

Defibrillation Energy, Current, and Voltage

When one selects the strength of the shock for defibrillation, one selects an energy level in watt-seconds or joules. However, it is not the energy that defibrillates the patient. When the capacitor of the defibrillator discharges, the output can be measured in current and voltage. An analogy can be made with the cardiovascular system. When the heart ejects blood, the result can be measured in terms of blood flow and blood pressure. The current is analogous to the flow and the voltage to the pressure. When the defibrillator capacitor is charged, this

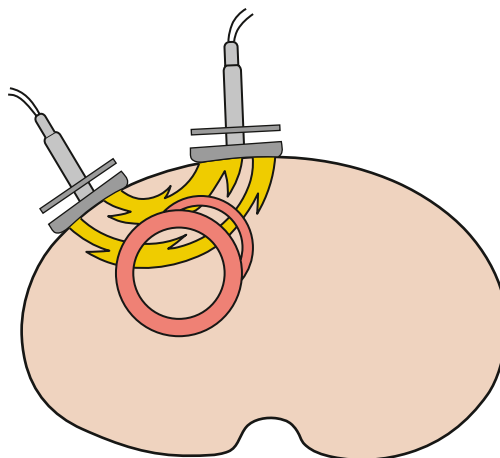


Figure 52-9. Improper electrode placement for defibrillation of ventricular fibrillation. If the electrodes are too close together, the current does not traverse enough of the left ventricle to defibrillate.

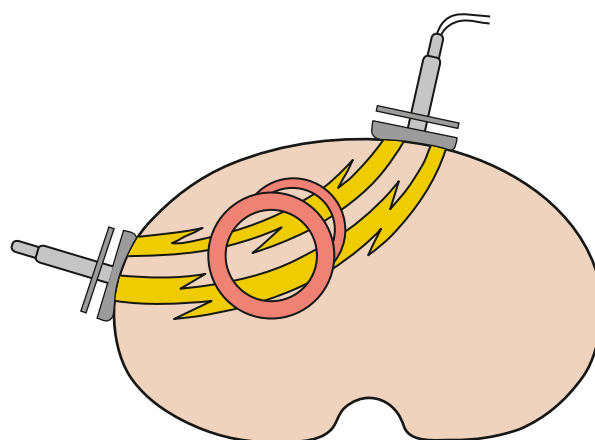


Figure 52-10. Proper electrode placement for defibrillation of ventricular fibrillation.

charge is measured in volts because there is no current flow. If, upon discharge, the voltage in volts is multiplied by the current in amperes, the result is expressed in watts. The watt is a unit of power. If this is done at each point along the discharged current and voltage wave, a power wave can be constructed (Fig. 52-11). When the area under the power wave is time-integrated in seconds, one derives energy measured in watt-seconds or joules. One watt-second is equal to one joule. Energy is the unit of strength that is indicated on defibrillators. As shown (Fig. 52-12), when the simultaneous current (I) and voltage (V) waves from a defibrillator, with the same stored energy, are delivered into 25, 50, and 75 ohms of resistance or impedance, the delivered peak current decreased with increasing resistance or impedance. Since it is the current that defibrillates, impedance or resistance is important. With constant energy selected, defibrillation effectiveness is related to the resistance between the defibrillator and the patient's heart. The lower the resistance or impedance, the higher the defibrillation success (Fig. 52-13). Impedance or resistance to defibrillation or cardioversion becomes critical to success.

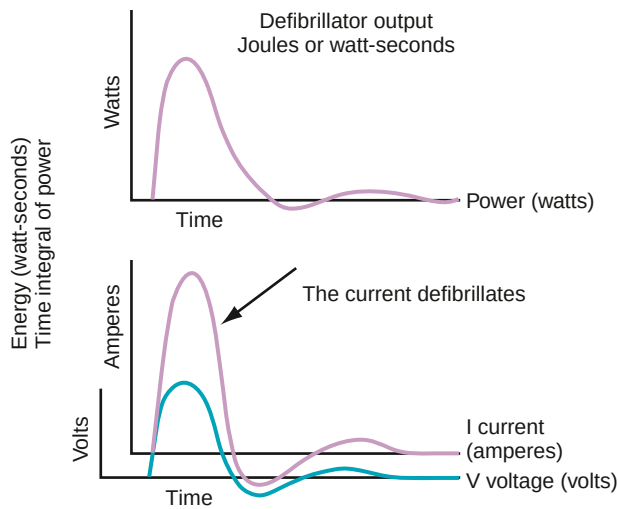


Figure 52-11. Current, voltage, and power waves of a defibrillator discharge delivering a damped half-sinusoidal waveform. Power equals the watts in amperes $\times$ the volts. Energy is the time integral of the power wave. The charge is the time integral of power. (From Ewy GA: *Cardiac arrest and resuscitation: defibrillators and defibrillation*. In: *Current Problems in Cardiology*, Vol 2, No. 2. Chicago, Year Book Medical Publishers, 1978.)

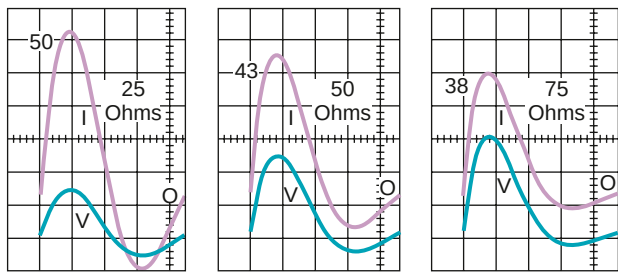


Figure 52-12. Improving effectiveness of defibrillator shock by reducing transthoracic impedance. Simultaneous voltage (V) and current (I) waveforms delivered from a direct current defibrillator with the same energy settings. The defibrillator was discharged into resistive (impedance) loads of 25 Ω , 50 Ω , and 75 Ω . The current decreases with increasing resistance.

Factors Determining Transthoracic Impedance

Transthoracic impedance varies widely among victims of cardiac arrest. Kerber and associates found that transthoracic impedance could range from 15 to 143 Ω , thereby varying by a factor of nearly 10.⁷⁵ The author measured transthoracic impedance during elective cardioversion. In these studies, the variation in transthoracic impedance to defibrillator discharge was not as large, and the mean transthoracic impedance was about 55 Ω .⁷⁶

The lower the impedance, the greater is the defibrillation success. There are several factors that influence transthoracic impedance or resistance of defibrillation discharge. One factor is the diameter of the electrode. As one increases the diameter of the electrodes, the impedance decreases and defibrillation success increases. In our laboratory cardiac arrest model this proved to be true. Standard 8 cm diameter paddles applied within the first minutes of ventricular fibrillation successfully defibrillated 71%. A larger paddle with a 12.8 cm diameter successfully defibrillated 88%.⁷⁷ Kerber showed lower impedance

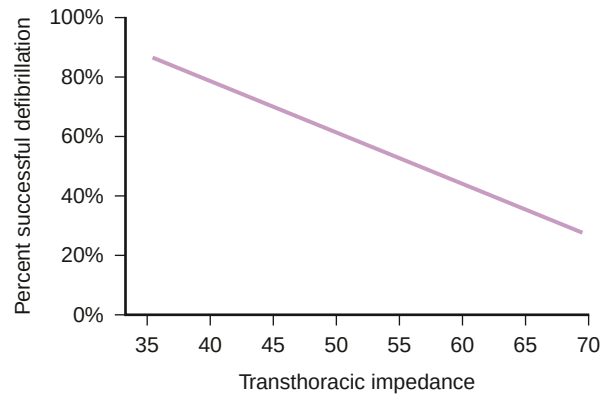


Figure 52-13. Relationship between defibrillation shock success and transthoracic impedance when shock strength is held constant. This observation shows that it is the delivered current and not the energy that defibrillates. (After Thomas ED, Ewy GA, Dahl CF, Ewy MD: *Effectiveness of direct current defibrillation: role of paddle electrode size*. *Am Heart J* 1977;93:463.)

with larger (13 cm) paddles in human defibrillation and, when coupled with firm pressure to the chest, better current delivery.⁷⁵ In very large electrodes (larger than those commercially available)—that is, much larger than the diameter of the heart—defibrillation success decreases, showing that in fact it is not current but current density through the heart that is the major factor in defibrillation.⁷⁷

A second factor known to effect transthoracic impedance, and thus defibrillation success, is the interface used between the skin of the chest wall and the electrode.⁷⁸ Impedance is relatively high if the electrodes are applied directly to the skin without some form of conductive medium. The impedance will drop by adding appropriate gels, pastes, or saline-soaked gauze pads.⁷⁸

We found a wide discrepancy in the impedance of commercially available creams, pastes, and gels. Of the 26 products tested, we found Hewlett Packard's Redux paste to have the lowest impedance.^{76,79-82} One should avoid gels that have not been shown to have a low resistance. For example, the gels used for echocardiography are very poor conductors of electricity and have very high impedance.

An alternative to paste and gels are self-adhesive electrodes. Self-adhesive disposable electrodes are effective for routine defibrillation and cardioversion, and provide an advantage in certain circumstances, such as in the electrophysiologic laboratory and in the transportation of the high-risk patient with cardiac disease, but because of their somewhat higher impedance they are, in our opinion, not optimal for cardioversion or defibrillation in patients with other factors that predispose to a higher transthoracic impedance to defibrillator discharge. This includes individuals with large and barrel-shaped chests. Other disadvantages include cost, and when purchased in quantity, the fact that they often become out-dated before their use.

Another determinant of transthoracic impedance to DC shock is the phase of respiration. Our laboratory found higher impedance and decreased defibrillation effectiveness when shocks are delivered at full inspiration compared with full expiration induced by firm pressure on the paddle electrodes.⁸¹ Likewise, defibrillation is rarely possible if there is a left-sided pneumothorax, one of the few indications for open-chest defibrillation.

Adequate pressure must be applied to the paddles to ensure a low impedance electrode thoracic interface. Typical recommendations are for application of at least a 25-pound pressure.⁷⁵ Self-adhesive electrode pads are said to have an advantage when applied before the need of defibrillation in high-risk patients, thereby ensuring correct positioning should defibrillation be required at a later time. Their disadvantage, however, is the lack of firm pressure and less than optimal impedance characteristics. If the initial shocks with self-adhesive pads are not successful in defibrillating a large individual, one should apply pressure over the chest electrode with a towel during the shock. This forces air from the lungs, decreasing resistance, and increases the chances of defibrillation success. There is no danger to the individual applying the pressure on the towel if that is all that is touched.

Other factors that have been shown to affect transthoracic impedance to defibrillation shocks include the number, strength, and time interval of previous shocks.^{75,83} Transthoracic impedance decreases with subsequent shocks. Kerber and associates found that for at least 1 month following open heart surgery, the transthoracic impedance remains lower.⁸⁴ The impedance is also higher with greater distance between the electrodes.

Defibrillation Waveforms

The first waveform used for ventricular defibrillation was the 60 Hz alternative current (AC) similar to that used as standard household current. AC current can be used to induce ventricular fibrillation and to defibrillate the heart. Because of myocardial damage from AC defibrillation, direct current (DC) units were developed. Initially, most defibrillators delivered monophasic waveforms. Biphasic waveforms are more effective than monophasic waveforms, and therefore all new defibrillators deliver biphasic waveforms. However, the monophasic defibrillators are effective, so there is no need to replace monophasic with biphasic defibrillators until monophasic replacement is necessary.¹² Experimental triphasic and even multiphasic defibrillators have been developed and are being evaluated.

Defibrillation Threshold

Irrespective of the theories of defibrillation, there is a defibrillation threshold. Shock strength below this threshold will not defibrillate. The shock strength must be above the defibrillation threshold to defibrillate. The defibrillation threshold is increased by some antiarrhythmic drugs. Those that have been shown to increase the defibrillation threshold include lidocaine and flecainide and perhaps high doses of the Class I antiarrhythmic drugs. If the patient has an implanted cardioverter-defibrillator (ICD), these drugs must be added to the medical regimen with caution and the ICD's defibrillation threshold rechecked once therapeutic drug levels have been obtained.

Larger patients have a higher defibrillation threshold, and as our population increases in size and weight, this may become a concern.

Shock Strength

Shock strength must be adequate for defibrillation.⁸⁵ Shocks of subthreshold strength are of insufficient strength to defibrillate. Shock strength in considerable excess of this threshold causes myocardial damage.^{86,87} Gettes and associates showed that over a wide range of body size, the smaller the animal the less energy is needed for defibrillation.⁸⁵ The larger the animal, the

higher the shock strength that is needed. Less energy is needed to defibrillate small children than is needed to defibrillate large adults.

Recurrent ventricular fibrillation may occur after successful defibrillation. In such circumstances, it is reasonable to use energy levels similar to those that were previously effective. Particularly in the cases where ventricular fibrillation reoccurs frequently, shock strength should be kept as low as effective to minimize myocardial damage. Myocardial injury associated with defibrillation corresponds not only with total joules used (energy), but also with the time interval between the defibrillation shocks.^{86,87}

Electrical Cardioversion of Atrial Arrhythmias

Atrial Fibrillation

Atrial fibrillation is the most common arrhythmia and its prevalence increases with age. Accordingly it has not only been called the *grandfather of arrhythmias*, but also the *arrhythmia of grandfathers*.

The major predisposing factors for atrial fibrillation are increasing age and left atrial enlargement. In the absence of valvular heart disease, left ventricular diastolic dysfunction is a major predisposing cause of left atrial enlargement. In fact it has been said that left atrial size is to diastolic function as left ventricular ejection fraction is to systolic function. The aging of our population and the increased incidence of hypertension are two major causes of left ventricular diastolic dysfunction.

Atrial fibrillation is undesirable for a number of reasons. It is a major cause of thromboembolism and it results in a decreased contribution of atrial filling to ventricular function. A rapid ventricular response rate may cause symptoms and if prolonged may produce the myopathy of tachycardia. The major therapeutic intervention should be anticoagulation, even if the atrial rhythm is paroxysmal or if the rhythm is atrial flutter.

Who Should Be Cardioverted?

The theory of cardioversion, as Lown stated decades ago, is that the sustaining mechanism is different from the initiating mechanism.⁸⁸ Therefore, it is not logical to perform cardioversion in someone in whom the initiating mechanism for the atrial fibrillation or flutter is still present. Accordingly, successful cardioversion is not the only goal. Almost everyone can be cardioverted, but some for only one beat, some for several beats, and others for short periods of time. The goal is to select the patient in whom the initiating mechanism has been eliminated or mitigated. If the initiating mechanism is still present and cannot be corrected, the clinical decision is simple: the patient must be managed with rate control.

Accordingly, an important question the physician has when confronted with a patient with atrial fibrillation is: rhythm control (cardioversion) or rate control? Since it is often difficult to determine if the initiating mechanism for atrial fibrillation is still present, both approaches may appear to be logical. In the past the approach has usually been rhythm control with chemical or electrical cardioversion. This approach was used in the belief that rhythm control was associated with better survival, fewer symptoms, better exercise tolerance, lower risk of stroke, better quality of life, and the absence of the need for long-term

anticoagulation. However, several clinical trials comparing rate control with rhythm control have failed to demonstrate these advantages.⁸⁹⁻⁹⁴

If rhythm control, should this be done with direct current cardioversion, medications, ablation techniques, or both? A discussion of medications and the ablation techniques is beyond the scope of this chapter. However, the reported marked improvement in the left ventricular ejection fraction with ablation of atrial fibrillation in patients with congestive heart failure suggests that in many patients with atrial fibrillation and a decreased left ventricular ejection fraction, the myopathy of tachycardia is a contributor to this dysfunction.⁹⁵

Rate Control or Rhythm Control

Should atrial fibrillation be treated with rate control or rhythm control? If rate control, the most effective therapy appears to be the combination of digoxin and a β -adrenergic blocker.⁸⁹ If, however, the patient has asthma or other contraindications to β -blockers, the combination of diltiazem and digoxin or verapamil and digoxin could be considered.⁸⁹ Digoxin should be given during the evening or at bedtime so that when one measures the digoxin level in the morning, there has been appropriate time for blood tissue equilibration. The most common cause of an elevated serum digoxin level is that the blood was obtained within 6 or so hours of digoxin dosing. Although possible, rhythm control should not be accomplished with toxic doses of digoxin.

For rhythm control the major question is whether the patient has heart disease. If no or minimal heart disease, propafenone, sotalol, or flecainide should be considered first. If these drugs are not effective, consideration should be given to amiodarone. If these drugs are not effective, consideration might be given to nonpharmacologic options.⁹⁶ If heart disease is present, the type often determines the initial choice of medical therapy. For patients with heart failure, once the patient is compensated, the drugs of choice are amiodarone and β -adrenergic blockers. If ischemic heart disease is present, the initial drug might be sotalol, followed by amiodarone, and perhaps quinidine.⁹⁶ If hypertension is present with marked (greater than 1.4 cm) left ventricular hypertrophy, a reasonable choice is amiodarone, and if less than 1.4 cm, flecainide or propafenone, and if these fail, amiodarone.⁹⁶

Electrical Cardioversion of Atrial Fibrillation or Flutter

Essential to successful cardioversion of atrial fibrillation or flutter is the fact that it requires the delivery of adequate current density through the fibrillating or fluttering chambers. In the case of atrial fibrillation or flutter the affected chambers are the atria. The same considerations of electrode size and transthoracic impedance apply for cardioversion as for defibrillation. However, electrode positioning should be significantly different for atrial cardioversion than for ventricular defibrillation since the goal is to pass the current through the atria rather than the ventricles. The shock must be synchronized with the intrinsic electrical activity of the ventricles by sensing the R wave of the ECG to ensure that the electrical shock does not occur during the vulnerable phase of the cardiac cycle.⁸⁸

Electrode Positions

Electrode position is often decisive since the current must traverse a critical mass of the atrial muscle for cardioversion to occur. Lown reported that the anterior-posterior electrode

position was more effective for cardioversion of atrial fibrillation than the anterior-anterior electrode position.^{88,97} Lown wrote, "The anterior paddle is held with pressure over the upper sternum at the level of the third intercostal space. . . . This anterior-posterior position, compared with the previously employed anterior-lateral placement, shortens the pathway between the electrodes and augments the density of the electrical field which traverses the heart, thereby diminishing by about 50% the energy required for reversion."⁹⁸ In contrast, Kerber and associates reported that the electrode position or size made little difference to cardioversion success.⁹⁹ However, in Kerber's study the 111 patients with atrial fibrillation were divided into four groups, each with high success rates, making a statistical β -error so likely that the study is not definitive.⁹⁹

Analysis of CT scans of the thorax at the level of the heart provides insight into appropriate electrode positions for defibrillation of the atria. For successful cardioversion the current vector must traverse a critical mass of the atrial muscle. The anterior-posterior positions fulfill these criteria the best. The right anterior-left posterior position or Lown's sternal-posterior are the position of choice if the pathology involves both atria (i.e., atrial fibrillation due to atrial septal defect or diffuse cardiomyopathy). This position has more of the right atria between the electrodes. The anterior-anterior electrode or the apical-left posterior positions are at times effective but are not recommended for elective electrical cardioversion of atrial fibrillation because these positions probably do not provide optimal current flow through the atria.

Predictors of Long-Term Cardioversion Success

Lown's initial enthusiasm for elective cardioversion of all patients in atrial fibrillation was dampened by the high recurrence rate in some subsets of patients. As Lown emphasized, often the initiating mechanism and the sustaining mechanism of atrial fibrillation were different.⁸⁸ If the initiating mechanism was no longer present, then cardioversion would have lasting success. If, however, the initiating mechanism was still present, atrial fibrillation would recur. Such patients are not suitable candidates for cardioversion. Untreated thyrotoxicosis, significant untreated mitral valve disease, and congestive heart failure are obvious examples of situations where the initiating mechanism is still present. Atrial fibrillation of more than 1 year's duration, first degree heart block greater than 0.24 second before the onset of atrial fibrillation, and significant left atrial enlargement are markers that the initiating pathology is still present, since these factors predict early recurrence.

Anticoagulation before Elective Cardioversion

Hemodynamically unstable patients or patients with marked ischemia secondary to recent-onset atrial fibrillation may need urgent cardioversion. In this setting there may be no time for anticoagulation.

Patients should be anticoagulated before elective cardioversion if at all possible. The landmark study of Bjerkelund and Orning was not randomized since all patients admitted on oral anticoagulation, including all patients with previous emboli, were placed in the anticoagulated group.¹⁰⁰ The incidence of postcardioversion emboli was 5.3% in the group not anticoagulated and 0.8% in the anticoagulated group.¹⁰⁰ Based on this study, most physicians have routinely anticoagulated patients before pharmacologic or electrical cardioversion. Anticoagulation is just as

important in patients with atrial flutter as in those with atrial fibrillation.

For elective cardioversion without transesophageal evaluation before elective cardioversion, the patient's INR/PT should be in therapeutic range for 3 months.

Heparin anticoagulation is recommended for patients undergoing earlier cardioversion, even when transesophageal echocardiograms do not reveal evidence of left atrial or left atrial appendage clot because the shock itself may result in atrial stunning and possible clot formation. The shock itself results in atrial stunning and blood stasis for some period of time that evidently predisposes to clot formation.

Another issue concerning the timing of elective cardioversion is the effect of the duration of atrial fibrillation on the time of the return of atrial contractile function following cardioversion. The longer the duration of atrial fibrillation, the longer it takes for normal atrial contractile function to return.⁸⁹ Manning and associates found in patients with relative brief duration of atrial fibrillation (less than 6 weeks) a near complete return of atrial function within 1 week of restoration of sinus rhythm. This fact would argue in favor of a transesophageal echocardiographic evaluation of patients with documented recent onset atrial fibrillation, with the possibility of 2 days of intravenous heparin therapy, followed by cardioversion. If pharmacologic therapy did not result in cardioversion, one could proceed with electrical cardioversion. At the same time the heparin is initiated, the patient is started on oral anticoagulation.

For a number of reasons, including the difficulty in determining the duration of atrial fibrillation, most patients with atrial fibrillation may require a different approach. If the patient is hemodynamically stable and hospitalization is not required for some other reason, the patient may receive oral anticoagulant therapy with warfarin for 3 months before elective outpatient cardioversion. If hospitalization is necessary for other reasons, and cardioversion is necessary, transesophageal echocardiography to rule out intra-atrial thrombi followed by 2 days of heparin therapy prior and 1 day of heparin therapy postcardioversion is recommended.⁸⁹

Our practice is to keep patients on chronic oral anticoagulation therapy for 6 months after cardioversion because of the high recurrence rate during this time. If they have no other reason for chronic anticoagulation, we obtain an ambulatory electrocardiography monitor because many patients go in and out of atrial fibrillation and are not aware of the rhythm change. Twenty-four hour monitoring is not enough to ensure that patients do not have intermittent atrial fibrillation, but longer durations of monitoring are presently not economically feasible.

Role of Antiarrhythmic Therapy before Electrical Cardioversion

Lown instituted quinidine therapy 1 or more days before attempted electrical reversion, stating that quinidine: (1) improved the chance of the patient remaining in normal sinus rhythm immediately after cardioversion, (2) decreases by about 40% the energy required, (3) diminishes the incidence of post-cardioversion arrhythmias, and (4) to "obtain a small dividend of repeat cardioversions which results in about 10% of patients."⁹⁸ Quinidine is seldom used now, but if one prescribes quinidine, the digoxin dose should be held or halved because quinidine doubles the serum digoxin level. Now, the drugs of choice are amiodarone, flecainide, and propafenone. Amiodarone is not a

very effective drug for cardioversion, but it is an effective drug for maintenance of sinus rhythm postcardioversion. Its selection for use, however, must be balanced against its many adverse side effects and reactions.

Flecainide in low doses (50 mg twice a day) is often prescribed for 2 to 3 days, followed by 100 mg flecainide twice a day for 3 days before elective cardioversion in patients without ischemic heart disease. Electrocardiographic monitoring is critical if flecainide is used to ensure the patient does not develop the electrocardiographic signs of Brugada syndrome on flecainide. Other commonly used antiarrhythmic drugs include propafenone and sotalol. A safer precardioversion drug is sotalol, but it is less likely to be effective.⁹⁶

Shock Strength

If biphasic units are used for the cardioversion, the initial dose should be 150 J. The strength of the initial shock for cardioversion of atrial fibrillation with monophasic defibrillators should be 200 J (stored energy) since only 50% of patients will be successfully cardioverted with 100 J.⁷⁶ About 85% of those who will electrically convert will do so at 200 J.⁹⁸ The next shock should be 360 J since almost all patients who will convert electrically via the external technique will do so at the maximum setting.⁹⁸ If the first 360 J shock is not successful, one should assess electrode position. If the electrode positions are to be unchanged, one should wait a full 3 minutes before delivering a final 360 J shock.¹⁰¹ This 3-minute wait allows a greater decrease in transthoracic impedance from the previous DC shock than will occur with shocks delivered at 15-second or 1-minute intervals. In addition, a number of patients will not revert to sinus rhythm immediately after the shock but will do so a few seconds or minutes later.¹⁰¹ This phenomenon is thought to represent depolarization of a major portion but not all of the atrium. The remaining rhythm does not have a large enough area for continued re-entry and dies out. This "delayed" cardioversion is thought to occur in about 4% of electrical cardioversions.¹⁰¹

Does Electrode Type Make a Difference?

The electrode type does make a difference. Based on our animal research and measurement of transthoracic impedance during elective cardioversion, we have long recommended the use of hand-held paddle (Fig. 52-14) electrodes for external



Figure 52-14. Anterior-posterior metal electrodes for cardioversion of atrial arrhythmias.

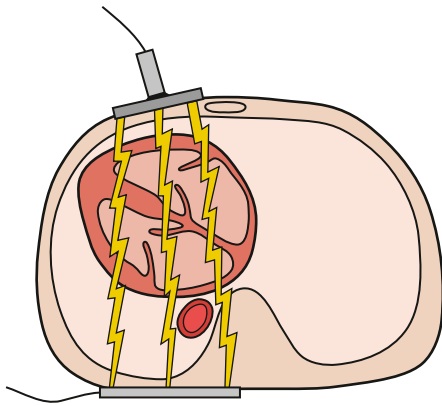


Figure 52-15. Proper electrode placement for electrical cardioversion of atrial fibrillation.

cardioversion of atrial fibrillation.^{76,78,80,81,101-105} Recently a study by Kirchhof and associates confirmed that the use of reusable hand-held steel paddle electrodes, including a back paddle electrode instead of adhesive gel-covered patch electrodes, improved cardioversion success.¹⁰⁶ They noted that the increase in effectiveness was similar in magnitude to the increase in cardioversion success achieved with biphasic shocks.¹⁰⁶ They concluded that the combination of biphasic shocks, paddle electrodes, and an anterior-posterior position (Fig. 52-15) renders outcome of external cardioversion almost always successful.¹⁰⁶ In their study, this technique resulted in successful cardioversion 100% of the time in the 104 patients reported.¹⁰⁶

Summary

The optimal approach to electrical cardioversion includes appropriate patient selection, anticoagulation, careful selection and monitoring of antiarrhythmic therapy, and proper electrical cardioversion technique. The optimal technique is one that uses metal electrodes with one electrode at least 8 cm in diameter placed over the sternum or in the left parasternal anterior position. The second 12.8-cm diameter metal electrode is placed on the back just below the left scapulae, with generous amounts of the appropriate low impedance gel (such as Hewlett-Packard Redux Paste) as the electrode-skin interface. Firm pressure to the paddle electrode is applied with the patient in the expiratory phase of ventilation, thus decreasing the anterior-posterior chest diameter and ensuring less air between the electrodes.

Electrode pads are commonly used and work most of the time, but in larger adults, optimal techniques are necessary. This may include applying pressure with a folded towel over the anterior electrode, decreasing the anterior-posterior diameter of the chest, and decreasing the amount of air between the electrodes. Appropriate energy is selected. The shock is synchronized with the electrocardiographic QRS complex.

Conclusion

Book chapters are useful to gain a basic knowledge of a subject. However, it is important to stress that medicine is a rapidly evolving discipline and recommendations will certainly change as the profession learns more about problems and new approaches and new forms of therapy become available.

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American College of Cardiology/ American Heart Association Management Guidelines

Dileep Menon, Allen Jeremias

APPENDICES

Color Key to ACC/AHA Management Guidelines: Estimate of Certainty (Precision) of Treatment Effect

APPENDIX

1

	Size of Treatment Effect		
	Level A	Level B	Level C
	Multiple (3-5) population risk strata evaluated; general consistency of direction and magnitude of effect	Limited (2-3) population risk strata evaluated	Very limited (1-2) population risk strata evaluated
Class I Benefit >>> risk Procedure/treatment <i>should</i> be performed/administered	Recommendation that procedure or treatment is useful/effective Sufficient evidence from multiple randomized trials or meta-analyses	Recommendation that procedure or treatment is useful/effective Limited evidence from single randomized trial or nonrandomized studies	Recommendation that procedure or treatment is useful/effective Only expert opinions, case studies, or standard-of-care
Class IIA Benefit >> risk Additional studies with focused objectives needed <i>It is reasonable</i> to perform procedure/administer treatment	Recommendation in favor of treatment or procedure being useful/effective Some conflicting evidence from multiple randomized trials or meta-analyses	Recommendation in favor of treatment or procedure being useful/effective Some conflicting evidence from single randomized trial or nonrandomized studies	Recommendation in favor of treatment or procedure being useful/effective Only diverging expert opinion, case studies, or standard-of-care

(Continued)

<i>Size of Treatment Effect—cont'd</i>			
	Level A <i>Multiple (3-5) population risk strata evaluated; general consistency of direction and magnitude of effect</i>	Level B <i>Limited (2-3) population risk strata evaluated</i>	Level C <i>Very limited (1-2) population risk strata evaluated</i>
Class IIB Benefit $\geq$ risk Additional studies with broad objectives needed; additional registry data would be helpful Procedure/treatment <i>may be considered</i>	Recommendation's usefulness/efficacy less well established Greater conflicting evidence from multiple randomized trials or meta-analyses	Recommendation's usefulness/efficacy less well established Greater conflicting evidence from single randomized trial or nonrandomized studies	Recommendation's usefulness/efficacy less well established Only diverging expert opinion, case studies, or standard-of-care
Class III Risk $\geq$ benefit No additional studies needed Procedure/treatment should <i>not</i> be performed/administered <i>because it is not helpful and may be harmful</i>	Recommendation that procedure or treatment is not useful/effective and may be harmful Sufficient evidence from multiple randomized trials or meta-analyses	Recommendation that procedure or treatment is not useful/effective and may be harmful Limited evidence from single randomized trial or nonrandomized studies	Recommendation that procedure or treatment is not useful/effective and may be harmful Only expert opinion, case studies, or standard-of-care

ACC/AHA Guidelines for Primary Percutaneous Coronary Intervention of ST Segment Elevation Acute Myocardial Infarction

APPENDIX

2

	A	B	C
Class I	STEMI or MI with new-onset LBBB and <12 hr since onset or >12 hr with persistent ischemic symptoms if performed in a timely fashion (door-to-balloon time <90 min) by operators skilled in the procedure* and performed in a PCI skilled facility† Primary PCI should be performed for patients <75 yr old with STEMI or LBBB who develop shock within 36 hr of MI, and are suitable for revascularization that can be performed within 18 hr of shock	Primary PCI should be performed as quickly as possible, with the goal of a door-to-balloon time of <90 min Symptom onset <3 hr and the expected door-to-balloon time minus the expected door-to-needle is: (a) <1 hr—PCI preferred; (b) >1 hr—fibrinolytic therapy (fibrin-specific agents) Symptom onset >3 hr, primary PCI should be performed with a door-to-balloon time as brief as possible (<90 min) Primary PCI should be performed in patients with severe congestive heart failure or pulmonary edema or both and onset of symptoms <12 hr with a door-to-balloon time as brief as possible (<90 min)	
Class IIa		Primary PCI is reasonable for selected patients >75 yr old with STEMI or LBBB who develop shock within 36 hr of MI, and are suitable for revascularization that can be performed within 18 hr of shock	Primary PCI may be reasonable for patients with onset of symptoms within the prior 12-24 hr and one or more of the following: (a) severe congestive heart failure; (b) hemodynamic or electrical instability; (c) persistent ischemic symptoms
Class IIb			Primary PCI for STEMI patients eligible for fibrinolysis is not well established when performed by an operator who performs <75 PCI procedures/yr
Class III			Primary PCI should not be performed in a noninfarct artery in patients without hemodynamic compromise Primary PCI should not be performed in asymptomatic patients >12 hr after onset of STEMI if they are hemodynamically and electrically stable

LBBB, left bundle branch block; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST segment elevation myocardial infarction.

*Individuals who perform >75 PCI procedures/year.

†Performs >200 PCI procedures/year of which at least 36 are primary PCI for STEMI and has cardiac surgery capability.

ACC/AHA Guidelines for Early Hospital Care of Patients with Unstable Angina/Non–ST Segment Elevation Myocardial Infarction

APPENDIX

3

A. Anti-Ischemic and Analgesic Therapy

	A	B	C
Class I	ACE inhibitor should be administered orally within the first 24 hr to UA/NSTEMI patients with pulmonary congestion or LVEF $\leq 40\%$, in the absence of hypotension (SBP < 100 mm Hg or < 30 mm Hg below baseline) or known contraindications to that class of medications Angiotensin receptor blocker should be administered to UA/NSTEMI patients who are intolerant of ACE inhibitors and have either clinical or radiologic signs of HF or LVEF $\leq 40\%$	Intravenous NTG is indicated in the first 48 hr after UA/NSTEMI for treatment of persistent ischemia, HF, or hypertension Oral β-blocker therapy should be initiated within the first 24 hr for patients who do not have one or more of the following: (1) signs of HF; (2) evidence of a low-output state; (3) increased risk for cardiogenic shock; or (4) other relative contraindications to β-blockade (P–R interval > 240 ms, second-degree or third-degree AV block, active asthma, or reactive airway disease) In UA/NSTEMI patients with continuing or frequently recurring ischemia and in whom β-blockers are contraindicated, a nondihydropyridine calcium channel blocker (e.g., verapamil or diltiazem) should be given as initial therapy in the absence of clinically significant left ventricular dysfunction or other contraindications	Patients with UA/NSTEMI with ongoing ischemic discomfort should receive sublingual NTG (0.4 mg) every 5 min for a total of 3 doses, after which assessment should be made about the need for intravenous NTG, if not contraindicated Because of the increased risks of mortality, reinfarction, hypertension, HF, and myocardial rupture associated with their use, NSAIDs except for ASA, whether nonselective or COX-2 selective agents, should be discontinued at the time a patient presents with UA/NSTEMI
Class IIa		In the absence of contraindications to its use, it is reasonable to administer morphine sulfate intravenously to UA/NSTEMI patients if there is uncontrolled ischemic chest discomfort despite NTG, provided that additional therapy is used to manage the underlying ischemia	Intra-aortic balloon pump counterpulsation is reasonable in UA/NSTEMI patients for severe ischemia that is continuing or recurs frequently despite intensive medical therapy, for hemodynamic instability in patients before or after coronary angiography, and for mechanical complications of MI

A. Anti-Ischemic and Analgesic Therapy—cont'd

	A	B	C
Class IIb		It is reasonable to administer intravenous β-blockers at the time of presentation for hypertension to UA/NSTEMI patients who do not have one or more of the following: (1) signs of HF; (2) evidence of a low-output state; (3) increased risk for cardiogenic shock; or (4) other relative contraindications to β-blockade (P–R interval >240 ms, second-degree or third-degree AV block, active asthma, or reactive airway disease) Use of extended-release forms of nondihydropyridine calcium antagonists instead of a β-blocker may be considered in patients with UA/NSTEMI Immediate-release dihydropyridine calcium antagonists in the presence of adequate β-blockade may be considered in patients with UA/NSTEMI with ongoing ischemic symptoms or hypertension	
Class III	Immediate-release dihydropyridine calcium antagonists should not be administered to patients with UA/NSTEMI in the absence of a β-blocker It may be harmful to administer intravenous β-blockers to UA/NSTEMI patients who have contraindications to β-blockade, signs of HF or low-output state, or other risk factors for cardiogenic shock (age >70 yr, SBP <120 mm Hg, sinus tachycardia >110 beats/min or heart rate <60 beats/min, increased time since onset of symptoms of UA/NSTEMI)	Intravenous ACE inhibitor should not be given to patients within the first 24 hr of UA/NSTEMI because of the increased risk of hypotension (a possible exception may be patients with refractory hypertension)	Nitrate should not be administered to UA/NSTEMI patients with SBP <90 mm Hg, severe bradycardia (<50 beats/min), tachycardia (>100 beats/min) in the absence of symptomatic HF, or right ventricular infarction Nitrates should not be administered to patients with UA/NSTEMI who had received a phosphodiesterase inhibitor for erectile dysfunction within 24 hr of sildenafil or 48 hr of tadalafil use NSAIDs (except for ASA), whether nonselective or COX-2 selective agents, should not be administered during hospitalization for UA/NSTEMI because of the increased risks of mortality, reinfarction, hypertension, HF, and myocardial rupture associated with their use

B. Antiplatelet Therapy

	A	B	C
Class I	ASA should be administered to UA/NSTEMI patients as soon as possible after hospital presentation and continued indefinitely in patients not known to be intolerant to that medication Clopidogrel (loading dose followed by daily maintenance dose) should be administered to UA/NSTEMI patients who are unable to take ASA because of hypersensitivity or major GI intolerance In UA/NSTEMI patients in whom an initial invasive strategy is selected, antiplatelet therapy in addition to ASA should be initiated before diagnostic angiography (upstream) with either clopidogrel or an intravenous GP IIb/IIIa inhibitor For UA/NSTEMI patients in whom an initial conservative strategy is selected, clopidogrel (loading dose followed by daily maintenance dose) should be added to ASA and anticoagulant therapy as soon as possible after admission and administered for at least 1 mo	In UA/NSTEMI patients with a history of GI bleeding when ASA and clopidogrel are administered alone or in combination, drugs to minimize the risk of recurrent GI bleeding (e.g., proton pump inhibitors) should be prescribed concomitantly Abciximab as the choice for upstream GP IIb/IIIa therapy is indicated only if there is no appreciable delay to angiography, and PCI is likely to be performed; otherwise, intravenous eptifibatide or tirofiban is the preferred choice of GP IIb/IIIa inhibitor	
Class IIa		For UA/NSTEMI patients in whom an initial invasive strategy is selected, it is reasonable to initiate antiplatelet therapy with clopidogrel and an intravenous GP IIb/IIIa inhibitor Abciximab as the choice for upstream GP IIb/IIIa therapy is indicated only if there is no appreciable delay to angiography, and PCI is likely to be performed; otherwise, intravenous eptifibatide or tirofiban is the preferred choice of GP IIb/IIIa inhibitor	For UA/NSTEMI patients in whom an initial conservative strategy is selected and who have recurrent ischemic discomfort with clopidogrel, ASA, and anticoagulant therapy, it is reasonable to add a GP IIb/IIIa antagonist before diagnostic angiography
Class IIb		For UA/NSTEMI patients in whom an initial conservative strategy is selected, it may be reasonable to add eptifibatide or tirofiban to anticoagulant and oral antiplatelet therapy	
Class III	Abciximab should not be administered to patients in whom PCI is not planned		

C. Anticoagulant Therapy

	A	B	C
Class I	For patients in whom an invasive strategy is selected, regimens with established efficacy including enoxaparin or UFH should be added to antiplatelet therapy in UA/NSTEMI patients as soon as possible after presentation For patients in whom a conservative strategy is selected, regimens using either enoxaparin or UFH have established efficacy	In patients in whom a conservative strategy is selected and who have an increased risk of bleeding, fondaparinux is preferable	
Class IIa		For UA/NSTEMI patients in whom an initial conservative strategy is selected, enoxaparin or fondaparinux is preferable to UFH as anticoagulant therapy, unless CABG surgery is planned within 24 hr	

ACE, angiotensin-converting enzyme; ASA, acetylsalicylic acid; AV, atrioventricular; CABG, coronary artery bypass graft; COX, cyclooxygenase; GI, gastrointestinal; GP, glycoprotein; HF, heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSAIDs, nonsteroidal anti-inflammatory drugs; NTG, nitroglycerin; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; UA/NSTEMI, unstable angina/non–ST segment elevation myocardial infarction; UFH, unfractionated heparin.

ACC/AHA Guidelines for the Management of Chronic Heart Failure

APPENDIX

4

A. Patients at High Risk for Developing Heart Failure (Stage A)

	A	B	C
Class I	In patients at high risk for developing HF, systolic and diastolic hypertension and lipid disorders should be treated in accordance with contemporary guidelines	Ventricular rate should be controlled or sinus rhythm restored in patients with supraventricular tachyarrhythmias who are at risk for developing HF	For patients with diabetes mellitus, blood glucose should be controlled in accordance with contemporary guidelines Left ventricular function should be assessed in patients with a strong family history of cardiomyopathy or in patients receiving cardiotoxic interventions
Class IIa	ACE inhibitors can be useful in preventing HF in patients with a history of atherosclerotic vascular disease, diabetes mellitus, or hypertension with associated cardiovascular risk factors		ARB can be useful to prevent HF in patients with a history of atherosclerotic vascular disease, diabetes mellitus, or hypertension with associated cardiovascular risk factors
Class III			Routine use of nutritional supplements solely to prevent the development of structural heart disease should not be recommended for patients at high risk for developing HF

B. Patients with Cardiac Structural Abnormalities or Remodeling Who Have Not Developed Heart Failure Symptoms (Stage B)

	A	B	C
Class I	β -blockers and ACE inhibitors should be used in all patients with a recent or remote history of MI regardless of ejection fraction or presence of HF ACE inhibitors should be used in patients with a reduced ejection fraction and no symptoms of HF, even if they have not experienced MI	ARBs should be administered to post-MI patients without HF who are intolerant of ACE inhibitors and have a low LVEF	β -blockers are indicated in all patients without a history of MI who have reduced LVEF with no HF symptoms
Class IIa		ACE inhibitors or ARBs can be beneficial in patients with hypertension and left ventricular hypertrophy with no symptoms of HF ICD is reasonable in patients with ischemic cardiomyopathy who are at least 40 days post-MI, have an LVEF of $\leq 30\%$, are NYHA class I on long-term optimal medical therapy, and have reasonable expectation of survival with a good functional status of >1 yr	ARBs can be beneficial in patients with low ejection fraction and no symptoms of HF who are intolerant of ACE inhibitors

B. Patients with Cardiac Structural Abnormalities or Remodeling Who Have Not Developed Heart Failure Symptoms (Stage B)—cont'd

	A	B	C
Class IIb		ICD might be considered in patients without HF who have nonischemic cardiomyopathy and LVEF $\leq 30\%$ who are in NYHA class I with long-term optimal medical therapy, and who have a reasonable expectation of survival with good functional status of >1 yr	
Class III			Digoxin should not be used in patients with low ejection fraction, sinus rhythm, and no history of HF symptoms Calcium channel blockers with negative inotropic effects may be harmful in asymptomatic patients with low LVEF and no symptoms of HF after MI

C. Patients with Current or Prior Symptoms of Heart Failure (Stage C)

	A	B	C
Class I	ACE inhibitors are recommended for all patients with current or prior symptoms of HF and reduced LVEF unless contraindicated β-blockers (i.e., bisoprolol, carvedilol, and sustained-release metoprolol succinate) are recommended for all stable patients with current or prior symptoms of HF and reduced LVEF unless contraindicated ARBs (candesartan, losartan, and valsartan) are approved for the treatment of HF in patients with current or prior symptoms of HF and reduced LVEF who are intolerant of ACE inhibitors ICD is recommended as secondary prevention to prolong survival in patients with current or prior symptoms of HF and reduced LVEF who have a history of cardiac arrest, ventricular fibrillation, or hemodynamically destabilizing ventricular tachycardia ICD is recommended for primary prevention to reduce total mortality in patients with ischemic heart disease who are at least 40 days post-MI, have an LVEF $\leq 30\%$ with NYHA class II or III symptoms while receiving long-term optimal medical therapy, and have reasonable expectation of survival with a good functional status for >1 yr	Addition of an aldosterone antagonist is recommended in patients with moderately severe to severe symptoms of HF and reduced LVEF who can be carefully monitored for preserved renal function and normal potassium concentration	Diuretics and salt restriction are indicated in patients with current or prior symptoms of HF and reduced LVEF who have evidence of fluid retention

(Continued)

C. Patients with Current or Prior Symptoms of Heart Failure (Stage C)—cont'd

	A	B	C
	ICD is recommended in patients with nonischemic cardiomyopathy who have an LVEF $\leq 30\%$, with NYHA class II or III symptoms while receiving long-term optimal medical therapy, and have reasonable expectation of survival with a good functional status for >1 yr Cardiac resynchronization therapy is recommended in patients with LVEF $\leq 35\%$, sinus rhythm, and NYHA class III or IV despite optimal medical therapy and who have QRS duration >120 ms		
Class IIa	ARBs are an alternative to ACE inhibitors in patients with mild to moderate HF and reduced LVEF	Digoxin can be beneficial in patients with current or prior symptoms of HF and reduced LVEF to decrease hospitalizations for HF Hydralazine and nitrate can be added for patients already on ACE inhibitors and β-blockers for symptomatic HF and who have persistent symptoms ICD is reasonable in patients with LVEF 30-35% with NYHA class II or III who are receiving optimal medical therapy, and who have reasonable expectation of survival with good functional status of >1 yr	
Class IIb		Addition of ARBs may be considered in persistently symptomatic patients with reduced LVEF who are already being treated with conventional therapy	Hydralazine and nitrate combination might be reasonable in patients with current or prior symptoms of HF and reduced LVEF who cannot be given ACE inhibitors or ARBs because of drug intolerance, hypotension, or renal insufficiency
Class III	Calcium channel blockers are not indicated as routine treatment		Combined use of ACE inhibitors, ARBs, and aldosterone antagonists is routine Long-term use of an infusion of a positive inotropic drug is recommended

D. Patients with Refractory End-Stage Heart Failure (Stage D)

	A	B	C
Class I	Referral to HF program with expertise in management of refractory HF is recommended	Control of fluid retention is indicated Referral for cardiac transplantation is recommended	Options for end-of-life care may be discussed
Class IIa		Left ventricular assist device is recommended as permanent or destination therapy in patients with a 1-yr mortality of $\geq 50\%$	Pulmonary catheter placement may be reasonable to guide therapy Continuous intravenous infusion of a positive inotropic agent may be considered for palliation of symptoms in patients with refractory end-stage HF
Class IIb			
Class III		Routine intermittent infusions of positive inotropic agents are not recommended	Partial left ventriculectomy is not recommended in patients with nonischemic cardiomyopathy and refractory end-stage HF

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association.

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