

Contributions to Nephrology

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Fluid Overload

Diagnosis and Management

Editors

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Claudio Ronco Vicenza



Fluid Overload

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Contributions to Nephrology

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Contents

VII Preface

Ronco, C. (Vicenza); Costanzo, M.R. (Naperville, Ill.); Bellomo, R. (Melbourne, Vic.); Maisel, A.S. (San Diego, Calif.)

Definition and Classification

1 Heart Failure: Pathophysiology and Clinical Picture

Palazzuoli, A.; Nuti, R. (Siena)

11 Heart Failure Classifications – Guidelines

Jankowska, E.A.; Ponikowski, P. (Wrocław)

24 Acute Kidney Injury: Classification and Staging

Cruz, D.N. (Vicenza); Bagshaw, S.M. (Edmonton, Alta.); Ronco, C. (Vicenza); Ricci, Z. (Rome)

33 Cardiorenal Syndromes: Definition and Classification

Ronco, C. (Vicenza)

Pathophysiology

39 Oliguria and Fluid Overload

Rimmelé, T.; Kellum, J.A. (Pittsburgh, Pa.)

46 Pathophysiology of Fluid Retention in Heart Failure

Chaney, E.; Shaw, A. (Durham, N.C.)

54 Fluid Overload as a Biomarker of Heart Failure and Acute Kidney Injury

Bagshaw, S.M. (Edmonton, Alta.); Cruz, D.N. (Vicenza)

69 Fluid Balance Issues in the Critically Ill Patient

Bouchard, J. (Montréal, Qué.); Mehta, R.L. (San Diego, Calif.)

79 Prerenal Azotemia in Congestive Heart Failure

Macedo, E.; Mehta, R. (San Diego, Calif.)

Diagnosis

88 Use of Biomarkers in Evaluation of Patients with Heart Failure

Slavin, L.; Daniels, L.B.; Maisel, A.S. (San Diego, Calif.)

118	Oliguria, Creatinine and Other Biomarkers of Acute Kidney Injury	Ronco, C.; Grammaticopoulos, S. (Vicenza); Rosner, M. (Charlottesville, Va.); De Cal, M.; Soni, S.; Lentini, P.; Piccinni, P. (Vicenza)
128	Current Techniques of Fluid Status Assessment	Peacock, W.F.; Soto, K.M. (Cleveland, Ohio)
143	Bioelectric Impedance Measurement for Fluid Status Assessment	Piccoli, A. (Padova)
	Therapy	
153	Diuretic Therapy in Fluid-Overloaded and Heart Failure Patients	Bellomo, R.; Prowle, J.R.; Echeverri, J.E. (Melbourne, Vic.)
164	Pharmacological Therapy of Cardiorenal Syndromes and Heart Failure	House, A.A. (London, Ont.)
173	Extracorporeal Fluid Removal in Heart Failure Patients	Costanzo, M.R. (Naperville, Ill.); Agostoni, P.; Marenzi, G. (Milan)
199	Technical Aspects of Extracorporeal Ultrafiltration: Mechanisms, Monitoring and Dedicated Technology	Nalesso, F.; Garzotto, F.; Ronco, C. (Vicenza)
209	Use of Brain Natriuretic Peptide and Bioimpedance to Guide Therapy in Heart Failure Patients	Valle, R. (Chioggia); Aspromonte, N. (Rome)
217	Fluid Management in Pediatric Intensive Care	Favia, I.; Garisto, C.; Rossi, E.; Picardo, S.; Ricci, Z. (Rome)
227	Fluid Assessment and Management in the Emergency Department	Di Somma, S.; Gori, C.S.; Grandi, T.; Risicato, M.G.; Salvatori, E. (Rome)
237	Author Index	
238	Subject Index	

Preface

The condition of fluid overload is often observed in patients with heart failure and secondary oliguric states. In those conditions, a thorough assessment of the fluid status of the patient may help guide the therapy and prevent complications induced by inappropriate therapeutic strategies. For these reasons, it seems appropriate to collect a series of contributions in which the reader can start with the information relevant to the type of syndromes involved in the observed clinical picture, to progress subsequently towards the pathophysiologic foundations of such syndromes, to further advance in the analysis of diagnostic criteria and to finally conclude with the available therapeutic strategies. The present book represents a practical tool for physicians and professionals involved in the management and care of patients with combined heart and kidney disorders. It may also represent a reference textbook for medical students, residents and fellows dealing in everyday practice with fluid overloaded and oliguric patients. The book is an important source of information about new emerging diagnosing tools, therapies and technologies devoted to the treatment of patients with severe fluid-related disorders. Different conditions leading to fluid overload are described together with the possible diagnostic approaches and the therapeutic strategies. Various types of cardiorenal syndrome are discussed in detail with information concerning pathophysiology, biomarkers, pharmacological treatment and extracorporeal support. New definitions for heart failure, acute kidney injury and cardiorenal syndromes are reported to facilitate the reader in the process of understanding the complex link between the heart and the kidney.

The delicate concept of fluid balance is discussed with specific attention to the different components involved in the final composition of the body. Body hydration status is of remarkable importance, and bioimpedance vector analysis together with other techniques for the assessment of fluid status is discussed in depth. Pharmacological therapies together with extracorporeal treatments are presented in detail with special emphasis on critical care, cardiology, nephrology and emergency department populations. Pediatric populations are also taken into consideration.

The technology for extracorporeal ultrafiltration is described in detail, allowing the readers to appreciate the importance of this therapeutic approach in refractory oliguric states. The simplicity and effectiveness of modern equipment can make ultrafiltration a treatment easy to apply and safe to perform. Additional support to safety can be offered by chemical biomarkers, on-line blood volume monitoring and sequential bioimpedance determinations.

Based on all these considerations, the creation of a book covering all the important issues in the field as well as the available technology and methods represents an important project and a significant educational effort. We think that a book on this subject will constitute an important contribution in the field of cardiology and nephrology and may be particularly suited for being included in the series *Contributions to Nephrology*.

We are indebted to BELLCO who provided an unrestricted grant for the publication of the volume and to Karger for the professional editorial assistance and the usual quality of printing.

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Heart Failure: Pathophysiology and Clinical Picture

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Abstract

Despite its high prevalence and significant rates of associated morbidity and mortality, the syndrome of decompensated heart failure (HF) remains poorly defined and vastly understudied. HF is due to several mechanisms including pump dysfunction disorder, neurohormonal activation disorder, and salt-water retention disorder. The first step of the syndrome includes cardiac damage and remodeling in terms of coronary disease systolic dysfunction and myocardial metabolism alterations. Neurohormonal activation and hydrosaline retention occur during successive steps in response to cardiac injury for compensatory reasons. Both mechanisms provide inotropic support to the failing heart increasing stroke volume, and peripheral vasoconstriction to maintain mean arterial perfusion pressure. However, they are deleterious to cardiocirculatory homeostasis in the late stage. Further factors involve structural changes, such as loss of myofilaments, apoptosis and disorganization of the cytoskeleton, as well as disturbances in Ca homeostasis, alteration in receptor density, signal transduction, and collagen synthesis. Each disorder contributes at a different time to HF development and worsening. Clinical presentation depends on pulmonary congestion, organ perfusion, presence of coronary disease, fluid retention and systemic pressure. For these reasons, the picture of HF is widely varied.

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Heart failure (HF) is the leading cause of hospital admissions in the Medicare population. In addition to its high prevalence, hospitalization for decompensated HF is associated with extraordinarily high rates of morbidity and mortality. Estimates of the risk of death or rehospitalization within 60 days of admission for this disease vary from 30 to 60%, depending on the population studied in the US [1, 2]. Despite its high prevalence and significant rates of associated morbidity and mortality, its pathophysiologic mechanisms and treatment options remain poorly defined and vastly understudied. In addition, there is no

consensus definition of the clinical problem that HF syndromes presents, no accepted nomenclature to describe its clinical features, and no recognized classification scheme for its patient population [3].

HF should be defined as a clinical syndrome that develops in response to an insult resulting in a decline of the pump and release capacity of the heart. This is subsequently characterized by the continuous interaction between the underlying myocardial dysfunction and the compensatory neurohormonal mechanisms that are activated. During the last 30 years, physicians have viewed HF primarily as hemodynamic and edematous disorder, in which fluid retention occurs because the heart cannot pump adequate quantities of blood to the kidneys. This conceptual model led to the successful utilization of diuretics for HF, but it failed to obtain an outcome improvement. More recently, a new concept regarding neurohormonal overdrive has been proposed and demonstrated: HF develops and progresses because endogenous neurohormonal systems that are activated by the initial injury to the heart exert a deleterious effect on the circulation. Both hemodynamic and neurohormonal mechanisms help during early stages of the inotropic state, but when sustained for long periods, their ability to augment cardiac contractility wanes, and, instead, these same mechanisms act to enhance ventricular wall stress, thereby impairing ventricular performance. As the heart failure state evolves, endogenous mechanisms that are normally activated to control wall stress become exhausted, and peripheral vasoconstriction and sodium retention occur [4]. Unopposed activation of hemodynamic stresses and neurohormonal systems leads to further destruction of the myocardium and progression of the underlying disease. The acceptance of this hemodynamic-neurohormonal model has led to the development of vasodilators and neurohormonal antagonists that have been shown to be useful alone or when added to diuretics in the treatment of HF [5]. Several ‘actors’ could contribute to HF development and impairment. To simplify the problem, we would divide them into three principal disorders: pump dysfunction disorder, neurohormonal activation disorder, and salt-water retention disorder.

Pump Dysfunction and Cardiac Remodeling

HF syndrome is primary characterized by cardiac cell loss due to myocardial necrosis and ischemia with inotropic function reduction, peripheral vasoconstriction reduction of tissue perfusion, afterload and preload increase, and further cardiac function impairment. This represents, in brief, the mostly accepted hemodynamic theory in the 1970–1980s. Behind the pump function incapacity, several cellular, biochemical, and metabolic mechanisms exist. In patients with coronary artery disease (CAD), acute myocardial infarction leads to loss of contractile tissue with the development of both replacement and interstitial fibrosis [6]. However, HF in the setting of CAD is itself a heterogeneous condition, with many possible

factors contributing to left ventricular (LV) dysfunction. Eventually, LV remodeling and severe myocardial dysfunction ensues, and the clinical syndrome of HF is fully expressed. The mechanisms whereby LV hypertrophy progresses to overt HF are highly complex and not well understood. Structural abnormalities of the heart, including cardiomyocyte and cytoskeletal abnormalities, as well as interstitial fibrosis, may contribute importantly to chamber dysfunction. Hypertrophy, often a response to pressure overload, may initially manifest itself as diastolic HF; there is then emergence of abnormal LV filling. A hypertrophied ventricle is a stiff chamber that fails to relax completely, leading to elevated LV filling pressures [7]. So-called 'diastolic HF' occurs more commonly in the elderly, in women, and in patients with a long-standing history of systemic hypertension. Tissue damage in HF is also characterized by activation of specific myocardial collagenases or matrix metalloproteinases that are activated in response to a number of signals, including alteration of the myocardial tissue and oxidative stress state [8, 9]. These collagenases are likely responsible for disruption of the collagen strut network that normally weaves the cardiac myocytes together. The net result of cardiac matrix metalloproteinase activation is loss of the normal interstitial supporting structure. When LV wall stress and strain are heightened as a result of changes in LV geometric size and shape, there may be slippage of myocytes away from each other, leading to further distortions in LV shape and size [10]. The proportional importance of myocyte slippage in the progression of the remodeling process is still not clear and remains debated. It is well known that cardiac mass is increased in patients with HF. This appears to be the result of a combination of reactive fibrosis and myocyte hypertrophy, along with altered cytoskeletal structure within the cardiomyocyte [8]. The abnormal growth of the heart undoubtedly contributes to increased stiffness of the various chambers. Mechanical deformation of the myocyte cell membrane, as might occur during progressively increased LV filling pressure, is linked to early gene expression, protein synthesis, and enlargement of cardiac myocytes. In addition to mechanical signals, neuroendocrine factors, including angiotensin II, norepinephrine and endothelin, are associated with an increase in myocyte size and cardiac hypertrophy. Cytokines and tumor necrosis factor are both overexpressed in HF and further increase both hypertrophy and fibrosis processes.

During HF syndrome many Ca metabolism alterations have been well demonstrated: free intracellular Ca increase during the rest phase, Ca reduction during repolarization phase and Ca reuptake deficit from the sarcoplasmic reticulum. Therefore, most of these processes are modulated by ATP disposal that is reduced during HF. All these abnormalities lead to a dysfunction in excitation/contraction system with cardiac muscle incapacity to improve physiologically strength contraction and elastic release [11]. Failed myocardium reduces its energy metabolism to keep an adequate perfusion and protect myocytes from imbalance between energy request and production. Troponin release during HF destabilization can reflect both myocyte loss for ischemia and apoptosis. Because of

neurohormonal and inflammatory activation with oxidative stress increase, cardiac cells could initiate a programmed death with progressive functional tissue decrease. Myocardial injury could also be due to classic coronary disease (CAD) that is often associated with HF. In this case, myocardial damage may be related to hemodynamic and/or neurohormonal abnormalities or the result of an ischemic event (myocardial infarction). Injury may also be the consequence of a high LV diastolic pressure, further activation of neurohormones, and/or inotropic stimulation, resulting in a supply and demand mismatch (increased myocardial oxygen demand and decreased coronary perfusion) [12]. These conditions may precipitate injury, particularly in patients with CAD, who often have hibernating and/or ischemic myocardium. The convergence of myocyte hypertrophy, myocyte slip-page, reactive and reparative fibrosis, cytoskeletal alterations, and apoptosis are believed to ultimately modulate the size, shape, and stiffness of the heart, leading to progressive remodeling and to the development of the syndrome of HF.

Neurohormonal Activation

Activation of vasoactive neurohormonal systems – sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system (RAAS) during early stages permits to maintain circulatory homeostasis. RAAS activation induces direct systemic vasoconstriction and activates other systems (arginine vasopressin – AVP, aldosterone) that contribute to maintaining adequate intravascular volume. However, chronic activation of these systems can have deleterious effects on cardiac function and contributes to the progression of CHF [13]. The activity of the RAAS is central to the maintenance of water and electrolyte balance and blood volume. The enzyme renin is released primarily by the juxtaglomerular cells of the kidney in response to the activity of the SNS, changes in renal perfusion pressure, reduced sodium absorption by the distal renal tubules, or AVP release [14]. Renin converts a precursor molecule (angiotensinogen) to angiotensin I, which is then converted by ACE to angiotensin II. Angiotensin II produces vasoconstriction and stimulation of aldosterone from the adrenal cortex, which increases sodium ion reabsorption by the distal renal tubules [15]. Angiotensin II also modulates the thirst center. The production of angiotensin II by renin and ACE takes place systemically in plasma and also within specific tissues, including the brain, heart, and blood vessels. In acute CHF, the decrease in renal blood flow, caused by progressive CHF, activates the RAAS. This increase in RAAS activity contributes to systemic vascular resistance. The increased vasoconstriction resulting from RAAS activation results in increased LV afterload. This, in turn, increases myocardial demand, LV end-diastolic pressure, pulmonary capillary wedge pressure, and pulmonary congestion while decreasing cardiac output. Angiotensin also promotes inflammatory pathways with TNF and interleukin overexpression, tissue remodeling with vascular cell growth and increase in

growth factors, endothelial dysfunction by nitric oxide reduction and platelet aggregation, and oxidative stress by induction of reactive oxygen species [15, 16]. Vascular remodeling and fluid overload are also potentiated by the SNS and AVP. The increased intravascular volume induced by AVP-mediated reabsorption of free water results in elevated intracardiac pressure as well as pulmonary congestion and edema. Systemic vasoconstriction mediated by angiotensin II increases LV afterload and can also directly induce cardiac myocyte necrosis and alter the myocardial matrix structure. Counterregulatory mechanisms consisting of natriuretic peptides, nitric oxide, and prostaglandins are generally not adequate to maintain cardiac function, systemic perfusion, or sodium balance. The end result of RAAS activation in CHF is clinical deterioration and progressive LV dysfunction. It is well documented that the degree of neurohormonal activation is correlated with severity of HF. RAAS promotes the SNS activity that in turn, increases cardiac contractility and heart rate, increasing stroke volume and peripheral vasoconstriction [17]. However, the cardiac work increase leads to an acceleration of disease progression. Activation of SNS has been attributed to withdrawal of normal restraining influences and enhancement of excitatory inputs including changes in: (1) peripheral baroreceptor and chemoreceptor reflexes; (2) chemical mediators that control sympathetic outflow; (3) central integratory sites. The sympathetic hyperactivity observed in HF is closely related to abnormalities in cardiovascular reflexes: the sympatho-inhibitory cardiovascular reflexes are significantly suppressed, whereas the sympatho-excitatory reflexes, including the cardiac sympathetic afferent reflex and the arterial chemoreceptor reflex, are augmented [18]. Sympathetic activation in the setting of impaired systolic function reflects the net balance and interaction between appropriate reflex compensatory responses to impaired systolic function and excitatory stimuli that elicit adrenergic responses in excess of homeostatic requirements. All these changes drive towards an altered cardiac and vascular vasodilating capacity, renal arterial vasoconstriction and kidney flow redistribution with increased sodium reabsorption. The cardiac oxygen utilization and vascular resistance increase, β -receptor down-regulation and sympatho-vagal imbalance occur [19].

If not stopped, the sympathetic activity becomes the principal reason of impairment and mortality in the advanced stages of disease. The physiological answer of the body to HF is 'adrenergic defense', which involves inotropic, chronotropic and vasoconstrictive reserves. Unfortunately, this 'sword' later becomes deleterious to those who handle it (fig. 1).

Salt and Water Retention

Baroreflex activation is one of the principal alterations in HF; it is mediated by several systems with hydro-saline retention activity (RAAS, SNS, aldosterone, endothelin and vasopressin). In particular, augmented baroreceptorial sensibility

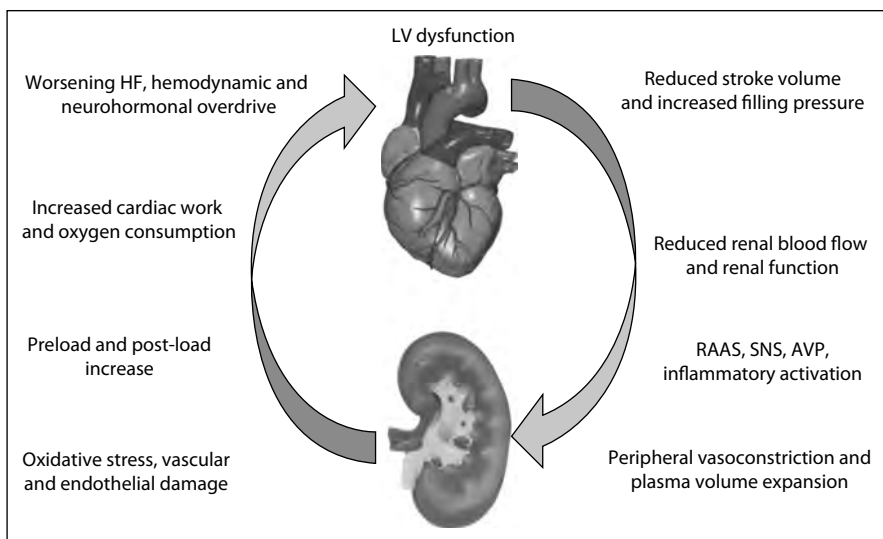


Fig. 1. Neurohormonal activation in HF.

occurs together with RAAS and adrenergic activity preceding vasopressin increase. Vasopressin mediates its effects via adenylcyclase-dependent signaling in the renal collecting ducts increasing water retention, which is accomplished by upregulation of the aquaporin-2 water channels [20]. This upregulation results in an increased movement of water from the collecting ducts back into the plasma, increasing free water reabsorption, which leads to further increase in water retention [21]. This effect, may contribute to volume expansion and hyponatremia, a common condition in moderate and severe CHF. AVP could potentially contribute directly and indirectly to well-characterized load-dependent and load-independent mechanisms that may aggravate progressive ventricular remodeling and failure, as well as the expression of the clinical HF syndrome. Congestion, in particular, is a hallmark of decompensated or severe CHF, and the volume retention secondary to excessive AVP secretion adds to the volume retention of sodium and water caused by aldosterone and other renal mechanisms [22]. Inflammatory activation may have a role in HF by both contributing to vascular dysfunction and magnifying fluid overload. The amount of fluid in the pulmonary interstitium and alveoli is tightly controlled by an active process of reabsorption. Reduction in intrarenal perfusion and the consequent fall in GFR lead to reflex activation of the RAAS with tubular reclamation of salt and water. In addition, some of the neurohormonal and inflammatory activation, commonly observed in HF patients, probably also contributes to renal dysfunction. The result is kidney dysfunction with hypoxic and vasoconstrictive injury which may also lead to tubular necrosis [23]. Besides, high renal venous pressure contributes to this vasomotor nephropathy

and further amplifies renal dysfunction. Progressive renal dysfunction, by inducing salt and fluid retention, stimulates the HF process inducing an important vicious cycle to HF exacerbation. Fluid overload is also caused by fluid redistribution rather than by fluid accumulation. Increased vascular resistance/stiffness may lead to both reduced capacitance in the large veins together with increased arterial resistance. The decrease in capacitance in large veins will lead to increased venous return and heightened preload [24]. This could explain the mechanism of fluid redistribution in specific district (lung) rather than fluid overload in peripheral organs during HF worsening.

Clinical Pictures

The clinical picture of HF is widely varied. The most common classification is based on the initial clinical presentation; it makes a distinction between new onset acute HF, and transient and chronic CHF. Clinical presentation can depend on hemodynamic status, primary cardiac disorder, systemic pressure and organ perfusion/damage. Classical definition and classification divide HF syndrome into pulmonary edema, right HF, HF with acute coronary syndrome, hypertensive HF, and cardiogenic shock [25].

Another distinction is about the type of LV dysfunction: most patients with HF have both systolic and diastolic LV dysfunction, but in some cases the syndrome can occur with isolated systolic or diastolic dysfunction. HF with preserved left ventricular ejection fraction (LVEF) is characterized by a non dilated, usually hypertrophied left ventricle in which LVEF is preserved at rest, and the parameters of LV relaxation and filling are markedly deranged. Patients with preserved LVEF and HF are a heterogeneous and understudied group that includes those with both hypertensive heart disease and hypertrophic cardiomyopathy. Epidemiologic data regarding the proportion of patients hospitalized with decompensated HF who have preserved LVEF demonstrate that almost half of all HF patients have preserved LVEF, and mortality rates were similar between those with preserved and those with impaired ejection fraction (EF) [26].

The categorization of patients with decompensated HF by hemodynamic profiles has been proposed; it classifies patients as either 'wet' or 'dry', 'warm' or 'cold', and addresses the two primary hemodynamic derangements in HF: elevated filling pressures and organ perfusion damage. The differentiation between the 'wet' and 'dry' patient with decompensated HF can usually be made at the bedside; a bedside evaluation, however, may require that great care be taken to identify volume overload in some patients with 'occult' excess fluid [27, 28] (fig. 2).

More recently, a new simple classification taking into consideration etiology, LV defect, and presentation has been proposed: patients may be classified into HF presenting for the first time (de novo) or worsening chronic HF. In both groups, the presence and extent of CAD may determine the initial, in-hospital,

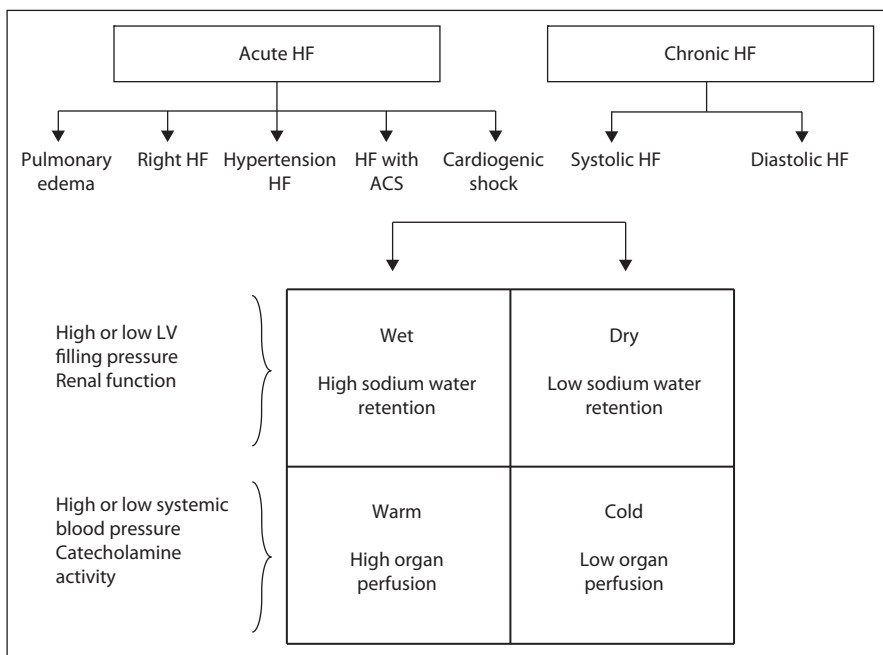


Fig. 2. HF presentations: there are many types of HF with different clinical aspects and outcome on the basis of structural heart disease.

and postdischarge management. The EF may influence postdischarge rather than initial management, which should be based on the presenting clinical profile. Several associated clinical conditions such as low blood pressure, renal impairment, and/or signs and symptoms refractory to standard therapy characterize advanced HF [29] (table 1). De novo HF represents the remainder of AHF, and may be further divided into those with preexisting risk for HF (e.g. hypertension, CAD) without evidence of prior LV dysfunction or structural abnormalities and those with preexisting cardiac structural abnormalities (e.g. reduced EF).

Conclusions

HF is a clinical syndrome characterized by the continuous interaction between the myocardial dysfunction and the compensatory neurohormonal mechanisms that are activated. Many ‘actors’ including myocardial dysfunction, RAAS, SNS, vasopressin and inflammatory systems contribute to HF development and impairment.

Clinical presentation differs in relation to hemodynamic status, primary cardiac disorder, systemic pressure and organ perfusion/damage. For this reason,

Table 1. Clinical conditions frequently associated with HF

CAD
Hypertension
Anemia
Diabetes
Renal insufficiency
Pulmonary diseases
Obesity
Atrial fibrillation

the traditional division between acute and chronic HF tends to be substituted by more actual classification that takes into account clinical presentation, primary cardiac defect, and etiology such as hemodynamic involvement.

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Heart Failure Classifications – Guidelines

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Abstract

The clinical syndrome of heart failure is hugely heterogeneous. In this chapter, the authors discuss several distinct classifications of this syndrome that have been developed in order to better characterize an individual case and subsequently apply an optimal management. Classifications are based on the time course of the clinical presentation of heart failure, severity of symptoms and signs of heart failure, structural changes within the heart, predominant etiology and comorbidities.

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It has always been difficult to propose a widely acceptable definition of the ‘syndrome of heart failure’ precisely describing the complex nature and essential principles of the disease, which could be unanimously acceptable by clinical scientists, epidemiologists and physicians, and at the same time be easily applicable in everyday clinical practice. In the recent decades, the definition of heart failure (HF) has evolved along with the revolutionary progress in the understanding of the pathophysiology and mechanisms underlying cardinal signs and symptoms of this syndrome [1]. Current approach is to base the definition on the coexistence of three distinct elements: abnormal heart structure and/or function with signs and symptoms of the disease. Such a definition was initially proposed in 1995 by the first European Society of Cardiology (ESC) guidelines [2] and remained virtually unchanged until today [3].

According to the most recent ESC guidelines [3], HF is defined as a clinical syndrome when all the following conditions are fulfilled:

- 1 Presence of typical HF symptoms (breathlessness at rest or on exercise, fatigue, tiredness, ankle swelling);
- 2 Presence of typical HF signs (tachycardia, tachypnea, pulmonary rales, pleural effusion, raised jugular venous pressure, peripheral edema, hepatomegaly);

- 3 Objective evidence of an abnormal structure or/and function of the heart at rest (cardiomegaly, third heart sound, cardiac murmurs, abnormality on the echocardiogram, raised natriuretic peptide concentration).

In principle, the American College of Cardiology (ACC)/American Heart Association (AHA) definition is practically identical, describing HF as ‘a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood. The cardinal manifestations of HF are dyspnea and fatigue, which may limit exercise tolerance, and fluid retention, which may lead to pulmonary congestion and peripheral edema’ [4, 5].

Thus, the diagnosis of HF should be always based on a careful clinical history, physical examination and subsequent investigations, among which echocardiography and assessment of circulating natriuretic peptides play a major role.

Clinical improvement as a response to treatment directed at HF (being an element of the original ESC definition of HF [2]) is no longer sufficient for the diagnosis, but may be helpful in some circumstances. It is emphasized that an etiology of the heart disease underlying HF should be an obligatory element of the final diagnosis.

The clinical syndrome of HF is hugely heterogeneous. Several distinct classifications of this syndrome have been proposed in order to better characterize an individual case and subsequently apply an optimal management. They will be discussed in this chapter.

Time Course of the Clinical Presentation of Heart Failure

Based on the time course of the clinical presentation of HF, the heart disease can be classified as: (a) new onset HF (the first presentation of symptoms and signs, with the acute or slow onset); (b) transient HF (recurrent or episodic symptoms and signs, over a limited time period, although long-term treatment may be indicated); (c) chronic HF (persistent symptoms and signs; can be stable, worsening or decompensated).

This classification has been originally introduced in the recent ESC guidelines [3].

Classifications Based on the Severity of Heart Failure Symptoms and Structural Changes within the Heart

Shortness of breath and/or fatigue (either during exercise or at rest) are typical and cardinal symptoms of HF. However, they are subjective, nonspecific for HF, and the clinical presentation may be difficult to distinguish from numerous noncardiac disorders such as chronic obstructive pulmonary disease, obesity,

Table 1. NYHA functional classification of the severity of HF based on symptoms and physical activity [7, 8], adapted in ESC guidelines [3]

Class I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea.
Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity results in fatigue, palpitation, or dyspnea.
Class IV	Unable to carry on any physical activity without discomfort. Symptoms at rest. If any physical activity is undertaken, discomfort is increased.

depression, cognitive disorders, normal aging. Ideally, they should be assessed with standardized methods (e.g. validated and reproducible scales [6] or different forms of exercise testing).

Paroxysmal nocturnal dyspnea and orthopnea can also occur in HF patients and may precede pulmonary edema by several days and coexist with elevated filling pressure of the left ventricle. Orthopnea can be tested by putting the patient in the supine position for a defined period of time while monitoring the development of dyspnea. Supine positioning mobilizes fluid from dependent venous reservoirs in the abdomen and the lower extremities, which increases venous return to the thoracic compartment. It should be also remembered that at the later stage HF affects almost all body organs, and other subjective complaints may dominate the clinical picture of HF.

Despite these potential drawbacks, symptoms are often used to classify severity of HF, monitor therapy and evaluate prognosis. The New York Heart Association (NYHA) functional classification (class I–IV) reflects HF severity and is based on symptoms and exercise capacity (table 1) [7, 8]. The NYHA functional classification has proved to be clinically useful, and is employed routinely in most randomized clinical trials. HF patients in NYHA class I should be distinguished from asymptomatic subjects with left ventricular (LV) dysfunction. The former have objective evidence of cardiac dysfunction and a past history of HF symptoms/signs that have entirely resolved due to HF treatment, whereas the latter have never experienced the clinical syndrome of HF. However, asymptomatic LV dysfunction carries a high risk of overt HF development.

Additionally, to describe clinical symptoms the terms mild, moderate, or severe HF are used [3]. Mild HF is used for subjects who can perform everyday activities with no important limitations due to dyspnea or/and fatigue. Severe HF is applied for those who are markedly severely symptomatic and

Table 2. Weber’s exercise functional classification of patients with HF based on the measurement of oxygen consumption [9]

Class	Peak/maximal oxygen consumption, ml/min/kg	Oxygen consumption at anaerobic threshold, ml/min/kg
A	>20	>14
B	16–20	11–14
C	10–15	8–10
D	<10	<8

Table 3. ACC/AHA stages of HF based on the structural changes within the heart and symptoms [4, 5], adapted in ESC guidelines [3]

Stage A	At high risk for developing HF. No identified structural or functional abnormality; no signs or symptoms.
Stage B	Developed structural heart disease that is strongly associated with the development of HF, but without signs or symptoms.
Stage C	Symptomatic HF associated with underlying structural heart disease.
Stage D	Advanced structural heart disease and marked symptoms of HF at rest despite maximal medical therapy.

need frequent medical attention, whereas moderate HF is used for the remaining patients.

Based on the objective measure of exercise intolerance derived from cardiopulmonary exercise testing (oxygen consumption at peak exercise or at anaerobic threshold), Weber [9] proposed the exercise functional classification (classes A–D) of patients with HF (table 2).

The ACC/AHA guidelines [4, 5] recommend the classification of HF based on the structural changes within the heart and symptoms (stages A–D; table 3). It distinguishes four consecutive stages involved in the development and progression of HF syndrome. The first two stages (A and B) although not being HF themselves allow to identify patients who are at risk for developing HF. Stage C indicates patients with current or past symptomatic HF associated with underlying structural heart disease, whereas stage D denotes advanced structural heart disease and marked-severe HF symptoms at rest despite maximal medical therapy (and is often referred to as refractory HF – see below).

Over the last years, we have witnessed a revolutionary improvement in the comprehensive management of HF syndrome, which has substantially changed

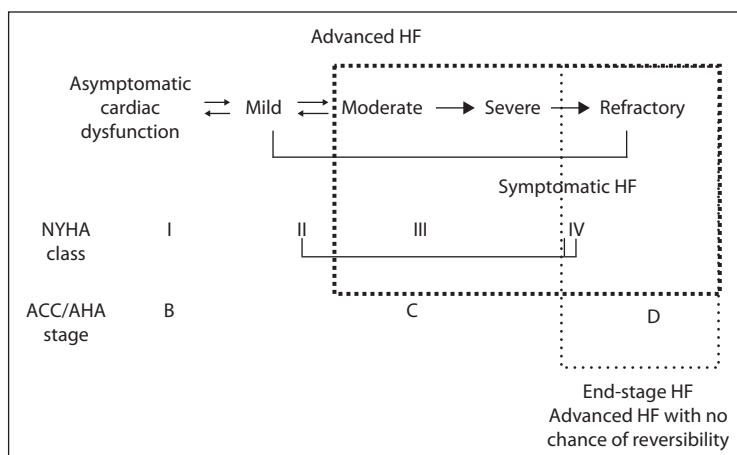


Fig. 1. Conceptual presentation and differentiation between advanced, refractory and end-stage HF according to Metra et al. [10].

the clinical characteristics of these patients. There is a growing number of long-term HF survivors who progress to the advanced stages of the disease, characterized by severe symptoms, marked hemodynamic impairment, frequent hospital admissions and very poor outcome. Thus, an emerging population of patients with advanced chronic HF needs to be better identified and characterized, which fully justifies a need for new classification. In the recent position paper of the Study Group of Heart Failure Association of the ESC [10], advanced chronic HF was defined as: (a) severe symptoms of HF with dyspnea and/or fatigue at rest or with minimal exertion (NYHA functional class III or IV); (b) episodes of fluid retention and/or of reduced cardiac output at rest; (c) objective evidence of severe cardiac dysfunction, at least 1 of the following: low LV ejection fraction (LVEF $\leq 30\%$), a severe abnormality of cardiac function on Doppler echocardiography (pseudonormal or restrictive mitral inflow pattern), high LV filling pressures, high BNP or NT-proBNP plasma levels (absence of noncardiac causes); (d) severe impairment of functional capacity, at least 1 of the following: inability to exercise, 6-min walking distance <300 m, peak oxygen consumption $<12\text{--}14$ ml/kg/min; (e) history of ≥ 1 HF hospitalization in the past 6 months; (f) presence of all the previous features despite attempts to optimize therapy according to the ESC guidelines.

The term advanced chronic HF comprises also cases traditionally labeled as refractory HF and/or end-stage HF (fig. 1). The former term applies to patients with stage D according to the ACC/AHA guidelines, where it is defined by the presence of marked symptoms at rest despite maximal medical therapy. The

Table 4. Killip-Kimball classification designed to provide a clinical estimate of the severity of circulatory derangement in the treatment of acute myocardial infarction [11], adapted in ESC guidelines for acute HF [3].

Stage I	No HF. No clinical signs of cardiac decompensation.
Stage II	HF. Diagnostic criteria include: rales, S3 gallop and pulmonary venous hypertension. Pulmonary congestion with wet rales in the lower half of the lung fields.
Stage III	Severe HF. Frank pulmonary edema with rales throughout the lung fields.
Stage IV	Cardiogenic shock. Signs include hypotension (systolic BP <90 mm Hg), and evidence of peripheral vasoconstriction such as oliguria, cyanosis and diaphoresis.

Table 5. Forrester classification designed to describe clinical and hemodynamic status in acute myocardial infarction [12], adapted in ESC guidelines for acute HF [3]

Group 1	Normal perfusion and pulmonary capillary wedge pressure (PCWP; an estimate of left atrial pressure).
Group 2	Poor perfusion and low PCWP (hypovolemic status).
Group 3	Near-normal perfusion and high PCWP (pulmonary edema).
Group 4	Poor perfusion and high PCWP (cardiogenic shock).

latter indicates an extremely advanced condition where no improvement with conventional HF treatment is possible, and palliative care, ventricular assist devices or heart transplantation are indicated [10]. This condition should be distinguished from advanced chronic HF, in which a certain degree of reversibility may be present [10].

Classifications Based on Signs of Heart Failure

Typical signs of HF are those related to fluid retention (increase in body weight, elevated jugular venous pressure, hepatojugular reflux, ascites, peripheral edema, hepatomegaly, splenomegaly, rales, pulmonary congestion, pulmonary edema) and/or peripheral hypoperfusion (low systemic blood pressure – BP, cyanosis, prerenal renal failure, confusion, abdominal discomfort).

The assessment of HF symptoms (both congestion and hypoperfusion) are the major clinical criteria applied in the Killip-Kimball classification (stages

		Congestion at rest?		
		No	Yes	
Low perfusion at rest ?	No	Warm and dry A	Warm and wet B	
	Yes	Cold and dry L	Cold and wet C	

Low perfusion:

- Narrow PP (<25%)
- Cool extremities
- ACEI intolerance
- ↓ Na, ↓ GFR

Congestion:

- Orthopnea
- ↑ JVP
- Rales (often absent)
- Edema insensitive to ↑ LVEDP
- elderly –caused by local factors

Fig. 2. Clinical assessment of hemodynamic profile of acute HF based on the presence/absence of congestion and low perfusion at rest [13, 14], adapted in ESC guidelines [3]. ACEI = Angiotensin-converting enzyme inhibitor; LVEDP = LV end-diastolic pressure; JVP = jugular venous pressure; PP = pulse pressure.

I–IV) for the risk stratification of patients with acute myocardial infarction complicated by HF (table 4) [11].

Forrester et al. [12] proposed another classification, taking into account the presence of peripheral hypoperfusion and pulmonary congestion on the basis of the Swan-Ganz catheterization. The authors distinguished four hemodynamic profiles, and the Forrester classification (groups 1–4) was originally designed for patients with acute myocardial infarction (table 5). It has been recently demonstrated that also in patients with HF similar hemodynamic profiles can be identified on the basis of careful physical examination and further used in clinical practice for meaningful distinction of these patients [13, 14]. These clinical profiles can be defined by: (1) the absence or presence of signs of congestion (congestion evidenced by a recent history of orthopnea and/or physical examination evidence of jugular venous distention, rales, hepato-jugular reflux, ascites, peripheral edema, leftward radiation of the pulmonic heart sound, or a square wave BP response to the Valsalva maneuver), and (2) the evidence suggesting adequate or inadequate perfusion [hypoperfusion evidenced by presence of a narrow proportional pulse pressure ($[\text{systolic} - \text{diastolic BP}] / \text{systolic BP} < 25\%$), pulsus alternans, symptomatic hypotension (without orthostasis), cool extremities, and/or impaired mentation; fig. 2]. Such profiles are easily assessed at the bedside and provide useful prognostic information and may be of particular importance in patients with advanced HF or those who developed decompensation.

Right and left HF are the other descriptive terms often used to classify HF, and they refer to syndromes presenting predominantly with the congestion of the systemic or pulmonary veins leading to signs of fluid retention with peripheral edema, ascites, hepatomegaly or pulmonary edema, respectively.

Less frequently, right and left HF may be related to the signs and symptoms of hypoperfusion within pulmonary or systemic vascular beds, respectively [3]. Forward and backward HF are terms that can be used to emphasize the signs and symptoms resulting from peripheral hypoperfusion or an increase in atrial pressures with fluid congestion, respectively [3].

Heart Failure with Preserved and Reduced Ejection Fraction (Systolic and Diastolic Heart Failure)

In the past, there was a clear distinction between systolic and diastolic HF, arbitrarily based on the cut-off value of LVEF. Patients with typical symptoms and/or signs of HF and preserved LVEF (i.e. >45 – 50%) tended to be differentiated from those with clinical picture of HF and reduced LVEF. It has a clear historical background as many clinical and epidemiological studies and clinical trials included only HF patients with reduced LVEF.

Currently, there is a view that these pathologies should not be considered as separate entities [15]. In fact, the majority (almost all) of patients with the clinical syndrome of HF have evidence of diastolic dysfunction assessed during echocardiography, whereas only a subset of these subjects demonstrate reduced LVEF (<40 – 45%) indicating impaired systolic function. Therefore, current guidelines recommend distinguishing between systolic HF and HF with normal ejection fraction or HF with preserved systolic function [3].

Echocardiography plays a major role in confirming the diagnosis of HFPEF. The diagnosis of HFPEF requires three conditions to be fulfilled [3, 16]:

- 1 Presence of typical signs and symptoms of HF;
- 2 Confirmation of normal or only mildly abnormal LV systolic function (LVEF ≥ 45 – 50%);
- 3 Evidence of diastolic dysfunction based on echocardiography examination.

There are three major patterns of abnormal filling, indicating abnormal LV relaxation and/or diastolic stiffness (abnormal relaxation, pseudonormalization, restrictive filling) [3, 16]. A detailed description of echocardiographic parameters reflecting diastolic function of LV has recently been provided in a consensus paper from the Heart Failure Association of ESC [16].

Acute and Decompensated Heart Failure

The terms ‘acute’ or decompensated’ HF are often used, although there are no commonly accepted definitions of these conditions. In most cases, these terms reflect the clinical need to characterize patients who are acutely admitted to hospital with signs and symptoms of HF.

According to ESC guidelines [3], acute HF is defined as a rapid onset or a gradual or rapid change in the symptoms and signs of HF, resulting in the need for urgent therapy or/and hospitalization for relief of symptoms. Acute HF indicates predominantly the medical emergency and the need for urgent therapy. However, the dynamic changes in the signs and symptoms of HF also constitute a crucial element of the clinical presentation in acute HF. Irrespective of the precipitating factor, pulmonary and/or systemic congestion due to elevated ventricular filling pressures, with or without a decrease in cardiac output, is nearly a universal finding. Acute HF may present as new-onset HF, in those without previous history of HF, or most frequently as decompensation in the presence of chronic HF. The former after clinical stabilization often progresses to chronic HF.

The classification of clinical presentations of acute HF according to ESC guidelines [3] comprises the following clinical scenarios (some of them may overlap each other): (a) worsening or decompensated chronic HF (peripheral edema/congestion) – usually a progressive worsening of chronic HF, evidence of systemic and/or pulmonary congestion; (b) pulmonary edema – severe respiratory distress, tachypnea and orthopnea with rales over lungs, arterial O₂ saturation usually <90% on room air; (c) hypertensive HF – high systemic BP, usually preserved LVEF, increased sympathetic drive with tachycardia and vasoconstriction, patients may be euvolemic or only mildly hypervolemic and present frequently with signs of pulmonary congestion without signs of systemic congestion; (d) cardiogenic shock – evidence of tissue hypoperfusion induced by HF after adequate correction of preload, reduced systolic BP (<90 mm Hg or a drop in mean arterial pressure of >30 mm Hg) and absent or low urine output (<0.5 ml/kg/h), evidence of organ hypoperfusion and pulmonary congestion develop rapidly; (e) right HF – low output syndrome in the absence of pulmonary congestion, with low left ventricle filling pressures, with increased jugular venous pressure, with or without hepatomegaly; (f) HF in the course of acute coronary syndrome.

The other classification of clinical profiles of acute HF at presentation has been recently proposed by Gheorghiade and Pang [17] and Gheorghiade et al. [18]: (a) elevated systolic BP (>160 mm Hg) – predominantly pulmonary (radio-graphic/clinical) congestion, with or without systemic congestion, typically with preserved LVEF, usually signs and symptoms develop abruptly; (b) normal or moderately elevated systolic BP – signs and symptoms develop gradually (days or weeks), associated with significant systemic congestion; (c) low systolic BP (<90 mm Hg) – mostly related to low cardiac output and often associated with impaired renal function; (d) cardiogenic shock – rapid onset, primarily complicating acute myocardial infarction, fulminant myocarditis, acute valvular disease; (e) flash pulmonary edema – abrupt onset, often precipitated by severe systemic hypertension; (f) acute coronary syndrome and acute HF – rapid or gradual onset, in many cases signs and symptoms of HF resolve after resolution

Table 6. Clinical features distinguishing acute HF into ‘vascular’ and ‘cardiac’ failure [19]

Clinical features	Vascular failure	Cardiac failure
BP	high	normal
Worsening	rapid	gradual (days)
Pulmonary congestion	present	systemic rather than pulmonary congestion
PCWP	acutely increased	chronically high
Rales	present	may be absent
Radiographic congestion	severe	may be absent
Weight gain	minimal	significant (edema)
LVEF	relatively preserved	usually low
Response to therapy	relatively rapid	continue to have systemic congestion in spite of the initial symptomatic response

of ischemia; (g) isolated right HF – rapid or gradual onset due to primary or secondary pulmonary artery hypertension or RV pathology (e.g. RV infarct), no epidemiological data; (h) postcardiac surgery HF – rapid or gradual onset, occurring in patients with or without previous ventricular dysfunction, often related to worsening diastolic function and volume overload immediately after surgery, can also be caused by intraoperative cardiac injury.

Another more simplified classification of acute HF into ‘vascular’ versus ‘cardiac’ failure has also been proposed [19]. The former often develops suddenly and comprises those with elevated BP, predominantly pulmonary congestion, preserved LVEF and rapid response to therapy. The latter develops gradually (days or weeks) and is associated with normal BP, systemic congestion usually on the background of chronic HF (table 6).

However, it should be noted that in the recent ACC/AHA guidelines [5] the term ‘acute HF’ has not been introduced. Instead, the authors have referred to a ‘hospitalized patient’ (clinical scenario when acute or progressive symptoms of HF develop and require hospitalization) [5]. Three distinct clinical profiles characterizing such patients have been described [5]: (a) volume overload – manifested by pulmonary and/or systemic congestion, often precipitated by an acute increase in chronic hypertension; (b) profound depression of cardiac output – manifested by hypotension, impaired renal function, and/or a shock syndrome; (c) signs and symptoms of both fluid overload and shock.

Heart Failure Etiology and Comorbidities

HF syndrome can be also classified according to the predominant etiology of the heart disease. Coronary artery disease and arterial hypertension are currently the leading causes of HF. The other causes of heart dysfunction may be valvular disease, tachyarrhythmias, diabetes mellitus, myocarditis, infiltrative disorders, to name but a few. This classification may be of clinical importance because in some cases it directly implies a particular causal therapy of HF.

Moreover, in the case of worsening of chronic HF, the diagnostic measures should be implemented to establish the major precipitating factor. Numerous cardiovascular conditions may trigger an acute event. The most common precipitating factors include: systemic or pulmonary hypertension, volume overload or fluid retention, myocardial ischemia, infection, anemia, thyrotoxicosis, nonadherence to HF medications or medical advice, drugs (such as: NSAIDs, COX inhibitors, thiazolidinediones), comorbidities (such as: chronic obstructive pulmonary disease, renal dysfunction).

Some authors also make a distinction between low and high cardiac output HF. In fact, it should be emphasized that all cases of HF are related to low cardiac output. However, some medical conditions may lead to a clinical presentation that mimics the signs and symptoms of HF. Precisely, in these conditions the primary abnormality is not disease of the heart (pregnancy, anemia, thyrotoxicosis, beriberi disease, etc.), but in a maladaptive manner these conditions induce high cardiac output in order to balance the increased circulatory demand. The conditions should rather be called circulatory failure, but importantly they are treatable and should be excluded when diagnosing HF.

Currently, there is mounting evidence to show that the complex pathophysiology of HF begins with an abnormality of the heart, but involves dysfunction of most body organs, including the cardiovascular, musculoskeletal, renal, neuroendocrine, hemostatic, immune, and inflammatory systems. Therefore, HF can also be classified according to the confirmed comorbidities, such as renal failure, anemia, iron deficiency, hormone deficiencies, diabetes, cachexia, etc.

Conclusions

The clinical syndrome of HF is hugely heterogeneous, comprising a wide spectrum of clinical conditions. Several distinct classifications of this syndrome have been introduced in order to better characterize an individual case and subsequently apply optimal management. None is free of inherent limitations, but many are commonly used in everyday clinical practice.

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Acute Kidney Injury: Classification and Staging

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Abstract

It was not until recently that consensus definitions for acute kidney injury (AKI) were proposed and published. The RIFLE (Risk-Injury-Failure-Loss-End-stage renal disease) and AKIN (Acute Kidney Injury Network) classifications were designed in order to be easily understood and applied in a variety of clinical and research settings. Their creation was intended to uniformly establish the presence or absence of the AKI and to give a quantitative idea of the severity of the disease unifying the commonly used parameters of serum creatinine and urine output. Subsequent validation showed that both the presence and severity of AKI, defined using RIFLE/AKIN, correlate well with patient outcome. This review will briefly describe the RIFLE/AKIN consensus definitions, its subsequent revisions and its successful validation and application to clinical research. The potential of extending the use of RIFLE/AKIN to the clinical setting of cardiorenal syndromes is also discussed.

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Introduction

Acute kidney injury (AKI) is an important clinical issue, especially in the setting of critical care and cardiovascular disease. In a large cohort of over 325,000 patients admitted to Veterans Affairs ICUs in the US, the frequency of AKI related to primary intensive care unit (ICU) admission diagnoses of cardiovascular disease and cardiovascular surgery were 28 and 14%, respectively [1]. In a multinational study from the Beginning and Ending Supportive Therapy for the Kidney, cardiovascular surgery was the most common diagnostic group identified among AKI patients, followed by medical respiratory, medical

cardiovascular and sepsis. Furthermore, in 27% of all patients, the AKI was secondary to cardiogenic shock [2].

AKI has been shown in multiple studies to be a key independent risk factor for mortality, even after adjustment for demographics, severity of illness and other relevant factors [3, 4]. It is a complex clinical syndrome for which there was no accepted definition for quite some time. Reported incidence and mortality rates vary widely in the literature, with incidence ranging from 1 to 31% and mortality from 28 to 82% [5]. This wide variation stems not only from the diverse patient populations in the different studies, but also from the disparate criteria used to define AKI in these studies. Over 30 definitions of acute renal failure/AKI have been used in the literature.

There is wide agreement that a generally applicable classification system is required for AKI which helps to standardize estimation of severity of renal dysfunction and to predict outcome associated with this condition [5, 6]. Such a classification was needed to bring order to the AKI literature, in much the same way that consensus definitions for sepsis [7], acute respiratory distress syndrome and acute lung injury [8] have done.

Importantly, the definition of AKI for clinical and translational research purposes may be somewhat different than what is used for clinical or epidemiological purposes. While clinicians can manage significant uncertainty in a diagnosis and treat patients as diagnostic studies unfold, interventional studies require operational definitions of disease that are more stringent, and specific formal rules for inclusion, exclusion and outcome adjudication.

Therefore, the essential components of a workable consensus definition are: (1) It should clearly establish the presence or absence of the disease, (2) must give an idea of the severity of the disease, (3) should correlate disease severity with outcome, and most importantly, (4) it should be easy to understand and apply in a variety of clinical and research settings [6].

In this light, the Acute Dialysis Quality Initiative [9], and subsequently the Acute Kidney Injury Network (AKIN) [10], have recognized such requirements and have worked to identify a uniform standard definition for diagnosing and classifying AKI. Hence, the RIFLE (Risk-Injury-Failure-Loss-End-stage renal disease) and AKIN classifications were developed. These classifications are discussed in detail elsewhere [6, 9, 10]. In this paper, we present a brief summary of their main features and drawbacks and their potential usefulness in the context of the cardiorenal syndromes (CRS).

RIFLE and AKIN

In 2004, the Acute Dialysis Quality Initiative group published their consensus definition for AKI, called the RIFLE classification [9]. Being a definition, it is intended to establish the presence or absence of the clinical syndrome of AKI

in a given patient or situation, and to describe the severity of this syndrome. RIFLE uses two criteria: (1) change in blood creatinine or GFR from a baseline value, and (2) urine flow rates per body weight over a specified time period (1). Patients are classified on the basis of the criteria which places them in the worse category. Risk is the least severe category of AKI, followed by Injury, and Failure is the most severe category. RIFLE is therefore also able to describe the change or trend in AKI severity over time. Loss and ESRD are outcome categories; a patient with AKI is considered to have a clinical outcome of loss if he continues to require renal replacement therapy (RRT) for >4 weeks. If such a patient continues to require RRT for >3 months, he is considered to have reached ESRD.

In 2007, a modified version of the RIFLE classification was published, also known as the AKIN classification (table 1) [10]. Five modifications are readily recognized: (1) Risk, Injury, and Failure have been replaced with stages 1, 2 and 3, respectively; (2) the change in GFR criteria has been eliminated; (3) an absolute increase in creatinine of at least 0.3 mg/dl has been added to stage 1; (4) patients starting RRT are automatically classified as stage 3, regardless of creatinine and urine output, and (5) the outcome categories of Loss and ESRD have been eliminated. The AKIN classification also introduces a dynamic component. It proposes an observation period of 48 h for the defined changes in each stage of AKI to occur, providing a measure of acuity which can be used for differentiation from slow changes in renal function occurring over longer periods. Additionally, by this definition changes in renal function may be determined independent of the baseline creatinine values. Furthermore, AKIN attempts to exclude transient changes in creatinine or urine output due to volume depletion or other easily reversible causes by recommending the 'exclusion of urinary tract obstructions or... easily reversible causes of decreased urine output' and application of the diagnostic criteria ideally '... following adequate resuscitation'.

Since their publication, the use of these consensus definitions has increased substantially in the medical literature. To date, over 45 studies have used either RIFLE or AKIN to define AKI [11–17]. Although, as noted above, differences exist between the two classifications, these appear to be relatively minor. In these studies, AKI diagnosed using either criteria is associated with poor clinical outcome. Overall, worse RIFLE or AKIN class is associated with higher mortality, and longer ICU or hospital stay. This biological gradient generally held true regardless of the type of patient population studied [11]. Furthermore, even mild AKI (RIFLE class Risk or AKIN stage I), is significantly associated with adverse patient events.

In a recent systematic review of AKI studies, we estimated risk ratio for mortality for patients with Risk, Injury or Failure levels compared with non-AKI patients [11]. Over 71,000 patients were included in the analysis of published reports. The majority of the studies looked at patients in general or specialized

Table 1. RIFLE and AKIN classifications for AKI

RIFLE			AKIN		
category	creatinine/ GFR criteria	UO criteria	stage	creatinine criteria	UO criteria
Risk	Increased creatinine $\times$ 1.5 or GFR decreased $>25\%$	UO ≤ 0.5 ml/kg/h $\times$ 6 h	Stage 1	Increased creatinine $\times$ 1.5 or ≥ 0.3 mg/dl	UO ≤ 0.5 ml/kg/h $\times$ 6 h
Injury	Increased creatinine $\times$ 2 or GFR decreased $>50\%$	UO ≤ 0.5 ml/kg/h $\times$ 12 h	Stage 2	Increased creatinine $\times$ 2	UO ≤ 0.5 ml/kg/h $\times$ 12 h
Failure	Increased creatinine $\times$ 3 or GFR decreased $>75\%$ or creatinine ≥ 4 mg/dl (with acute rise of ≥ 0.5 mg/dl)	UO ≤ 0.3 ml/kg/h $\times$ 24 h or anuria $\times$ 12 h	Stage 3	Increased creatinine $\times$ 3 or creatinine ≥ 4 mg/dl (with acute rise of ≥ 0.5 mg/dl) or RRT ¹	UO ≤ 0.3 ml/kg/h $\times$ 24 h or anuria $\times$ 12 h
Loss (outcome category)	Persistent acute renal failure = complete loss of renal function >4 weeks (but ≤ 3 months)	N/A		None	
ESRD (outcome category)	Complete loss of renal function >3 months	N/A		None	

UO = Urine output; RRT = renal replacement therapy. Adapted from Bellomo et al. [9] and Mehta et al. [10].

¹ Patients who receive RRT are considered to have met the criteria for stage 3 irrespective of the stage they are in at the time of RRT commencement.

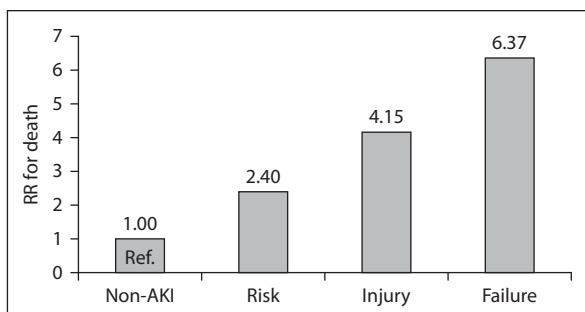


Fig. 1. Risk for all-cause mortality by severity of AKI (n = 71,527). Pooled data show a stepwise increase in relative risk (RR) for death with increasing AKI severity (risk, 2.40, 95% CI 1.94–2.97; injury, 4.15, 95% CI 3.14–5.48; failure, 6.37, 95% CI 5.14–7.90, with respect to non-AKI patients). Adapted from Ricci et al. [11].

ICU settings, one study analyzed all hospital admissions over a 3-year period, while another study made a population-based estimate of AKI incidence. Most studies were retrospective in design; only two of the included studies were prospective in design [12, 13]. The analysis of pooled data showed a stepwise increase in relative risk for death with increasing AKI severity (fig. 1; Risk, 2.40, 95% confidence interval (CI) 1.94–2.97; Injury, 4.15, 95% CI 3.14–5.48; Failure, 6.37, 95% CI 5.14–7.90, with respect to non-AKI patients) [11]. This result was verified regardless of the type of patient population studied, with the possible exception of patients dialyzed for AKI.

Thakar et al. [1] retrospectively examined the effect of AKI severity and of renal recovery on risk-adjusted mortality across a largest cohort of critically ill patients (more than 300,000) from 191 Veteran Affairs ICUs. They evaluated AKI utilizing AKIN classification. Their finding was that, overall, 22% of patients developed AKI (stage I: 17.5%; stage II: 2.4%; stage III: 2%); 16.3% of patients met AKI criteria within 48 h, with an additional 5.7% after 48 h of ICU admission. AKI frequency varied between 9 and 30% across ICU admission diagnoses. After adjusting for severity of illness in a model that included urea and creatinine on admission, odds of death increased with increasing severity of AKI, from stage I with odds ratio = 2.2, to stage II with odds ratio = 6.1, to stage III with odds ratio = 8.6. The absolute level of creatinine was also useful to identify patients with higher mortality risk than those who recovered. Interestingly, renal recovery after 72 h from ICU discharge was associated with a protective effect compared to patients that survived without a complete renal recovery. Finally, patients who decreased their creatinine level relative to ICU admission had less chance of dying than their illness severity score might predict. The authors concluded that strategies to prevent even mild AKI or promote renal recovery may improve survival [1].

AKI and Fluid Balance

The potential downstream effect of positive fluid balance on patient outcome is probably underestimated. In the clinical setting of heart failure, a positive fluid balance (often expressed in the literature as weight gain) is used by disease management programs as a marker of heart failure decompensation. Among ambulatory heart failure patients, it is associated with increased risk for hospitalization for heart failure [18, 19]. In another study focusing on inpatients, increases in weight (presumably due to positive fluid balance) during hospitalization for worsening heart failure was predictive of repeat hospitalization events, but not mortality in the postdischarge period [20].

In contrast to heart failure, there are more data about fluid balance in critically ill adults. With the advent of early goal-directed therapy, a large fluid volume amount is infused in order to target hypovolemia and organ perfusion. There have been a number of clinical investigations that evaluated the impact that fluid balance has on clinical outcomes in critically ill adults with AKI, and we propose that assessment of fluid balance should be considered as a potentially valuable biomarker of critical illness [21]. Recently, a secondary analysis of the SOAP (Sepsis Occurrence in Acutely Ill Patients) study, Payen et al. [22] examined the influence of fluid balance on survival of critically ill patients with AKI. In patients with AKI, average daily fluid balance was obviously more positive than in non-AKI patients. Interestingly, average daily fluid balance was significantly more positive also in patients receiving RRT even if, within this subgroup, those receiving earlier RRT (<2 days after ICU admission) had lower 60-day mortality, despite more oliguria and greater severity of illness. These data support the view that there is a potential survival benefit from early initiation of continuous RRT to prevent fluid accumulation and overload in critically ill patients, once initial fluid resuscitative management has been accomplished. To say it in another way, the prevention, and not just the correction, of fluid overload should perhaps be considered a primary trigger for extracorporeal fluid removal, independent of the need for solute clearance [21]. In the study by Payen et al. [22], AKI was defined by a renal Sequential Organ Failure Assessment score of 2 or greater, or by urine output under 500 ml/day. Data examining the relationship between fluid balance and AKI using the RIFLE/AKIN classifications are currently lacking.

AKI and the Cardiorenal Syndromes

Kidney and cardiac disease are exceedingly common, are increasing in prevalence and frequently coexist. Observational and clinical trial data have accrued to show that acute/chronic cardiac disease can directly contribute to acute/chronic worsening kidney function and vice versa. A consensus definition and

classification scheme for the CRS and its five specific subtypes has recently been proposed [23], and is discussed in detail in another article in this issue. A unifying definition for AKI is most relevant for CRS types 1 (acute CRS) and 3 (acute renocardiac syndrome). The five CRS subtypes are characterized by significant heart-kidney interactions that share similarities in pathophysiology; however, they are also likely to have important discriminating features, in terms of predisposing or precipitating events, risk identification, natural history and outcomes.

A description of the epidemiology of heart-kidney interaction stratified by the CRS subtypes is a critical initial step towards understanding not only the overall burden of disease for each CRS subtype, but also their natural history, associated morbidity and mortality, and potential health resource implications [24]. Likewise, a surveillance of the epidemiology is vital for determining whether there exist important gaps in knowledge and for the design of future epidemiologic investigations and clinical trials. Type 1 CRS is characterized by acute worsening of heart function leading to AKI and/or dysfunction. The spectrum of acute cardiac events that may contribute to AKI and the development of acute CRS (type 1 CRS) includes acute decompensated heart failure (ADHF), acute coronary syndrome (ACS), cardiogenic shock and cardiac surgery-associated low cardiac output syndrome. Conversely, type 3 CRS is characterized by acute worsening of kidney function (i.e. AKI) that leads to acute cardiac dysfunction (i.e. acute myocardial infarction, congestive heart failure, arrhythmias). In the cardiology literature, numerous operational definitions are used in epidemiologic and investigative studies for defining these exposures and outcomes.

The term 'worsening renal function' (WRF) has regularly been used to describe the acute and/or subacute changes in kidney function following ADHF or ACS. The incidence estimates for WRF associated with ADHF and ACS have ranged between 24–45% and 9–19%, respectively [25–31]. The broad range in reported incidence is largely attributable to variations in the definitions of WRF, the observed time at risk and the selected populations under study. For example, WRF has been defined as increases in serum creatinine (SCr) $\geq 26.5 \mu\text{M}$ (0.3 mg/dl) [26–28, 30], $\geq 44.2 \mu\text{M}$ (0.5 mg/dl) [27, 28, 30, 31], $\geq 25\%$ relative to SCr at the time of hospital admission, $\geq 50\%$ at the time of hospital admission, and as the combined increase of $\geq 26.5 \mu\text{M}$ (0.3 mg/dl) and $\geq 25\%$ increase [29]. This variation therefore presents a challenge for summarizing the epidemiology of CRS types 1 and 3 and for making valid comparisons across studies.

We therefore suggest the use of an established consensus definition for AKI, such as the RIFLE/AKIN criteria, in both clinical practice and future studies to aid in the investigation and analysis of future epidemiologic studies on CRS types 1 and 3 [24]. In addition, we suggest that AKI severity should also be classified according to the RIFLE/AKIN criteria. We also favor the use of the term AKI rather than WRF. The term AKI better represents the entire spectrum of acute renal failure, and would enable integration of these CRS subtypes into the broader context of AKI.

Conclusions

In recent years, the use of the consensus definitions of AKI (RIFLE and AKIN) in the literature has increased substantially. This suggests a highly encouraging acceptance by the medical community of a unifying definition for AKI. In these studies, AKI diagnosed using either criteria has been shown to associate with poor clinical outcome. Incorporation of these recently validated consensus definitions into the context of CRS will aid future epidemiologic and interventional studies as well as the integration of these CRS subtypes into the broader context of AKI.

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Cardiorenal Syndromes: Definition and Classification

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Abstract

To include the vast array of interrelated derangements, and to stress the bidirectional nature of the heart-kidney interactions, the classification of the cardiorenal syndrome (CRS) includes today five subtypes whose etymology reflects the primary and secondary pathology, the time-frame and simultaneous cardiac and renal codysfunction secondary to systemic disease. The CRS can be generally defined as a pathophysiologic disorder of the heart and kidneys, whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ. Type 1 CRS reflects an abrupt worsening of cardiac function (e.g. acute cardiogenic shock or decompensated congestive heart failure) leading to acute kidney injury. Type 2 CRS describes chronic abnormalities in cardiac function (e.g. chronic congestive heart failure) causing progressive and permanent chronic kidney disease. Type 3 CRS consists in an abrupt worsening of renal function (e.g. acute kidney ischemia or glomerulonephritis) causing acute cardiac disorder (e.g. heart failure, arrhythmia, ischemia). Type 4 CRS describes a state of chronic kidney disease (e.g. chronic glomerular disease) contributing to decreased cardiac function, cardiac hypertrophy and/or increased risk of adverse cardiovascular events. Type 5 CRS reflects a systemic condition (e.g. diabetes mellitus, sepsis) causing both cardiac and renal dysfunction. The identification of patients and the pathophysiological mechanisms underlying each syndrome subtype will help to understand clinical disorders and to design future clinical trials.

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Introduction

Cardiac disease is often associated with worsening renal function and vice versa. The coexistence of cardiac and renal disease significantly increases mortality, morbidity, and the complexity and cost of care [1, 2]. Syndromes describing the interaction between the heart and the kidney are recognized, but have never

Table 1. Definition and classification of the CRS

CRS general definition:

Disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other

Acute CRS (Type 1)

Acute worsening of cardiac function leading to renal dysfunction

Chronic CRS (Type 2)

Chronic abnormalities in cardiac function leading to renal dysfunction

Acute Renocardiac Syndrome (Type 3)

Acute worsening of renal function causing cardiac dysfunction

Chronic Renocardiac Syndrome (Type 4)

Chronic abnormalities in renal function leading to cardiac disease

Secondary CRS (Type 5)

Systemic conditions causing simultaneous dysfunction of the heart and kidney

been clearly defined and classified. Several different definitions have been proposed [1, 3–8] with limited understanding of epidemiology, diagnostic criteria, prevention and treatment.

In response to these issues, a consensus conference was organized under the auspices of the Acute Dialysis Quality Initiative (ADQI) by bringing together key opinion leaders and experts in the fields of nephrology, critical care, cardiac surgery, cardiology and epidemiology. A consensus definition and classification system for the cardiorenal syndromes (CRS) was reached [9].

Methodology and ADQI Process

The ADQI process was applied using previously described methodology [10]. In brief, the ADQI methodology comprises a systematic search for evidence with review and evaluation of relevant literature, establishment of clinical and physiologic outcomes for comparison of different treatments, description of current practice and analysis of areas in which evidence is lacking and future research is required. A full description of the used methodology can be found in the official ADQI website www.ADQI.net.

Three key questions regarding definition and classification were identified by the entire ADQI group, and a subgroup deliberated on these questions, bringing forth recommendations to the group as a whole.

- 1 Is there a need for an overall definition of the clinical syndromes derived from cardiac and renal interactions?

- 2 What should be the principles of such a definition system?
- 3 How should they be defined and classified?

Results

There was unanimous agreement that a consensus definition was needed for the CRS. It was perceived that the existing literature was inconsistent or lacking, that disciplines tended to be organ centered, and that the bidirectional nature of these syndromes was poorly appreciated. A new definition would provide a common platform for multidisciplinary approaches. It was agreed that a large umbrella term be preferred, using the plural, to indicate the presence of multiple syndromes. Subtypes would recognize the primary organ dysfunction (cardiac versus renal) as well as the acute versus chronic nature of the condition. Both organs must have or develop structural or functional abnormalities. An additional subtype was desired to capture systemic conditions that affect both organs simultaneously [3–9].

Consensus Definition and Classification

CRS were defined as ‘disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other’. Five subtypes of the syndromes were identified and defined as reported in table 1.

Acute Cardiorenal Syndrome (Type 1)

This appears to be a syndrome of worsening renal function that frequently complicates hospitalized patients with acute decompensated heart failure and acute coronary syndrome. Many previous attempts to define ‘cardiorenal syndrome’ correspond to this subtype. This entity has specific epidemiology, pathogenesis, treatment and prevention strategies. In the US, over one million patients are hospitalized each year with acute decompensated heart failure, and it is estimated that 27 to nearly 40% of these patients will develop acute kidney injury as defined by an increase in serum creatinine of at least 0.3 mg/dl [2, 11]. Those who experience worsening renal function have a higher mortality and morbidity, and increased length of hospitalization.

Chronic Cardiorenal Syndrome (Type 2)

This subtype is a separate entity from acute CRS as it indicates a more chronic state of kidney disease complicating chronic heart disease. This is an extremely common problem. For instance, in patients hospitalized with congestive heart failure, approximately 63% meet the K/DOQI definition [12] of stage 3–5

chronic kidney disease, representing an estimated glomerular filtration rate <60 ml/min/1.73m² [13].

Acute Renocardiac Syndrome (Type 3)

Although acute kidney injury is recognized as an important cause of acute heart disorder, the pathophysiological mechanisms likely go beyond simple volume overload and hypertension, and the recent consensus definition for acute kidney injury [14] will aid in the investigation and analysis of epidemiologic data. The incidence and prevalence of this syndrome are currently unknown; however, the development of new biomarkers, and the study of prevention and management strategies in acute kidney injury following radiocontrast or cardiac surgery, for example, will increase our knowledge of this syndrome.

Chronic Renocardiac Syndrome (Type 4)

A large body of evidence has accumulated demonstrating the graded and independent association between level of chronic kidney disease and adverse cardiac outcomes. In a recent meta-analysis, an exponential relation between the severity of renal dysfunction and the risk for all-cause mortality was described. Compared with a 'normal' glomerular filtration rate of 100 ml/min, the adjusted relative odds for death associated with glomerular filtration rate of 80, 60, and 40 ml/min were 1.9, 2.6, and 4.4, respectively [15]. Overall mortality was driven by excess cardiovascular deaths, which constituted over 50% of the total mortality.

Secondary Cardiorenal Syndromes (Type 5)

Although this subtype does not have a primary and secondary organ dysfunction, situations do arise where both organs simultaneously are targeted by systemic illnesses, either acute or chronic. Examples include sepsis, systemic lupus erythematosus, amyloidosis and diabetes mellitus.

Many patients may populate or move between subtypes during the course of their disease describing the possibility that a vicious circle is instituted when heart and kidney present simultaneous or combined dysfunction (fig. 1) [16]. The classification was not meant to fix patients into one immovable category. The group discussed and considered further subclassification, to include situations of transient or reversible dysfunction, slowly or acutely progressive versus stable disease, however chose a more parsimonious and simple scheme for this iteration.

Conclusions

Through the ADQI consensus on CRS, other processes will now be facilitated, including a better or clearer understanding of the epidemiology of these

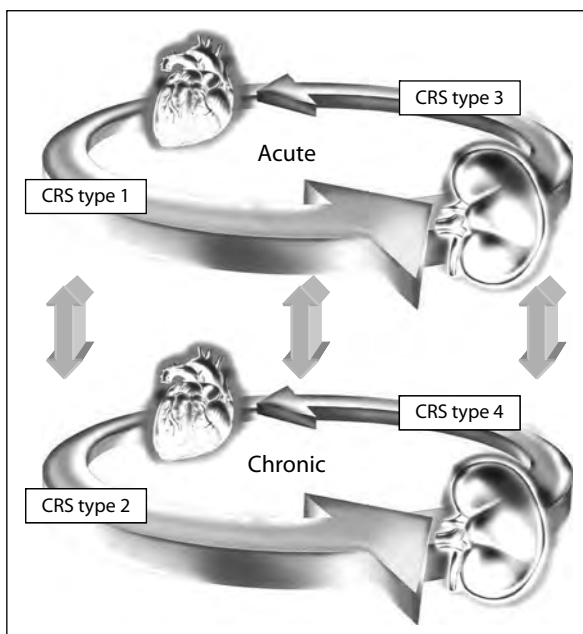


Fig. 1. Different types of CRS can be interconnected and patients may move from one type to another during the time course of the combined disorders.

conditions, opportunities for early diagnosis through biomarkers, the development of preventive strategies and application of evidence-based management strategies (where available). The application of these consensus definitions will also allow the identification of gaps in the literature, and provide direction for future research including clinical trials.

This classification indeed represents a tool to promote new interaction between cardiology and nephrology in the attempt to build a new pathway of collaboration and a new holistic approach to patients suffering from combined heart and kidney disorders.

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Oliguria and Fluid Overload

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Abstract

Oliguria is a very common clinical situation that is also often difficult to interpret since it may represent either the expression of a disease or an appropriate response of the kidneys to extracellular volume depletion or decreased renal blood flow. In patients with acute kidney injury, oliguria is independently associated with mortality. Fluid overload is a complication of the impaired sodium and water excretion observed in patients with oliguric acute kidney injury. Fluid overload leads not only to cardiopulmonary complications such as congestive heart failure and pulmonary edema requiring mechanical ventilation but also to several others such as delayed wound healing, tissue breakdown, and impaired bowel function. The aim of this short review is to point out the deleterious effects of these two related clinical situations emphasizing their pathophysiology.

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Oliguria

Oliguria is one of the most common clinical situations encountered by physicians. Its interpretation is often difficult since it may represent either the expression of a disease or the normal response of the kidneys to extracellular volume depletion or decreased renal blood flow. In terms of epidemiology, the Acute Dialysis Quality Initiative group has defined oliguria as urine output less than 0.3 ml/kg/h for at least 24 h. However, since any delay in treatment can lead to a dangerous progression of the acute kidney injury (AKI), early clinical recognition of oliguria appears to be crucial. Thus, oliguria should rather be suspected when the urine flow rate is <0.5 ml/kg/h for two consecutive hours. Indeed, 69% of ICU patients who developed AKI in one study were oliguric [1], and these patients represent a subgroup of AKI patients with poor prognosis. Many epidemiologic studies have found the presence of oliguria, in the context of AKI, to

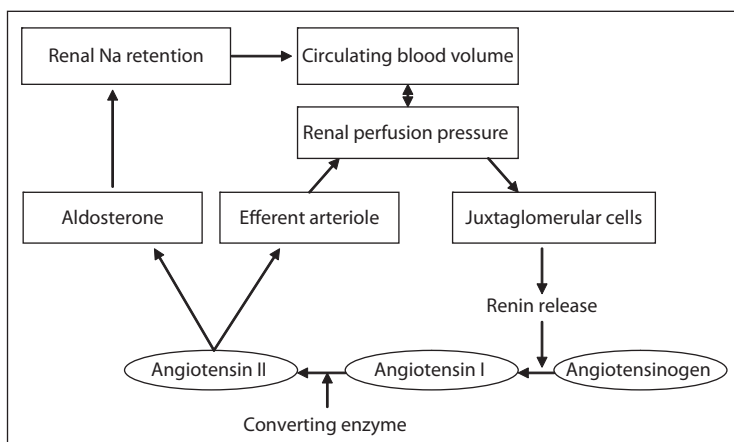


Fig. 1. Network of effects and feedback loop for the renin-angiotensin-aldosterone system. As circulating blood volume or renal perfusion changes, renin secretion changes resulting in downstream effects that ultimately influence renal resistance and sodium handling by the kidney. Changes in urine output are a direct result of these changes.

be independently associated with mortality [1–3]. Although not all severe forms of AKI are characterized by oliguria [4], the association of oliguria and mortality is explained at least partially by the fact that oliguria represents a surrogate for a more significant injury or greater severity of AKI [5]. The fact that non-oliguric AKI is reported to have a better prognosis compared with oliguric AKI is important because it probably partially explains why many ICU practitioners want to preserve or increase urine flow by using loop diuretics [6, 7].

Urine output is a function of glomerular filtration and tubular secretion and reabsorption. Glomerular filtration is directly dependent on renal perfusion, which is a function of 3 determinants: circulating blood volume, cardiac output and renal perfusion pressure which depends on arterial pressure and renal vascular resistances. The intra-renal vasculature is capable of preserving glomerular filtration rate (GFR) in the face of varying systemic pressure through important neurohumoral autoregulating mechanisms that affect the afferent and efferent arterioles modulating the renal perfusion pressure. The renin-angiotensin-aldosterone system is perhaps the most significant one (fig. 1).

The relationship between urine output and renal function is complex: oliguria may indeed be more profound when tubular function is intact [8]. When volume depletion and hypotension occur, vasopressin secretion is strongly stimulated and, as a consequence, the distal tubules and collecting ducts become fully permeable to water. Concentrating mechanisms in the inner medulla are also aided by low flow through the loops of Henle and thus, urine volume is minimized and urine concentration maximized (>500 mosm/kg). Conversely,

Table 1. Biochemical indices useful to distinguish prerenal from intrarenal oliguria

	Oliguria	
	prerenal	intrarenal
Urine osmolality, mosm/kg	>500	<400
Urine Na, mm	<20	>40
Serum urea/serum creatinine	>0.1	<0.05
Urine/serum creatinine	>40	<20
Urine/serum osmolality	>1.5	≤1
Fractional excretion of Na, %	<1	>2
Fractional excretion of urea, %	<35	>35

Fractional excretion of Na = [(urine Na/serum Na)/(urine creatinine/serum creatinine)] ×100. Except for Fe urea, these indices are unreliable once the patient has received diuretic or natriuretic agents (including dopamine and mannitol)

when the tubules are injured, maximal concentrating ability is impaired and urine volume may even sometimes be normal (nonoliguric AKI). These physiologic effects form the basis of clinical rules to distinguish prerenal from renal oliguria (table 1). As described, a high urine osmolality coupled with a low urine Na in the face of oliguria and azotemia is strong evidence of intact tubular function. However, this situation should definitely not be interpreted as ‘benign’ or even as ‘prerenal azotemia’ since intact tubular function may also be seen with various forms of disease such as glomerulonephritis. Sepsis, the most common condition associated with AKI in the ICU [9], may also alter renal function without any characteristic changes in urine indices [10, 11].

Oliguria indicates either an important reduction in GFR related to a decreased renal perfusion or a mechanical obstruction to urine flow.

Reduction in GFR linked to decreased renal perfusion can be related to the following conditions:

- Absolute decrease in blood volume due to trauma, hemorrhage, burns, diarrhea or sequestration of fluid as in pancreatitis or abdominal surgery.
- Relative decrease in blood volume in which the primary disturbance is an alteration in the capacitance of the vasculature due to vasodilatation. This is commonly encountered in sepsis, hepatic failure, nephrotic syndrome, and use of vasodilatory drugs including anesthetic agents.
- Decreased cardiac output that can happen in many clinical situations (e.g. cardiogenic shock, cardiac tamponade).
- Decreased renal perfusion pressure that may be due to structural causes such as thromboembolism, atherosclerosis, dissection, inflammation (vasculitis

- especially scleroderma) affecting either the intra- or extrarenal circulation. Although renal arterial stenosis presents as subacute or chronic renal dysfunctions, renal atheroembolic disease can present as AKI with acute oliguria. Renal atheroemboli (usually due to cholesterol emboli) usually affects older patients with a diffusive erosive atherosclerotic disease. It is most often seen after manipulation of the aorta or other large arteries during arteriography, angioplasty or surgery [12]. This condition may also occur spontaneously or after treatment with heparin, warfarin or thrombolytic agents. Drugs such as cyclosporine, tacrolimus and ACE inhibitors cause intrarenal vasoconstriction resulting in reduced renal plasma flow. Rarely, decreased renal perfusion may also occur as a result of an outflow problem such as a renal vein thrombosis or abdominal compartment syndrome which is a symptomatic organ dysfunction that results from an increase in intra-abdominal pressure. Abdominal compartment syndrome leads to AKI and acute oliguria mainly by directly increasing renal outflow pressure, thus reducing renal perfusion. Other possible mechanisms decreasing renal perfusion pressure include direct parenchymal compression and arterial vasoconstriction mediated by stimulation of the sympathetic nervous and renin-angiotensin systems (renin-mediated arterial vasoconstriction) by the fall in cardiac output related to decreased venous return. However, emerging evidence suggests that the rise in renal venous pressure, rather than the direct effect of parenchymal compression, is the primary mechanism of renal dysfunction. Generally, intra-abdominal pressures >15 mm Hg can lead to oliguria and pressures >30 mm Hg usually lead to anuria [13].
- e Acute tubular necrosis which is often an end result of the above factors. It may also be due to direct nephrotoxicity of agents like antibiotics, heavy metals, solvents, contrast agents, crystals like uric acid or oxalate.

Reduction in GFR can also be related to mechanical obstruction to urine flow. This can be due to complete or severe partial bilateral ureteral obstruction (caused by stones, papillary sloughing, crystals or pigment), urethral or bladder neck obstruction (blood at the urethral meatus or urethral disruption after trauma, prostatic hypertrophy or malignancy, recent spinal anesthesia) or simply due to malpositioned or obstructed urinary catheter. Rarely, urine volume can be increased in cases of partial obstruction due to pressure-mediated impairment of urine concentration. Rapid increases in serum blood urea nitrogen and creatinine (especially more than double every 24 h) is a particularity of urinary obstruction.

Fluid Overload

Fluid overload is an obvious complication of the impaired sodium and water excretion observed in oliguric AKI. In addition, critically ill patients with

oliguric AKI are at increased risk for fluid imbalance due to widespread systemic inflammation, reduced plasma oncotic pressure and increased capillary leak [5]. All these phenomena make these patients very good candidates for rapid and severe fluid overload states leading to cardiopulmonary complications such as congestive heart failure, pulmonary edema requiring mechanical ventilation, pulmonary restrictive defects and reduced pulmonary compliance.

Fluid overload is also implicated (at least indirectly) in the occurrence of other complications such as leaking of surgical anastomoses, sepsis, bleeding requiring transfusion, wound infection or dehiscence. These associations are supported by studies evaluating different strategies of administration of perioperative fluid therapy during surgical procedures. Brandstrup et al. [14] randomized 172 patients undergoing colorectal surgery to either a goal-oriented replacement of measured fluid losses or a standard intraoperative and postoperative regimen which is known to greatly exceed the fluid losses leading to an excess of 3–7 kg in weight in the early postoperative period [15]. Postoperative complications described above were dramatically reduced for patients receiving the restrictive regimen (33 vs. 51%, $p = 0.01$) [14]. Another study confirmed these findings in 152 patients undergoing elective major gastrointestinal surgery [16].

As stated above, patients with oliguric AKI are particularly at risk of fluid overload and therefore a restrictive strategy of fluid administration should be used in these patients when possible. This is probably even of greater importance when considering recent changes in ICU practice worldwide with early goal-directed therapy meaning administration of large volumes of fluid therapy [17–20]. Indeed, intensivists are now more likely to try first to give additional fluid therapy during resuscitation rather than initiating vasopressors, and this may further compound fluid overload in oliguric AKI patients. While under-resuscitation should be avoided, fluid accumulation can be associated with harm [21–24]. In a small cohort of sepsis-induced AKI patients, Van Biesen et al. [23] reported that additional fluid therapy leading to positive fluid balance failed to impact kidney function while reducing lung function and oxygenation. Other studies have shown that a high positive cumulative fluid balance is an independent risk for hospital mortality [21, 22, 25]. More recently, the ARDS Clinical Trials Network reported a randomized trial comparing restrictive and liberal strategies for fluid management after complete resuscitation in 1,000 ICU patients with acute lung injury, of which most were septic [24]. Although no difference in the primary outcome of death at 60 days was found between the strategies (25.5% for restrictive vs. 28.4 for liberal, $p = 0.3$), the restrictive strategy had showed improved lung function, increased ventilator-free days, reduced ICU length of stay, no increase in the rate of nonpulmonary organ failure or shock and a trend for reduced need for RRT [24]. Thus, the practice of giving additional fluid in excess of the measured losses (resulting

in fluid overload) is not supported by evidence especially for patients that are not responsive to fluid [5, 21, 23, 24]. Conversely, there is emerging evidence that positive fluid accumulation in ICU patients can adversely impact outcomes [5, 21–25].

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Pathophysiology of Fluid Retention in Heart Failure

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Abstract

Background: Fluid retention in the face of an expanding extracellular fluid volume is a key contributing factor in the development and progression of heart failure. **Methods:** We performed a review of clinical texts as well as a Medline investigation for the pathophysiology of fluid and sodium retention in heart failure. **Results:** A breakdown in the integrity of the arterial circulation, seen in both high and low output heart failure, triggers a complex cascade of maladaptive events in an effort to maintain cardiorenal homeostasis. The activation of several neurohumoral mechanisms including the sympathetic nervous system, renin-angiotensin-aldosterone axis, nonosmotic arginine vasopressin release, and natriuretic peptide release initially compensates for depressed myocardial function. However, prolonged activation of these systems contributes to sodium and fluid retention, increased preload and afterload, and further damage to the myocardium. Improved understanding of this multifaceted pathophysiology has driven the development of improved treatment modalities, such as beta-blockers and angiotensin converting enzyme inhibitors which are now mainstays of heart failure therapy. **Conclusions:** Further investigation into the neurohumoral mechanisms activated in the heart failure patient is a promising avenue for advances in diagnosis, prognosis, and treatment of this prevalent and devastating disease.

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Alterations in the normal balance of sodium and water are key contributing factors to the progression of heart failure. In an effort to compensate for the failing heart, a complex cascade of physiologic events is triggered to improve delivery of oxygenated blood to metabolically active tissues. These include activation of the sympathetic nervous system, renin-angiotensin-aldosterone axis, and arginine vasopressin (AVP) release. However, the long-term effects of these physiologic changes eventually lead to deterioration in clinical status and inappropriate retention of sodium and water [1]. It is fluid retention that is responsible for the

clinical manifestations of heart failure, including fatigue, dyspnea, orthopnea, lower extremity edema, pleural effusions, and ascites. Enhanced understanding of these mechanisms has improved therapies to ameliorate symptoms, prevent progression of disease, and prolong survival, and promises continued advancement in the management of this increasingly prevalent health care problem. In this chapter, we will explore the alterations in normal circulatory and renovascular function that contribute to ongoing electrolyte and volume disturbances in the heart failure patient.

Arterial Underfilling Hypothesis

Normal fluid and electrolyte homeostasis is maintained by the kidneys in an intricate series of interactions with the heart and vasculature. The kidneys, commanding approximately 20% of the overall cardiac output, are sensitive to changes in hydrostatic pressure gradients, as well as osmotic gradients [2]. Changes in these factors trigger alterations in sodium and water retention in the nephron which serve to maintain a relatively unchanged total body water and solute composition. Additionally, multiple neurohumoral pathways are activated by changes in vascular hemodynamics, including the autonomic nervous system, renin-angiotensin-aldosterone system (RAAS), natriuretic peptides (NPs), and AVP. These pathways work in concert with the kidneys to preserve cardiorenal homeostasis [3], and maintain a relatively tight fluid and electrolyte balance in the face of changing intake, metabolic factors, exercise, and environment.

In edematous disease states such as heart failure, perturbations in this carefully maintained fluid and electrolyte balance predominate. Despite clinically evident expansion of total body fluid and a measurable increase in total blood volume [4], the kidneys actively retain sodium and fluid. Historically, this was ascribed to low cardiac output and diminished perfusion pressure, sensed in the renal afferent arteriole. However, this same fluid retention is noted in high cardiac output conditions such as pregnancy, beriberi, and thyrotoxicosis. Notably, it has been shown that kidneys from patients with heart or liver failure no longer exhibit aberrant sodium and fluid retention when transplanted into patients with normal cardiac or hepatic function [5, 6]. The etiology of such abnormal performance in otherwise healthy kidneys has been attributed to a unifying hypothesis of arterial underfilling [7–9].

In this hypothesis, a breakdown in the integrity of the arterial circulation is the key stimulus for renal retention of sodium and water. This is prompted either by low cardiac output states, or by diminished peripheral vascular resistance (as might occur in high-output heart failure). Since 85% of the total blood volume is distributed in the venous side of the circulation, total blood volume expansion may occur in the venous circuit without an effect on the 15% remaining on the

arterial side. In response to diminished arterial circulation, various neurohumoral systems are triggered as compensatory responses to maintain adequate perfusion pressure of vital organs. In heart failure, these mechanisms are chronically activated and eventually contribute to deterioration in clinical status, and worsening strain on the failing heart. We will explore each of these systems in further detail.

Sympathetic Nervous System

The sympathetic nervous system is responsible for many cardiovascular actions in the normally functioning heart, which serve to maintain cardiac output and peripheral perfusion pressure. Changes in mean arterial pressure (MAP) activate cardiovascular reflexes mediated by baroreceptors in the carotid sinus, aortic arch, and left ventricle, as well as cardiopulmonary 'low pressure' baroreceptors, and peripheral chemoreceptors. A diminishing MAP activates carotid sinus and aortic arch baroreceptors, generating an afferent signal that travels via the vagus and glossopharyngeal nerves to the cardio-regulatory centers in the medulla. This signal decreases inhibitory tone and thus activates the sympathetic nervous system, resulting in increased heart rate and contractility, reduction of venous capacitance, and vasoconstriction in the periphery. These effects are regulated by the catecholamines norepinephrine (NE) and epinephrine, which are released into the circulation from various locations throughout the body [10]. In the healthy heart, this is an integral part of homeostasis and the preservation of a relatively unchanging MAP in spite of varying physiologic conditions.

The aforementioned pathway is likewise activated in the failing heart, as the high pressure baroreceptors are unloaded by diminished myocardial contractility. Multiple studies have demonstrated a marked increase in the plasma concentration of NE as well as a reduction in peripheral NE stores in heart failure patients [11, 12]. This excess catecholamine has detrimental effects on the failing heart, including increased cardiac work and myocyte hypertrophy. In fact, high NE levels (>800 pg/ml) are known to be toxic to cardiac myocytes [13], and have been shown to be associated with $<40\%$ 1-year survival. Additionally, efferent renal sympathetic activity causes renal vasoconstriction and activation of the RAAS [3]. This stimulation, coupled with the direct effects of renal nerve activation on the proximal tubule [14], results in sodium and water reabsorption in the face of an expanding extracellular fluid volume. Compounding this insult, the activated SNS stimulates the supraoptic and paraventricular nuclei in the hypothalamus, causing nonosmotic release of AVP and further retention of free water in the kidney [9]. This begins a cycle of SNS activation, myocardial damage, and sodium and water retention that contributes to the progression of clinical heart failure.

Renin-Angiotensin-Aldosterone System

Renin is a proteolytic enzyme synthesized in the kidneys and released from juxtaglomerular cells in response to various stimuli. Such stimuli include baroreceptor unloading in the renal afferent arteriole (as might be seen with diminished cardiac output in heart failure), hyponatremia sensed by the macula densa, increased renal sympathetic activity or circulating catecholamines, and diuretics [15]. Renin converts angiotensinogen to angiotensin I, which in turn is converted to angiotensin II (ANG II) by angiotensin converting enzyme. ANG II causes peripheral vasoconstriction, and additionally stimulates the adrenal cortex to release aldosterone, augmenting the reabsorption of sodium in the collecting duct.

Heart failure patients are known to have elevated plasma concentrations of renin, ANG II, and aldosterone. The latter two are the primary mediators of sodium and fluid retention in heart failure. ANG II has multiple deleterious effects when activated in these patients, including hypertrophy, remodeling, and fibrosis of the myocardium [16]. ANG II enhances neuronal NE release peripherally and serves as a potent vasoconstrictor, increasing systemic vascular resistance and thus afterload. ANG II also directly stimulates sodium re-absorption in the proximal tubule. Aldosterone acts at the level of the distal nephron to enhance sodium reabsorption in exchange for protons and potassium ions. Aldosterone also promotes coronary and renovascular remodeling, baroreceptor dysfunction, and inhibits NE uptake in the myocardium [17]. Interestingly, when normal healthy subjects are given aldosterone, they exhibit the ability to ‘escape’ from mineralocorticoid effects, and edema is not observed [18, 19]. It is currently thought that increased ANG II and sympathetic activity in the heart failure patient diminish distal tubular sodium delivery, impairing the ability to escape from aldosterone effects.

Despite an effective increase in extracellular fluid volume resulting from release of these substances, the arterial underfilling effect remains and activation of this system is maintained throughout disease progression and in the face of excess total body water. Consequently, many chronic heart failure (CHF) therapies, including angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and mineralocorticoid antagonists target the RAAS to curb the maladaptive efforts of the kidney to maintain adequate ‘perceived’ circulating blood volume.

Arginine Vasopressin

AVP is a hormone with antidiuretic action synthesized in the supraoptic and paraventricular nuclei of the hypothalamus and secreted by the posterior pituitary. Common stimuli for release of AVP into the circulation are increases as

small as 1–2% in plasma osmolality [9], and decreases in circulating blood volume triggered by pressure-sensitive baroreceptors in the aortic arch, carotid sinus, left ventricle and renal afferent arteriole [20]. Conversely, AVP release is usually suppressed by 1–2% decreases in plasma osmolality. AVP is a potent arteriolar vasoconstrictor, causing increased vascular resistance. Additionally, AVP stimulates aquaporin-2 channels in the renal collecting duct to increase free water absorption, and also mediates ACTH release from the anterior pituitary to upregulate release of aldosterone.

Given the sodium and fluid retention described above in states of heart failure, one might expect suppression of AVP. However, multiple studies have demonstrated ‘non-osmotic’ plasma levels of AVP in patients with hyponatremia and hypo-osmolality seen in various edematous disorders [21, 22]. In fact, plasma AVP levels have been shown to correlate with adverse outcomes in CHF, and plasma concentrations increase linearly with severity of disease state [23]. The proposed reason for this nonosmotic release is again related to the arterial underfilling hypothesis, with unloading of high and low pressure baroreceptors as the primary stimulus for the nonosmotic release of AVP in cardiac failure. This overrides the hypo-osmotic effect to suppress AVP release [24]. Additionally, NE and ANG II are known to stimulate AVP release, both of which exist at elevated plasma concentrations in the heart failure patient. The net effect of this AVP release is worsening hyponatremia and water retention in the face of increased total body water. Antagonism of the AVP receptor in humans with heart failure has been shown to decrease urinary aquaporin-2 excretion and increase free water excretion by the kidneys [25]. However, this as of yet has not been correlated with improved clinical outcomes. Combined with the maladaptive behavior of the sympathetic nervous system, and activated renin-angiotensin-aldosterone axis, the heart failure patient with increased AVP release is rendered incapable of appropriately regulating fluid and electrolyte balance.

Endothelin and TNF- α

Additional vasoactive substances have been found to be elevated in patients with congestive heart failure, including endothelin-1, and tumor necrosis factor. Endothelin-1 is a potent vasoconstrictor, produced in the cells of the vascular endothelium and tubules of the kidney. High plasma concentrations of this substance have been linked with poor prognosis in heart failure patients [26]. Although not well elucidated, endothelin-1 may also significantly influence renovascular resistance and thus alter sodium and water handling in the kidney. Tumor necrosis factor is elevated in patients with heart failure as well. In addition to depressing myocardial function, TNF- α may contribute to further excitation of the sympathetic nervous system [27]. These factors as such promote a continued deleterious loop of vasoconstriction, neurohumoral activation, and

worsening renal perfusion exacerbating the maladaptive sodium and water retention manifest in heart failure.

Natriuretic Peptides

In contrast to the systems mentioned above, NPs are released in heart failure and fluid overload states in an attempt to counterbalance vasoconstriction and fluid retention. There are at least three members of the NP family: atrial NP (ANP), brain NP (BNP), and C-type NP (CNP). ANP is released primarily by the right atrium, while BNP is secreted predominantly in the ventricles. The secretion of both is enhanced by increased atrial or ventricular end-diastolic pressure. Both ANP and BNP have been shown to increase sodium and water delivery to the renal tubule, causing diuresis and natriuresis, and both relax vascular smooth muscle by antagonizing the vasoactive effects of ANG II, endothelin, AVP and catecholamines [28]. CNP is released by cells in the kidney, ventricles and intestine and has a similar effect, albeit more localized in its action.

Heart failure patients have increased plasma concentrations of the natriuretic peptides compared to normal subjects, and these levels are positively correlated with the severity of disease [29]. In spite of this increase, vasoconstriction and fluid retention prevail, suggesting that resistance to the NP system develops with progression of CHF. The reasons for this hyporesponsiveness are not well understood. It is known that the RAAS and specifically ANG II counteract the renal effects of ANP in normal healthy patients [30], possibly by afferent and efferent renal arteriolar vasoconstriction attenuating NP delivery. Also, it is likely that the sympathetic nervous system antagonizes the renal effects of the NPs again by alterations in renal blood flow and NP delivery. Other proposed mechanisms include the release of less active forms of NPs, downregulation of NP receptors, and increased degradation and elimination. Regardless of the reason, this hyporesponsiveness is critical in the development of a positive sodium and fluid balance.

Conclusions

The retention of fluid in patients with congestive heart failure involves the complex, interconnected activation of multiple neurohumoral systems. These systems are designed as protective mechanisms to maintain the integrity of the circulation and preserve organ perfusion during periods of perceived low cardiac output or arterial underfilling. While initially compensatory, the actions of the activated sympathetic nervous system, renin-angiotensin-aldosterone axis, nonosmotically released AVP, endothelin-1 and tumor necrosis factor eventually cause further damage to the failing heart. In turn, the neurohumoral

mechanisms remain stimulated propagating a destructive feedback loop of maladaptive volume expansion that diuretics alone are incapable of reversing. Improved understanding of the multifaceted, multi-organ system pathophysiology is central to the development of improved diagnostic and therapeutic modalities for this prevalent and devastating disease.

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Fluid Overload as a Biomarker of Heart Failure and Acute Kidney Injury

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Abstract

Background/Aims: Acute heart failure (HF) and acute kidney injury (AKI) are common. These syndromes are each associated with considerable morbidity, mortality, and health resource utilization and are increasingly encountered. Fluid accumulation and overload are common themes in the pathophysiology and clinical course of both HF and AKI. **Methods:** This narrative literature review provides an overview of the pathophysiology of fluid accumulation with a focus on HF and AKI, along with a discussion of the importance of assessment of fluid balance in these syndromes and how it correlates with clinical outcome. **Results:** In HF, fluid accumulation, defined as either a positive cumulative fluid balance or as an acute redistribution of fluid, represents a core precipitating mechanism of acute decompensation and is associated with worsening symptoms, hospitalization and death. Determining fluid balance in HF may be complex and depend largely on underlying pathophysiology; however, in addition to simple fluid balance (intake minus output) measurement, newer biomarkers (i.e. B-type natriuretic peptides) and novel technology (i.e. impedance cardiography) are proving to be useful for detection and risk identification for acute decompensated HF that may allow earlier intervention and translate into improved clinical outcomes. Recent data have also emerged showing the importance of fluid balance in both adult and pediatric patients with AKI. In general, a positive cumulative fluid balance portends higher morbidity and an increased risk for worse clinical outcome. Fluid balance should be recognized as a potentially modifiable biomarker and determinant of clinical outcome in these patients. **Conclusion:** To date, the impact of fluid balance in both of these syndromes, more so with AKI, has likely been underappreciated. There is little to no data specifically on fluid balance in the cardiorenal syndrome, where acute/chronic heart disease can directly contribute to acute/chronic worsening of kidney function that likely exacerbates fluid homeostasis. Additional investigations are needed.

Acute heart failure (HF) and acute kidney injury (AKI) are both common syndromes encountered in clinical practice. These syndromes are each associated with considerable morbidity, mortality, and health resource utilization, and both have recently been shown to be increasing in incidence and prevalence [1–5]. Moreover, heart and kidney disease frequently coexist [6, 7]. Observational and clinical trial data have accrued to show that acute/chronic heart disease can directly contribute to acute/chronic worsening kidney function and vice versa – termed the cardiorenal syndrome (CRS). Recently, a consensus definition and classification scheme for the CRS have been proposed [8]. The CRS and its subtypes are characterized by significant heart-kidney interactions that share fundamental principles in predisposing pathophysiology [9–12]. Fluid accumulation and overload are common themes in the pathophysiology and clinical course of both HF and AKI. A positive fluid balance has been shown to be associated with worse clinical outcomes across a range of clinical settings, including elective colorectal surgery, acute lung injury, septic shock, and critical illness as well as in both pediatric and adult populations [13–18]. New data have emerged showing a positive fluid balance in critically ill patients with AKI generally portends an increased risk for worse clinical outcome [19, 20]. This review provides an overview of the pathophysiology of fluid accumulation with a focus on HF and AKI, along with a discussion of the importance of assessment of fluid balance in these syndromes and how it correlates with clinical outcome.

Heart Failure

Epidemiology

Acute HF is a growing public health concern. Over 5 million adults in the US and another 10 million in Europe have a diagnosis of HF [2, 4]. The incidence of new HF increases markedly with advancing age, exceeding 8–15 per 1,000 population in persons aged ≥ 65 years. HF is most commonly associated with pre-existing coronary heart disease, hypertension, and diabetes mellitus, and currently represents the most common reason for hospitalization (approximately 20% of all admissions) for persons aged ≥ 65 years [2]. Moreover, the hospitalization and readmission rates for HF continue to rise, contributing to a projected economic burden of near USD 35 billion in the US alone [2, 21]. In-hospital mortality from acute HF ranges from 4 to 8% [22–25]; however, in survivors to hospital discharge, mortality rates are 8–15% at 3 months [22, 26, 27]. Within 3 months of the index hospitalization, the estimated rates of rehospitalization range between 30 and 38% [10, 24–26]. Overall, while the prognosis for persons with HF has improved with advances in therapy, it should be recognized that attributable mortality remains high, and that the absolute number of deaths due to HF continues to increase [28].

Pathophysiology

Numerous factors interact and contribute to the pathophysiology of acute HF. Fluid accumulation is perhaps one of the most important mechanisms in acute decompensated HF (ADHF). Fluid accumulation directly contributes to worsening clinical symptoms of ADHF that culminates in hospitalization [29]. HF is a progressive disorder that occurs in response to an acute and/or chronic ‘inciting event’ (i.e. myocardial infarction, left ventricular, LV, pressure/volume overload, familial cardiomyopathy) that damages cardiac muscle. This translates into loss of functioning cardiac myocytes and/or disruption of normal myocardial contractility [30]. This decline in LV pump function represents the common denominator in the pathophysiology of HF. In response, a host of compensatory mechanisms are activated that modulate and/or temporarily restore LV function to within the normal homeostatic range, but over time become maladaptive. These maladaptive changes contribute to fluid accumulation and clinical symptoms. Increased LV end-diastolic pressure, LV dilatation and relative end-organ hypoperfusion activate the sympathetic nervous system, the renin-angiotensin-aldosterone axis and stimulate the nonosmotic release of arginine vasopressin. These directly contribute to and/or worsen existing fluid accumulation by avid sodium retention and impaired free water excretion in order to preserve cardiac output. End-diastolic pressure/volume overload further contributes to coronary hypoperfusion and subendocardial ischemia. In addition, increased expression of inflammatory cytokines (i.e. tumor necrosis factor) has been observed in HF patients. Together, these compensatory mechanisms contribute to LV remodeling, myocardial stretch, valvular regurgitation, and further lead to downstream impairment of LV function. These mechanisms also predispose to AKI and may lead to chronic kidney disease. The decline in glomerular filtration rate (GFR) is an important exacerbating factor in HF by further reducing a patient’s capacity for managing fluid homeostasis, reducing responsiveness to key therapies (i.e. loop diuretics) and contributing to fluid accumulation. The aforementioned mechanisms of HF are more commonly described in chronic HF patients with acute decompensation, where fluid accumulation may have occurred more gradually. These patients are likely to be in a positive fluid balance. Recently, an additional subtype of acute HF, termed acute vascular failure, has been described [31, 32]. The underlying pathophysiology of acute vascular failure is characterized by acute hypertension, increased systemic vascular resistance and aortic impedance. Fluid accumulation in this setting is more acute, and may be more the result of redistribution of fluid from the peripheral circulation to the pulmonary circulation, manifesting as acute pulmonary edema [31, 32]. These patients may or may not be in a positive fluid balance. Fluid accumulation, defined as either a positive fluid balance or as an acute redistribution of fluid, represents a fundamental mechanism of decompensation in HF that leads to hospitalization. The management of HF patients requires appreciation of the importance of fluid balance as a biomarker of illness severity and/or progression.

Table 1. Summary of clinical symptoms/signs of fluid accumulation in studies of patients hospitalized with ADHF

Study	Year	Patients	Age years	Females %	HTN/ DM/ CKD, %	Morta- lity	Hospital stay days	Dys- pnea, %	Ortho- pnea, %	Rales %	Peri- pheral edema %
EuroHeart Failure Survey [74]	2003	46,788	71	47	53/27/ 17	6.9	–	–	–	–	23
ADHERE [23]	2005	105,388	72.4 (14)	52	73/44/ 30	4	4.3	89	–	68	66
IMPACT- HF [75]	2005	576	71 (12)	48	65/45/ 24	2.8	7.8	47	41	64	59
Italian survey on acute HF investi- gators [26] ¹	2006	2807	73 (11)	39.5	66/38/ 25	7.3	9	100	–	87	59
OPTIMIZE HF [24]	2006	48,612	73.1 (14.2)	52	32/–/ –	3.8	6.4	61	35	64	65
EFICA [76]	2006	599	73 (13)	41	60/ 27	27.4	15	–	–	82	27

HTN = Hypertension; DM = diabetes mellitus; CKD = chronic kidney disease. Values for age are expressed as mean (SD).

¹ Dyspnea/orthopnea not reported; however, jugular venous distention 39%; third heart sound 34%; wheezing 32%; venous congestion by chest X-ray 89.5%; pleural effusion 28%.

Fluid Accumulation in HF

Fluid accumulation can be detected and monitored in HF patients by a number of methods, including clinical bedside findings, biomarkers and novel technology, many of which have been proven to correlate with clinical decompensation. A summary of the clinical symptoms/signs of fluid accumulation in HF patients is shown in table 1. The symptoms of fluid accumulation in HF may include a history of fatigue, dyspnea, orthopnea, paroxysmal nocturnal dyspnea, and weight gain. However, changes to body weight alone are a relatively insensitive predictor of fluid accumulation and subsequent acute

decompensation. On physical examination, any evidence of pulmonary rales, jugular venous distention, third heart sound (S3), pleural effusions, ascites, peripheral edema and pulmonary venous congestion on chest X-ray all suggest clinically important fluid accumulation and/or redistribution. In a systematic review focused on the evaluation of patients presenting to the emergency department with dyspnea, Wang et al. [33] found five clinical factors that increased the probability of ADHF, including prior history of HF, symptom of paroxysmal nocturnal dyspnea, sign of third heart sound, chest X-ray showing venous congestion and electrocardiogram evidence of atrial fibrillation. While these clinical features strongly imply fluid accumulation, measurement of 'fluid balance' in patients with ADHF at the time of presentation may be challenging, and in outpatient settings accurate documentation of fluid intake and output are unavailable. Fluid balance as a biomarker of HF severity and/or response to therapy is likely to be more reliable when monitored in 'in-patient' settings.

Several biomarkers, specifically atrial (i.e. ANP) and B-type natriuretic peptides (i.e. BNP, NT-proBNP) [34], have been shown to have value for HF diagnosis, risk stratification, early detection of acute decompensation and for guiding and/or adjusting therapy for HF according to serial measurements [35]. Plasma levels of natriuretic peptides are positively correlated with LV end-diastolic volume and pressure, inversely related to LV systolic function, and correlate closely with clinical outcomes. In a systematic review of 19 studies of HF patients using BNP to estimate risk of HF events or death, Doust et al. [36] found each 100 pg/ml increase in BNP was associated with a corresponding 35% increase in relative risk of death. Point of care assays for BNP (and NT-proBNP) are now widely available for use in both in-patient and outpatient settings. These biomarkers show significant promise for improving outcomes when compared with adjusting HF therapy according to bedside clinical evaluation alone [37]. In a small randomized clinical trial of 69 patients with impaired LV systolic function, HF therapy guided by serial BNP measurements, when compared with a rigorously applied clinical algorithm, was associated with a significantly reduced rate of HF events and death [37]. While data from subsequent larger trials have been mixed, several have shown BNP-guided HF management was associated with more frequent physician assessments, more frequent titration of HF medications, and reduced hospitalizations for HF, in particular for patients aged <75 years [38–40]. Finally, in a cohort of 182 consecutive patients admitted to hospital with ADHF, Bettencourt et al. [41] stratified patients into three groups based on relative change in NT-proBNP values from admission to discharge ($\geq 30\%$ decline; no significant change; $\geq 30\%$ increase). By multivariate analysis, clinical evidence of fluid overload and change in NT-proBNP were the only factors independently associated with death or rehospitalization within 6 months. Measurement of BNP is increasingly playing an important adjuvant role for diagnosis, risk identification and monitoring of therapy in HF patients;

however, BNP values will likely be context-specific and necessitate individualization due to relatively wide inter-patient variability. Additional investigations are anticipated to broaden our understanding of the role of BNP in HF.

Recently, novel technology, such as implantable devices and noninvasive impedance cardiography (ICG), have been developed to better monitor fluid status, fluid redistribution and to detect early-onset fluid accumulation in HF patients and to guide therapy and reduce hospitalizations. In a prospective pilot study of 32 chronic HF patients, Adamson et al. [42] implanted a single-lead pacemaker into the right ventricle (RV) as a continuous hemodynamic monitor (IHM) to correlate whether changes to RV hemodynamics can guide HF therapy and predict clinical deterioration. Increases in RV pressures measured by the IHM device predicted episodes of ADHF approximately 4 days prior to event [42]. More specifically, during 36 volume overload events, RV systolic pressures increased by 25% ($p < 0.05$) and heart rate increased by 11% ($p < 0.05$) when compared with baseline. In 33 NYHA class III and IV patients, Yu et al. [43] implanted a pacemaker device capable of measuring intrathoracic impedance as a surrogate for lung fluid accumulation. Patients were serially monitored, and during hospitalizations fluid status and pulmonary artery wedge pressure (PAWP) were measured. In 10 patients requiring hospitalization for fluid overload, intrathoracic impedance was shown to decrease by 12% over an average of 18 days prior to overt acute decompensation and hospitalization. This change in impedance was inversely correlated with PAWP and fluid balance [43]. In a prospective observational study of 212 chronic stable HF patients, Packer et al. [44] performed serial clinical evaluation and blinded ICG as a surrogate of lung fluid accumulation, every 2 weeks for 26 weeks, and followed for occurrence of ADHF, hospitalization for HF or death. They found that three ICG parameters (i.e. velocity index, LV ejection time, thoracic fluid content index) combined into a composite score was a powerful predictor of an event occurring during the subsequent 14 days ($p < 0.001$). 'Fluid balance' and/or redistribution, as measured and defined by these devices, demonstrate the diagnostic and therapeutic potential of serial and/or continuous dynamic monitoring in HF.

In a small clinical trial of critically ill patients with pulmonary edema, defined as a high extravascular lung water (>7 ml/kg) measured by pulmonary artery catheterization, a positive fluid balance exceeding 1 l over 36 h was found to be associated with higher mortality, longer duration of mechanical ventilation and longer stays in ICU and hospital [45]. This study was one of the first to show that measurement of fluid balance has clinical relevance and that adopting a fluid strategy to achieve a neutral or negative fluid balance in this population may improve clinical outcomes without compromise to the hemodynamic profile of the patient or precipitating additional organ dysfunction such as AKI. This has subsequently been confirmed in larger studies of critically ill patients with acute lung injury [14, 17].

Acute Kidney Injury

Epidemiology

AKI is also a common clinical problem and typically portends a considerable increase in morbidity, mortality and health resource utilization [46–51]. Numerous epidemiological studies have provided a broad range of incidence estimates of AKI; however, inferences have often been limited due to a prior lack of a standardized definition and the selected populations being investigated [52–54]. Several recent large multicenter cohort studies have used the RIFLE criteria for AKI (acronym Risk, Injury, Failure, Loss, End-Stage Kidney Disease), a novel consensus definition and classification scheme, and have reported the occurrence of AKI in as many as 36–67% of all patients admitted to intensive care [47, 55–59]. Additional investigations have also found that the incidence of AKI continues to rise [1, 3, 5]. This large and increasing burden of AKI is likely, in part, attributed to a shift in demographics (i.e. older population, risk modification by concomitant comorbid illness), presentation with greater illness severity (i.e. multi-organ dysfunction syndrome) and development of AKI in association with new and more complex interventions (i.e. cardiac surgery, organ transplantation) [60]. AKI leads to impaired fluid and electrolyte homeostasis and is commonly associated with and/or precipitates fluid accumulation and overload.

Pathophysiology

Several mechanisms contribute to the accumulation of a positive fluid balance in AKI, in particular in the context of critical illness. Following an ‘inciting event’, which in critical illness is often multifactorial (i.e. sepsis, nephrotoxins, intra-abdominal hypertension), AKI ensues and is characterized by a rapid and sustained decline in GFR. This is clinically manifest by an increase in serum creatinine and/or a progressive reduction in urine output. This interrupts fluid and electrolyte homeostasis and markedly reduces capacity for free water and solute excretion. Fluid and solute retention can be further compounded by increased activation of the sympathetic nervous system, the renin-angiotensin-aldosterone axis and stimulation of nonosmotic release of arginine vasopressin. In critical illness, shock and systemic inflammation contribute to a reduced effective circulation, reduced oncotic pressure gradient (i.e. hypoalbuminemia) and alterations to capillary permeability which contributes to high obligatory fluid intake (i.e. active resuscitation, intravenous medications) and considerable leakage from the vascular compartment. Recent data have also shown AKI can contribute to systemic inflammation and lead to distant organ dysfunction [61, 62]. In an experimental ischemia/reperfusion injury (IRI) model of AKI, Rabb et al. [62] showed significant downregulation of pulmonary sodium channel receptors, Na-K-ATPase and aquaporin expression in AKI when compared with controls. In a similar IRI model, Kramer et al. [61] found AKI was associated with increased pulmonary vascular permeability within 24 h of injury that

correlated with changes in kidney function. Both of these studies have important implications for how AKI (and fluid therapy in AKI) may incite or exacerbate acute lung injury and contribute to extravascular lung water accumulation. In a small cohort study of septic critically ill patients with AKI, Van Biesen et al. [63] showed that in patients with apparent optimal hemodynamics, restored intravascular volume and a high rate of diuretic use, further fluid therapy failed to improve kidney function but led to unnecessary fluid accumulation and impaired gas exchange. Fluid accumulation and overload can also impact kidney function and worsen AKI. For example, fluid overload may contribute to or worsen intra-abdominal hypertension, in particular in critically ill trauma or burn-injured patients, leading to further reductions in renal blood flow, venous outflow, renal perfusion pressure and urine output [64]. Mechanical ventilation and positive end-expiratory pressure, by increasing intrathoracic pressure, can alter kidney function and contribute to fluid accumulation through stimulation of an array of hemodynamic, neural and hormonal responses that act on the kidney to reduce renal perfusion, reduce GFR and inhibit excretory function [65, 66]. Similarly, injurious mechanical ventilation (i.e. barotrauma, biotrauma, volutrauma, atelectrauma) has been shown to induce renal tubular cell apoptosis and AKI [67]. Finally, a positive fluid balance in those at-risk may precipitate acute reductions in cardiac function and exacerbate HF [68].

Fluid Accumulation in AKI

Several clinical studies of critically ill children with AKI have consistently identified fluid overload as an important independent factor associated with mortality [69–72] (table 2). Moreover, severity of fluid overload has been shown to correlate with worse clinical outcome. Goldstein et al. [71] evaluated 21 children with AKI and found a higher percent fluid overload (%FO) at the time of initiation of continuous RRT, independent of illness severity, was independently associated with lower survival. The formula used to calculate percentage fluid overload was:

$$\%FO = [(total\ fluid\ in - total\ fluid\ out)/admission\ body\ weight \times 100]$$

This finding has been further confirmed in additional investigations (one retrospective single-center and one prospective observational multicenter) of critically ill children with multiorgan dysfunction syndrome and AKI [69, 72]. In another retrospective review, Gillespie et al. [70] showed %FO >10% at CRRT initiation was independently associated with mortality (hazard ratio, HR, 3.02, 95% CI 1.5–6.1, $p = 0.002$). In a recent surveillance of 51 children receiving stem cell transplantation whose course was complicated by ICU admission and AKI, 88% had CRRT initiated for management of fluid overload (average %FO at initiation was 12.4%) [73]. These data have presented a strong argument for a survival benefit for early initiation of CRRT for prevention of fluid accumulation and overload in critically ill children once initial fluid resuscitative management has been accomplished.

Table 2. Summary of studies evaluating fluid balance in pediatric AKI initiated on continuous renal support

Study	Year	Pat- ients	Age years	Weight kg	PRISM	Diagnosis, %	Inter- vention	Mor- tality	Percent FO at RRT initiation by mortality	
Goldstein [71]	2001	21	8.8 (6.3) ¹	28.3 (20.8) ¹	13.1 (5.8) ¹	MODS (100) sepsis (52) cardiogenic (19)	CRRT	57	34.0	16.4
Foland [69]	2004	113	9.6 (2.5, 14.3) ²	31.2 (15.9, 55.3) ²	13.0 (9.0, 17.0) ²	MODS (91) renal (26) cardiogenic (16)	CRRT	43	15.5 ³	9.2
Gillespie [70]	2004	77	5.1 (5.7) ¹	77% <10 kg	12.2 (7.1) ¹	AKI (100)	CRRT	50	for %FO >10%, RR of death was 3.02, p = 0.002	
Goldstein [72]	2005	116	8.5 (6.8) ¹	11.1 (25.5) ¹	14.3– 16.2	MODS (100) sepsis (39) cardiogenic (20)	CRRT	48	25.4	14.2
Symons [77]	2007	344	80% >1 year	10% <10 kg	12 ²	sepsis (23.5) BMT (15.9) cardiogenic (11.9)	CRRT	42	when RRT initiated primarily for FO: 49% mortality	
Flores [73]	2008	51	11.2 (0.9) ¹	45.5 (6.1) ¹	12.7 (0.9) ¹	SCT (100)	CRRT	55	13.9	10.6

FO = Fluid overload; MODS = multi-organ dysfunction syndrome; PRISM = Pediatric risk of mortality score; SCT = stem cell transplantation; BMT = bone marrow transplantation.

¹ Mean (SD).

² Median (IQR).

³ Subgroup of children with MODS ≥3 organs.

In a secondary analysis of the Sepsis Occurrence in Acutely Ill Patients study, Payen et al. [20] have examined the influence of fluid balance on survival of critically ill patients with AKI. In this study, patients were compared by whether they developed AKI, defined by a renal Sequential Organ Failure Assessment score ≥2 or by urine output <500 ml/day. Of the 3,147 patients enrolled, 1,120 (36%) developed AKI with 75% occurring within 2 days of ICU admission. Mortality at 60 days was higher for those with AKI (36 vs. 16%, $p < 0.01$). In patients with

both early and late-onset AKI, average daily fluid balances through the first 7 ICU days were significantly more positive compared to non-AKI patients ($p < 0.05$ for each day). Similarly, average daily fluid balance was significantly more positive for those with oliguria (620 vs. 270 ml, $p < 0.01$) and those receiving RRT (600 vs. 390 ml, $p < 0.001$). Average daily fluid balance was significantly higher for nonsurvivors compared with survivors (1,000 vs. 150 ml, $p < 0.001$). By multivariable analysis, a positive fluid balance (per l/24 h) showed independent association with 60-day mortality (HR 1.21; 95% CI, 1.13–1.28; $p < 0.001$). While no data were available on fluid balance by timing of renal replacement therapy (RRT), those receiving earlier RRT (< 2 days after ICU admission) had lower 60-day mortality (44.8 vs. 64.6%, $p < 0.01$), despite more oliguria and greater illness severity. This study does have limitations; notably, it was not a randomized trial, and as such the observed associations are prone to bias from selection, confounding and random error.

In a further analysis of the 610 critically ill patients with AKI enrolled in the PICARD database [48], Bouchard et al. [19] evaluated the association of fluid overload with mortality and renal recovery. Complete data on fluid intake, output and balance from 3 days prior to enrollment until hospital discharge were available on 542 (88.9%) of the cohort. Cumulative fluid balance was standardized for body weight at hospital admission and defined as described by Goldstein et al. [71]. Fluid overload was defined as achievement of a percentage fluid accumulation $> 10\%$ over baseline body weight. The exposures of interest were the proportion of patients classified as fluid overloaded at AKI diagnosis, at initiation of RRT along with the duration (i.e. number of days) of fluid overload. The primary outcomes evaluated were 60-day mortality and recovery of kidney function stratified by fluid overload. Patients classified as fluid overloaded had higher illness severity and treatment intensity (i.e. mechanical ventilation), were more likely postoperative, and had lower serum creatinine and urine output at the time of enrollment. Crude mortality at 60 days was significantly higher for AKI patients with fluid overload (48 vs. 35%, $p = 0.006$). The adjusted odds of death for fluid overload at the time of AKI diagnosis was 3.1 (95% CI, 1.2–8.3). In those patients receiving RRT, average fluid accumulation was significantly lower in survivors compared with non-survivors (8.8 vs. 14.2%, $p = 0.01$) and the adjusted odds for death for fluid overload at RRT initiation was 2.1 (95% CI, 1.3–3.4). Moreover, there was evidence of near linear increases in mortality when stratified by cumulative fluid accumulation over the duration of hospitalization along with higher mortality for those patients with greater duration of being classified as fluid overloaded ($p < 0.0001$). Fluid overload at time of AKI diagnosis or at initiation of RRT was not independently associated with renal recovery. This study also has recognized limitations, including being a secondary post-hoc analysis of prospectively collected data and potentially prone to bias due to selection and residual confounding. In addition, the formula for calculation of percentage fluid overload in adult patients using ‘admission’ body weight has not been prospectively validated and

may predispose to misclassification. Finally, this study was not able to compare the association of fluid balance and outcome in critically ill non-AKI controls. However, the data from these two observational investigations, along with prior studies in critically ill adult and pediatric patients, provide compelling evidence that attention to fluid balance and prevention of volume overload, in particular in AKI, may be an important and underappreciated determinant of survival.

Conclusion

Acute HF and AKI are common and increasingly encountered in clinical practice. Fluid accumulation and overload are common themes in their pathophysiology and clinical course. Fluid balance represents an important 'biomarker' or parameter to serially measure in these patients that may provide important diagnostic, therapeutic and prognostic information. Determining fluid balance in HF may be complex and depend largely on underlying pathophysiology; however, in addition to simple fluid balance (intake minus output) measurement, newer biomarkers (i.e. BNP) and novel technology (i.e. ICG) are proving to be useful for early detection and risk identification for ADHF that may allow early intervention and translate into improved clinical outcomes. Several pediatric and adult observational studies focused on AKI have now shown data supporting the importance of fluid balance as a modifiable biomarker and determinant of clinical outcome. To date, the impact of fluid balance in both of these syndromes, especially AKI, has been underappreciated. There is little to no data specifically on fluid balance in the CRS, where acute/chronic heart disease can directly contribute to acute/chronic worsening of kidney function and likely exacerbates fluid homeostasis.

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Fluid Balance Issues in the Critically Ill Patient

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Abstract

In critically ill patients, fluid balance management is an integral part of the process of care. In patients in shock or severe sepsis, aggressive initial fluid resuscitation has been shown to improve overall prognosis. However, in critically ill patients, cumulative fluid accumulation is recognized as a potential contributing factor to increased morbidity and mortality. Randomized clinical trials are urgently required to assess the role of fluid overload in mortality and morbidity in this population. In the meantime, we should not only focus on acute fluid resuscitation but also on cumulative fluid balance as the amount and duration of fluid accumulation may influence outcomes.

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In critically ill patients, an adequate management of fluid balance is essential to the treatment of conditions such as hypotension, sepsis, heart failure and acute kidney injury. Fluid is usually administered based on an estimation of the intravascular volume compartment. Over the last decade, several new studies have emerged to guide clinicians for fluid management in critically ill patients. Rivers et al. [1] showed that an early aggressive resuscitative strategy, including appropriate fluid administration, could improve outcomes in patients with septic shock. Conversely, there are increasing observational data supporting that cumulative fluid overload should not simply be considered as a consequence of fluid resuscitation or severe acute kidney injury, but possibly as a mediator of adverse outcomes [2–9]. We discuss the pathophysiology of fluid shifts in critically ill patients as well as the timely use of fluid resuscitation along with its associated complications.

Pathophysiology of Fluid Shifts in Critically Ill Patients: Beyond the ‘Third Space’

Total body water (TBW) is equivalent to 60% of total body weight and has traditionally been divided into the intracellular and extracellular spaces. For an adult man weighing 70 kg, TBW is approximately 42 l, of which 20% is extracellular (14 l) and 40% is intracellular (28 l, which includes red cell volume). The extracellular space includes 10.5 l in the interstitium and 3.5 l as plasma volume. For decades, in critically ill patients and in patients undergoing major surgery, the so-called ‘third space’ was also considered as another extravascular compartment. Therefore, fluid administration was optimized to replace this ‘loss’, in addition to deficits due to insensible perspiration and fasting.

In reality, the ‘third space’ most probably accumulates in the interstitium due to the destruction of an integral structure of the vascular wall, the endothelial glycocalyx [10]. The endothelial glycocalyx seems to retain plasma proteins hydrostatically forced out of the vascular wall. In experimental studies, ischemia/reperfusion, tumor necrosis factor- α , and atrial natriuretic peptide (ANP) could all lead to the destruction of this structure. Since acute hypervolemia triggers ANP release, avoiding intravascular hypervolemia could theoretically protect the endothelial glycocalyx and therefore prevent protein-rich plasma shifts and subsequent interstitial edema. Interestingly, over the last decade, fluid overload and possibly interstitial edema have been increasingly recognized as issues that could jeopardize patients’ outcomes. However, the mechanisms by which fluid overload could influence outcomes have never been clearly demonstrated. Further studies on the mechanisms underlying fluid shifts between compartments could help our understanding.

Liberal/Standard and Restrictive/Conservative Approaches for Fluid Management

Over the last decades, a more liberal strategy of fluid administration was more commonly used to avoid complications attributed to hypovolemia. These included hypotension, tachycardia, acute kidney injury, shock and multiorgan failure [11, 12]. On the other hand, little attention was focused on the consequences of fluid accumulation, such as peripheral and tissue edema, respiratory failure, hypertension, and increased cardiac demand. In the perioperative period, these consequences also include poor wound healing and delayed bowel recovery [11, 12]. Unfortunately, the liberal and conservative approaches have never been properly defined, and therefore they vary in terms of intensity and timing among publications. We will discuss the consequences of liberal fluid management on outcomes in several different populations of critically ill patients with a view to define the pathophysiology of fluid accumulation.

Cumulative Fluid Balance and Morbidity and Mortality in Critically Ill Patients

In several critically ill conditions, such as acute respiratory distress syndrome (ARDS), acute lung injury (ALI), sepsis, acute pulmonary edema, AKI and following surgery, fluid overload has been associated with adverse outcomes [2, 3, 5–7, 9, 13, 14] (table 1). Unfortunately, since there are large variations in the definitions of fluid overload, any pooling of data is impossible. We propose definitions for the common terms pertaining to fluid balance and highlight the best studies focusing on fluid overload in critically ill patients, based on their level of evidence.

Definitions of Fluid Terms

The definition of *fluid overload* has been and is still subject to large variation; however, it usually implies a degree of pulmonary edema or peripheral edema. In this review, *fluid accumulation* specifies conditions when there is a positive fluid balance, with or without associated fluid overload. *Daily fluid balance* refers to the daily difference in all intakes and outputs, which generally does not include insensible losses. *Cumulative fluid balance* is the sum of daily fluid balance over a set period of time. The *percentage of fluid overload adjusted for body weight* is the cumulative fluid balance expressed as a percent of body weight at baseline, usually at the admission in the intensive care unit [8, 9]. In previous studies, a cut off of 10% has been associated with increased mortality [5, 7].

Randomized Trials

In a trial on ARDS, Wiedemann et al. [2] randomized 1,000 patients to either a conservative or a liberal strategy of fluid management. The mean ($\pm$ SE) cumulative fluid balance during the first 7 days was -136 ± 491 ml in the conservative group and $6,992 \pm 502$ ml in the liberal group ($p < 0.001$). Body weights were not reported in the study. The primary outcome, mortality rate at 60 days, was similar between the two groups and the duration of mechanical ventilation was improved with the conservative strategy. The incidence of AKI was not reported; however, there were no significant differences in mean creatinine values over the first 7 days.

Another randomized controlled trial has assessed the effect of fluid overload on outcomes; however, this trial was not powered to evaluate changes in mortality [3]. One hundred and seventy-two patients undergoing colorectal surgery were randomized to a standard or a restrictive regimen of fluid management. The quantity of fluid administered and changes in body weight from the day of the surgery were significantly higher in the standard group. This group presented decreased wound healing and increased postoperative cardiopulmonary complications compared to the restrictive one [3]. There was no difference in the survival rate or creatinine and blood urea nitrogen values between the two regimens throughout the study.

Table 1. Summary of studies assessing the effect of fluid accumulation on outcomes

First author	Patients	Population	Study design	Intervention	Significant results
Simmons, 1987 [26]	113	ARDS	prospective cohort	none	higher cumulative fluid balance and weight gain associated with increased mortality
Schuller, 1991 [14]	89	pulmonary edema	retrospective cohort	none	higher fluid balance associated with increased mortality, length of hospitalization and days on mechanical ventilation
Goldstein, 2001 [8]	21	pediatric AKI	retrospective cohort	none	higher fluid balance associated with mortality
Brandstrup, 2003 [3]	172	elective colorectal surgery	randomized controlled trial	restrictive vs. standard perioperative fluid strategy	restrictive strategy reduced cardiopulmonary and tissue-healing complications
Foland, 2004 [6]	113	pediatric AKI	retrospective cohort	none	higher fluid balance associated with mortality
Gillespie, 2004 [7]	77	pediatric AKI	retrospective cohort	none	higher fluid balance associated with mortality
Michael, 2004 [15]	26	pediatric AKI	retrospective interventional	percentage of fluid overload <10%	100% of survivors vs. 40% of nonsurvivors had a percentage of fluid <10%
Goldstein, 2005 [9]	116	pediatric AKI	prospective cohort	none	higher fluid balance associated with mortality
Sakr, 2005 [27]	393	ALI/ARDS	prospective cohort	none	higher fluid balance associated with mortality
Uchino, 2006 [28]	331	critically ill	prospective	none	higher fluid balance associated with mortality
Wiedemann, 2006 [2]	1,000	ARDS	randomized controlled trial	conservative vs. liberal fluid strategy	conservative strategy improved lung function and shortened the duration of mechanical ventilation
Payen, 2008 [4]	1,120	critically ill	prospective cohort	none	higher fluid balance associated with mortality
Bouchard, 2009 [5]	618	AKI	prospective cohort	none	higher fluid balance associated with mortality and possibly reduced renal recovery

Prospective Observational Trials

Prospective observational studies of critically ill patients have also shown a detrimental effect of fluid overload on outcomes. In 1,177 septic patients, a positive cumulative fluid balance was associated with increased mortality [13]. This association remained significant after adjusting for age and severity of illness scores.

In AKI, three multicenter prospective studies have shown a relationship between fluid overload and mortality, one in pediatric and two in adult patients [4, 5, 9]. In the pediatric study, the percentage of fluid overload adjusted for body weight at continuous renal replacement therapy (CRRT) initiation was significantly higher in nonsurvivors vs. survivors (25.4 ± 32.9 vs. $14.2 \pm 15.9\%$; $p < 0.03$) even after adjustment for severity of illness [9]. Fluid accumulation was also associated with decreased survival in 1,120 adults with sepsis-induced AKI [4]. In this study, patients had severe AKI; however, they were not necessarily dialyzed. The mean daily fluid balance was 0.15 ± 1.06 l/day in survivors versus 0.98 ± 1.5 l/day in nonsurvivors. The association between fluid overload and mortality remained significant only in patients with AKI within 2 days of intensive care unit admission (survivors: 0.14 ± 1.05 l/24 h vs. nonsurvivors: 1.19 l/24 h; $p < 0.001$). In the largest study on fluid overload and AKI from the PICARD group, patients with fluid overload, defined as a percentage of fluid accumulation $>10\%$ from admission body weight, had a significantly higher mortality at 60 days (46 vs. 32%; $p = 0.006$) [5]. Among dialyzed patients, survivors had a lower percentage of fluid accumulation at dialysis initiation compared with nonsurvivors (8.8 vs. 14.2%; $p = 0.01$ adjusted for dialysis modality and severity score). In patients who did not require dialysis, survivors also presented less fluid accumulation adjusted for body weight at peak creatinine (4.5 vs. 10.1%; $p = 0.03$ adjusted for severity score). Patients with fluid overload at peak creatinine were also less likely to regain kidney function (35 vs. 52%; $p = 0.007$); however, there were inconsistent results in the relationship between fluid overload at dialysis initiation and dialysis independence (41 vs. 32% in fluid overloaded patients; $p = 0.21$) [5]. These findings are in opposition to the common belief that fluid accumulation may protect the kidneys.

The PICARD study also looked at the effect of the duration and correction of fluid overload on survival [5]. Patients with higher percentage of fluid accumulation through their hospital stay were more likely to die, suggesting a cumulative effect of fluid overload on mortality, similar to a dose-response relationship. Patients who initiated dialysis with fluid overload and who had a percentage of fluid overload $<10\%$ at the end of the study had a better survival rate than patients who remained fluid overloaded. However, despite adjustment for severity of illness, this association does not prove that correcting fluid overload is beneficial in itself; patients who were able to tolerate ultrafiltration could have been less severely ill and therefore more likely to survive.

Retrospective Trials

In pediatric patients who received stem cell transplantation and developed AKI, limiting the degree of fluid overload with diuretics and CRRT was also associated with better survival [15]. In this study, all survivors ($n = 11$) maintained or remained with a percentage of fluid accumulation $<10\%$ with diuretics and CRRT. Among the 15 nonsurvivors, only 40% had percentage fluid accumulation $<10\%$ at the time of death.

A similar smaller study in septic shock also showed an association between the capacity of achieving a negative fluid balance of 500 ml by the 3rd day of treatment and survival [16]. All 11 patients who achieved a negative balance >500 ml on >1 of the first 3 days of treatment survived, whereas 5 of 25 patients who did not achieve a negative fluid balance of >500 ml by the 3rd day of treatment survived (RR, 5.0; 95% CI, 2.3–10.9; $p < 0.0001$) [16].

A recent retrospective study including 212 patients with septic shock and ALI confirmed the association between fluid accumulation and mortality following septic shock onset [17]. In this study, a conservative late fluid management was defined as even to negative fluid balance measured on at least 2 consecutive days during the first 7 days after septic shock onset.

More importantly, this study assessed at the same time the importance of an adequate initial fluid resuscitation on survival and will be discussed in the next section.

In summary, these results highlight the association of fluid overload and mortality and morbidity in several critical conditions; however, they do not provide any causal mechanism that could explain the association. In addition, there are controversial data on the accuracy of measurement of fluid balance. Some studies have shown that body weight is a more precise measurement than the estimated in and out fluid balance [18, 19], possibly due to the difficulty in measuring insensible losses and combustion of body mass [18]. Another study found a trivial difference (<250 ml) between the two measurements [20]. Moreover, there are very limited data on the relationship between calculated fluid balance and invasive measures of volume, such as central venous pressures or pulmonary capillary wedge pressures. These measurements are not frequently obtained and are usually not available for a long period of time. Assessing such a relationship could be very instructive in learning if differences in body fluid distribution, such as increased interstitial edema versus increased intravascular volume, are associated with specific outcomes.

Initial versus Cumulative Fluid Administration

In the previous section, we have highlighted the association between *cumulative* fluid accumulation and outcomes and presented increasing evidence that fluid administration should be restricted whenever possible to avoid significant fluid

accumulation. However, there are clinical scenarios during which sufficient fluid administration is also crucial for patients' outcomes. In a recent retrospective study, including 212 patients with ALI within 72 h of sepsis, those who received an adequate initial fluid resuscitation had better in-hospital survival rates [17]. In this study, an adequate fluid resuscitation required the administration of an initial fluid bolus of >20 ml/kg prior to and achievement of a central venous pressure of ≥ 8 mm Hg within 6 h after the onset of therapy with vasopressors. This study supported the concept of early goal-directed therapy proposed by Rivers et al. [1] 10 years ago in patients with severe sepsis or septic shock. However, once the acute condition subsides, a more restrictive strategy of fluid balance is associated with a better survival rate and should therefore probably be undertaken.

How Does Fluid Accumulation Contribute to Organ Dysfunction?

Fluid overload presenting as peripheral edema has been conceptualized as an imbalance between net transcapillary fluid filtration and fluid removal from the tissues by the lymphatic system [21]. Therefore, edema can occur secondary to an increase in net transcapillary hydrostatic pressure (e.g. in congestive heart failure) or capillary permeability to proteins (e.g. in sepsis), and a decrease in net transcapillary oncotic pressure (e.g. in nephrotic syndrome) or lymphatic drainage (e.g. positive end-expiratory pressure ventilation). In multiorgan dysfunction syndrome, edema is common and can occur during severe sepsis – without or without associated AKI – due to the release of complement factors, cytokines and prostaglandin products and altered organ microcirculation [21]. In this setting, edema is attributed to a combination of increased capillary permeability to proteins and increased net transcapillary hydrostatic pressure through reduced precapillary vasoconstriction.

Fluid accumulation can contribute to impair organ function by different mechanisms. First, tissue edema can directly impair gut absorption or kidney excretion. Fluid accumulation can also lead to increased abdominal pressure and/or renal venous congestion. The abdominal compartment syndrome has been increasingly recognized in surgical and medical patients following intense volume resuscitation, with consequent acute formation of ascites and visceral edema [22]. In one study on chronic congestive heart failure [23], among several hemodynamic parameters only right atrial pressure correlated weakly with serum creatinine ($r = 0.165$, $p = 0.03$). These results suggest that renal congestion may have an underestimated role in the development of chronic kidney disease; however, whether these findings are applicable in acute kidney injury needs to be determined.

Whether the type of fluid (colloids or crystalloids) contributes to fluid accumulation and increased permeability differently depending on the clinical

scenario needs to be better determined. For example, if infused during acute hemorrhage, 6% hydroxethylstarch or 5% human albumin will remain to almost 100% within the circulation, while if administered as hypervolemic boluses, most of the quantity infused will vanish out of the vasculature, and further contribute to increase the interstitial compartment [24]. This effect possibly confounds any meaningful short-term clinical difference between the administration of colloids versus crystalloids on outcomes.

In summary, various pathways could be involved in the interaction of fluid accumulation and organ dysfunction.

Recommendations for Clinical Practice and Research

According to current knowledge, during acute bleeding, in major trauma, or in patients suffering from sepsis, an aggressive initial fluid resuscitation should be attempted. However, once the acute condition subsides, the prevention of fluid shifting should probably be prioritized and fluid accumulation should be prevented by restricting fluids based on fluid responsiveness. In this review, we have highlighted the association between fluid overload and adverse outcomes in several acute conditions [4–9, 25]. However, none of these studies could conclude that the observed association between fluid overload and mortality is causal. Clinical trials are therefore required to assess the role of fluid overload in mortality and morbidity in critically ill patients. In the meantime, we should not only focus on daily fluid balance but also on cumulative fluid balance, since the amount and duration of fluid accumulation probably influence outcomes.

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Prerenal Azotemia in Congestive Heart Failure

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Abstract

Prerenal failure is used to designate a reversible form of acute renal dysfunction. However, the terminology encompasses different conditions that vary considerably. The Acute Kidney Injury Network group has recently standardized the acute kidney injury (AKI) definition and classification system; however, these criteria have not determined specific diagnostic criteria to classify prerenal conditions. The difference in the pathophysiology and manifestations of prerenal failure suggests that our current approach needs to be reevaluated. Several mechanisms are recognized as contributory to development of a prerenal state associated with cardiac failure. Because of the broad differences in patients' reserve capacity and functional status, prerenal states may be triggered at different time points during the course of the disease. Prerenal state needs to be classified depending on the underlying capacity for compensation, the nature, timing of the insult and the adaptation to chronic comorbidities. Current diagnosis of prerenal conditions is relatively insensitive and would benefit from additional research to define and classify the condition. Identification of high-risk states and high-risk processes associated with the use of new biomarkers for AKI will provide new tools to distinguish between the prerenal and established AKI. Achieving a consensus definition for prerenal syndrome will allow physicians to describe treatments and interventions as well as conduct and compare epidemiological studies in order to better describe the implications of this syndrome.

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Prerenal azotemia is accepted as a reversible form of renal dysfunction caused by factors that compromise renal perfusion. The term has been used as part of a dynamic process that begins with a reversible condition, prerenal state, and can progress to an established disease, acute tubular necrosis (ATN). The terminology encompasses different conditions that vary considerably in the pathophysiology and course of cardiac failure progression. Diagnostic strategies have usually been based upon a response to fluid challenge or increase in cardiac output. However,

the time frame for reversibility as well as the type and volume of fluid required are not clearly designated. Recent attempts to define and stage acute kidney injury (AKI) have not specifically addressed this condition even though it is an integral part of the spectrum of AKI. In this review, we discuss the pathophysiology of prerenal states associated with congestive heart failure (CHF) and provide a framework for refining the diagnosis and management of prerenal failure.

The Concept of Kidney Reserve – Pre-Prerenal State

Experimental models have largely informed our current understanding of the physiology of the kidney in various settings associated with prerenal failure. Before the onset of clinically evident prerenal failure, the kidney passes through a phase of remarkable compensation called pre-prerenal failure [1]. Three main steps are involved in this compensatory mechanism; (1) the cardiac output fraction that reaches the kidney, (2) plasma flow filtration by the glomerulus (filtration fraction), and (3) proportion of the glomerular filtrate that is reabsorbed by the tubules. Renal blood flow (RBF) depends on the tone of renal vascular resistance (RVR) in relation to systemic vascular resistance (SVR): if the RVR increases in relation to the SVR, the RBF decreases. At reduced levels of cardiac output, intrarenal factors are triggered increasing renal arterial vascular tone and, consequently, decreasing the RBF. In order to maintain the intraglomerular pressure, efferent arteriolar resistance increases, preserving the filtration pressure even when the pressure in the afferent arteriolar decreases to levels low enough to cease filtration. Augmented activity of the sympathetic nervous (SNS), renin-angiotensin-aldosterone (RAAS) systems and vasopressin secretion increase the amount of filtered fluid that is reabsorbed by the renal capillaries and veins.

These three mechanisms: control of blood flow to the kidney, fraction of plasma filtered and amount of fluid reabsorbed by the kidney are the components responsible for the kidney reserve. However, the efficiency of these mechanisms has limits imposed by structural changes and the severity of the injury. The reserve is diminished by the presence of underlying arterial and intrinsic renal diseases that interfere with the control of RBF, filtration fraction and the reabsorbed function, as well as by drugs that interfere with the vascular or neural humoral control of these mechanisms. When these compensatory mechanisms are overwhelmed, a prerenal state is discernible.

Pathophysiology of Prerenal Failure in Congestive Heart Failure

Several mechanisms are recognized as contributory to development of a prerenal state. Maintenance of intraglomerular filtration pressure is the key component

Table 1. Factors impairing compensatory mechanisms in response to renal hypoperfusion in CHF

<i>Comorbidities associated with CHF</i>	
Failure to decrease afferent arteriolar resistance	Atherosclerosis CKD Chronic hypertension Diabetes
Failure to increase efferent arteriolar resistance	Renal artery stenosis
<i>Factors associated with CHF treatment</i>	
Failure to increase efferent arteriolar resistance	Angiotensin converting enzyme inhibitors Angiotensin receptor blockers
<i>Other drugs</i>	
Decreased vasodilatory prostaglandin activity	Nonsteroidal anti-inflammatory drugs Cyclooxygenase-2 inhibitors
Increased afferent arteriolar vasoconstriction	Radiocontrast agents

and is influenced by the presence of underlying disease that interferes with the control of RBF, filtration fraction and the reabsorbed function. The afferent arteriole can dilate and maintain adequate perfusion pressure until the systemic blood pressure falls below approximately 80 mm Hg. After this point, the perfusion pressure starts to decline abruptly. Structural changes in the afferent arteriole interfere with the ability to decrease the vascular tone in response to changes in their wall pressure. Old age, arteriosclerosis, diabetic vasculopathy, chronic hypertension, and chronic kidney disease (CKD) are common causes impairing the appropriate vasodilatory response. This ability is also altered by drugs that interfere with prostaglandin release or the angiotensin action in the efferent arteriole, decreasing the potential arteriolar response to a fall in the glomerular pressure and predisposing patients to prerenal failure even during minor degrees of hypotension (table 1).

Patients with heart failure often present alterations of the vascular system such as vascular stiffening, intense neurohormonal activation, venous congestion, diminished RBF, and failure of intrinsic renal autoregulation. The neurohormonal compensatory mechanisms are already in use to preserve renal hemodynamics, and further decrease in cardiac output triggers a fall in the perfusion pressure and in the GFR.

Diagnosis of Prerenal Failure

The Acute Kidney Injury Network group has recently standardized the AKI definition and classification system; however, whether AKI refers only to ATN and other parenchymal diseases or includes prerenal remains to be determined. An elevation of serum creatinine or a reduction of urine output that is easily reversible with improved hydration or improved renal perfusion is the current accepted definition of prerenal failure. However, prerenal failure requires a consideration of other conditions such as pre-existing disease, time frame, and response to interventions.

The most applied parameter to distinguish prerenal failure secondary to volume depletion or hypotension from ATN is the response to fluid expansion. The return of renal function to previous baseline within 24–72 h is considered to represent prerenal disease, whereas persistent renal failure is called ATN. Unfortunately, there is no agreement on the time frame to return to baseline renal function, or regarding the amount, nature and duration of fluid resuscitation needed to establish a diagnosis of a prerenal state.

Although laboratory tests to distinguish prerenal failure from ATN have been used, these diagnostic parameters present frequent exceptions, and the distinction between prerenal and renal causes are frequently not accurate. The plasma (P) urea/creatinine ratio, urine (U) osmolality, U/P osmolality, U/P creatinine ratio, urinary Na level, and fractional excretion of Na (FE_{Na}) are the most frequently used ones [2, 3]. Serum U/P creatinine ratio helps to identify whether the oliguria is a result of water reabsorption ($U/P_{Cr} > 20$) or loss of tubular function ($U/P_{Cr} < 20$). In prerenal states, the reabsorption of sodium is increased, not only from the increase in proximal tubular reabsorption of water, but also by the increase in aldosterone level secondary to hypovolemia. The frequent use of diuretic therapy in CHF patients limits the value of FE_{Na} in these patients. In these cases, the fractional excretion of urea (FE_{UN}) can be helpful, as FE_{UN} relates inversely to the proximal reabsorption of water, urea reabsorption leads to a decrease in FE_{UN} and an increase in the blood urea nitrogen/creatinine ratio. Carvounis et al. [4] found that FE_{UN} has a high sensitivity (85%), a high specificity (92%) and a high positive predictive value; in that study, a FE_{UN} less than 35% was associated with a 98% chance of prerenal failure. Still, there are also some limitations for the use of FE_{UN} . In osmotic diuresis and with the use of mannitol or acetazolamide, the proximal tubular reabsorption of salt and water is impaired, so there can be an increase in FE_{UN} even in states of hypoperfusion [5]. The same can occur when a patient is given a high protein diet or presents an excessive catabolism. Urinary osmolality is also used to evaluate the urinary concentration ability, a function that becomes impaired in the early process of tubular dysfunction. A value greater than 500 mosm/kg indicates that tubular function is still intact, although there are also some considerations about this index; a low protein diet or low protein absorption by intestine edema can

impair the concentration ability of the urine and show a low osmolality even in prerenal states.

There are some promising new biomarkers for AKI that may be helpful in distinguishing between prerenal and established AKI [6, 7]. During the prerenal state, the persistent vasoconstriction associated with metabolic changes and inflammation promotes the release of cell functional markers that can be detected in the blood and urine. However, at the current time there are no specific markers representing prerenal conditions. Urinary NGAL levels were evaluated in emergency room patients and the AUC for NGAL (0.948) did not significantly differ from the curve for serum creatinine (0.921). There was very little overlap in NGAL values in patients with AKI and prerenal failure, whereas serum creatinine values overlapped significantly [6].

No studies have examined the performance of the indicators of prerenal states in heart failure. It would appear that the same parameters and cutoff points would be applicable but need additional investigation. The diagnosis of prerenal state in CHF is particularly challenging given the close relationship of renal compensatory mechanisms and cardiac output. Although serum creatinine is the most used parameter to identify patients with worsening renal function in cardiac failure patients, measuring serum creatinine can be misleading as these patients have a reduced creatinine clearance in spite of only slightly elevated levels of serum creatinine [8]. In addition to the low muscular bulk associated with chronic cardiac failure, the increased extravascular volume in these patients leads to a higher volume of distribution of creatinine [9]. Rising blood urea nitrogen and serum creatinine and the finding of contraction alkalosis suggest a prerenal state has been achieved with inadequate intravascular volume for renal perfusion.

Management of Prerenal Azotemia in Congestive Heart Failure

A recent definition of cardiorenal syndrome [10] has provided additional stratification based on five common types of heart-kidney interactions and the possibility of customizing approaches for management. In the acute cardiorenal syndrome (type 1), an abrupt worsening of cardiac function leads to AKI. In patients with previous normal renal function, the three kidney compensatory mechanisms are initially intact and will have to be overwhelmed before a decline in GFR is detected. How much and for how long the kidneys will maintain the capacity to return to baseline GFR without cellular injury or prerenal azotemia is currently unknown but would likely be determined by the renal reserve and the severity of the cardiac dysfunction.

In cardiorenal syndrome type 2, a long-term decrease in stroke volume causes chronic diminished renal perfusion. Although the dominant mechanism responsible for the acute fall in GFR is difficult to define, several contributing

factors are often present [11]. When persistent vasoconstriction is present, the use of vasodilators may improve cardiac output and renal perfusion. Conditions associated with high renal venous pressure such as pulmonary hypertension, right ventricular dysfunction, and tricuspid regurgitation may improve with the appropriate treatment. However, when the reserve mechanisms are already in place to compensate for the chronic decline in stroke volume, the ability to compensate for a further decline in cardiac function is limited and the prerenal state can take place even with small decreases in cardiac function. Excessive production of vasoconstrictive mediators (epinephrine, angiotensin, endothelin) and the altered release of endogenous vasodilatory factors (natriuretic peptides, nitric oxide) associated with microvascular and macrovascular disease are responsible for the lack of success of the compensatory mechanisms to maintain GFR.

In cardiorenal types 3 and 4, the presence of CKD and other comorbidities such as advanced renal myeloma and decompensated cirrhosis are associated with an inability to compensate for further decrease in cardiac function, and any additional insult determines a fall in the GFR. In these patients, chronic renal ischemia due to cardiac dysfunction causes progressive deterioration in renal function evidenced by fibrosis of the renal parenchyma and possibly permanent loss of kidney function. The degree of vascular disease in the renal arteries and in the glomerular afferent and efferent arterioles determines how much the blood flow to the kidney and glomerulus can be increased. The ongoing activation of the RAS further decreases the ability of the efferent arteriolar tone to maintain glomerular filtration pressure.

In cardiorenal syndrome type 5 acute or chronic systemic disorders causes cardiac and renal dysfunction [10]. Several acute and chronic diseases, such as diabetes, sepsis, systemic lupus erythematosus, and amyloidosis can affect both organs. Severe sepsis is the most frequent contributing factor to AKI in the hospital setting [12, 13], and frequently affects cardiac function simultaneously [14]. Although the mechanisms responsible for this deleterious interaction are still poorly understood, inflammatory mediators play a primary role [15]. Recent evidence suggests that AKI associated with sepsis may have a distinct pathophysiology [16]. As in cardiorenal type 1, the fall in stroke volume can disrupt the balance in the compensatory mechanisms and trigger a prerenal state. At the same time, renal ischemia can induce further myocardial injury [17] creating a vicious cycle responsible for increased injury of both organs. The role of prerenal states in systemic disease other than sepsis is not defined; still, the activation of the inflammatory mediators with decreased renal perfusion could affect the myocardial function before histological injury can be detected.

In all forms of cardiorenal syndrome, diuretic therapy is commonly utilized with or without additional agents. Diuretic therapy can induce hypovolemia, further activation of RAS, prevents the kidney from maintaining an effective

circulating volume and may contribute to the worsening hemodynamics and consequently progressive renal dysfunction in these patients. Balancing volume removal with optimization of cardiac performance is a major concern in all forms of cardiac failure. With a diminished ability to compensate for the cardiac dysfunction, interventions to restore the baseline GFR need to be well timed. During the treatment for decompensated heart failure either using diuretics or ultrafiltration, the mobilization of interstitial edema can lead to intravascular volume depletion, further RAAS activation and reduce GFR. However, the rate of this plasma refilling is limited by the transcapillary pressure gradient and the permeability of the capillary membrane [18]. The dose of diuretic or ultrafiltration should be titrated to achieve a rate of diuresis allowed by plasma refill rate, avoiding further reduction in intravascular volume and reduction in renal perfusion pressure. When the balance is not achieved and the rate of diuresis overcomes the plasma refill rate, activation of the RAAS and SNS may trigger a prerenal state. In order to prevent the prerenal state, the rate of diuresis has to be continuously monitored.

Adenosine A₁ receptor antagonists are now being evaluated in CHF based on the hypothesis that inhibition of these receptors will increase RBF and enhance diuresis without triggering tubuloglomerular feedback. In phase II studies, rolofylline enhanced diuresis in patients with CHF and significantly increased GFR and renal plasma flow in patients with HF [19, 20]. Although a pilot study with rolofylline in patients with acute HF demonstrated a reduction in the proportion of patients with ≥ 0.3 mg/dl increase in serum creatinine [21], these results were not confirmed in a larger cohort [22].

Gaps in Knowledge and Future Directions

As a consequence of the lack of standardized definition and observational studies that could differentiate prerenal from established AKI, the prognosis of prerenal azotemia has yet to be determined. In patients presenting with comorbid conditions and intrinsic factors associated with decreasing compensatory mechanisms, the frequency of subclinical episodes of prerenal failure is unknown. Whether the frequency and duration of these episodes can have an impact on the progression of renal dysfunction has also to be determined. The identification of high-risk states and high-risk process, as well as a standardized definition could help future studies investigate these questions.

It is evident that research in this area is urgently needed to bring further clarity to the field. We believe that the principles discussed above need to be considered in developing standardized definitions of prerenal states. Achieving a consensus definition for prerenal syndrome will allow physicians to describe treatments and interventions as well as conduct and compare epidemiological studies in order to better describe the implications of this syndrome.

Conclusion

Current diagnosis of prerenal conditions is relatively insensitive and would benefit from additional research to define and classify the conditions. Because of the broad differences in patients' reserve capacity and functional status, prerenal states may be triggered at different time points. Additionally, given the variety of insults and compensatory mechanisms triggered, it is unlikely that single biomarkers of renal injury would be able to distinguish all these events. Future studies would need to focus on populations at risk for prerenal failure and discover biomarkers representing the compensatory mechanisms triggered during prerenal states. It is likely that several different markers may be used in combination to distinguish prerenal states from structural changes in the kidney. Recognizing reversible renal dysfunction early and accurately will enable timely intervention and will likely improve our ability to improve outcomes from AKI.

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Use of Biomarkers in Evaluation of Patients with Heart Failure

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Abstract

Despite advances in the understanding of the pathophysiology of heart failure, its diagnosis and management still remain challenging. Biomarkers have added significant value to the clinical evaluation of heart failure. While their use is not intended as a substitute for clinical judgment, their relevance in diagnosis, management, and prognosis has been proven. This review focuses on biomarkers resulting from hemodynamic stress, injury and inflammation, and their clinical relevance in modern practice.

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Heart failure (HF) is a serious public health matter in modern medicine. HF, at its simplest conceptualization, is the inability to adequately propel blood forward leading to a devastating cascade of events resulting in significant morbidity and mortality. The approach to the diagnosis of acute HF is complex and challenging due to its heterogeneous presentations and nonspecific signs and symptoms [1]. Classically, one is taught that a careful history in patients presenting with congestive HF (CHF) will elicit symptoms of dyspnea, orthopnea, and paroxysmal nocturnal dyspnea, while the physical exam will reveal elevated jugular venous pressure, rales, an S3 gallop, and pitting peripheral edema. However, it is well documented that, in practice, the clinical presentation of HF, even in combination with chest X-rays, electrocardiograms, and standard laboratory assessments, frequently does not clinch the diagnosis. Oftentimes, the clinician must entertain other etiologies of dyspnea such as chronic obstructive pulmonary disease or pneumonia, which can delay necessary treatment. The emergence of various classes of biomarkers is leading to a better understanding of the pathogenesis, diagnosis, and prognosis in HF.

Table 1. Desired properties of an ideal biomarker

Health-care-related features	Test-related features
Give objectivity to evaluation and diagnosis of patients, especially those in whom signs and symptoms are not very sensitive or specific	High sensitivity and specificity
Help with correct triage by assessment of prognosis and risk stratification	Reproducibility and accuracy
Help to objectively guide the therapy or management	Low coefficient of variation
Enable an optimum screening process	Easy to perform and analyze, possibly a point of care test
Guide the delivery of cost-effective medical care	Applicable across sexes, ethnicity and age spectra
	Make physiological sense
Adapted from Maisel et al. [2].	

Biomarkers in Heart Failure

Introduction

Table 1 demonstrates the desired properties of an ideal biomarker [2]. The biomarker should be highly reproducible, readily available, cost-effective, and have added value in the clinical decision-making process. There are currently few biomarkers that can fulfill all of these requirements. Biomarkers that do meet these criteria reflect a number of different mechanisms such as biomechanical stretch, inflammation and myocyte injury that are involved in the pathophysiology of HF. These markers individually and jointly provide important information in assessing the progression of disease, diagnosing acute exacerbations, and providing prognostic information.

Markers of Myocardial Stretch

Natriuretic Peptides

Biology

There are three major natriuretic peptides (NPs), atrial NP (ANP), B-type NP (BNP), and C-type NP (CNP), all of which counter the effects of volume

Table 2. NP subtypes and their actions

NP	Actions
ANP	arterial vasodilation, venodilation, natriuresis, diuresis, antagonizes renin-aldosterone-angiotensin system, increases renal GFR
BNP	arterial vasodilation, venodilation, natriuresis, diuresis, antagonizes renin-aldosterone-angiotensin system, antiproliferative
CNP	arterial vasodilation, venodilation, natriuresis, diuresis, antagonizes renin-aldosterone-angiotensin system, antiproliferative

overload or adrenergic activation of the cardiovascular system (table 2). ANP is primarily synthesized in the atria, stored in granules, and under minor triggers such as exercise is released into the circulation [3]. BNP has minimal storage in granules and is synthesized and secreted in bursts primarily by the ventricles [3]. CNP is a product of endothelial cells and may be protective in postmyocardial infarction remodeling [4]. Upon release into the circulation, ANP and BNP bind to various tissues and induce vasodilation, natriuresis, and diuresis [5].

Left ventricular pressure or volume overload results in myocardial wall stress that initiates the synthesis of pre-proBNP. Pre-proBNP is initially cleaved to proBNP and then to BNP, the biologically active form, and the inactive N-terminal fragment, NT-proBNP (fig. 1). The mechanism of action of NPs is mediated through membrane-bound NP receptors (NPRs). NPR-A preferentially binds ANP and BNP, and NPR-B primarily binds CNP. The NP-receptor interaction activates the enzyme guanylyl cyclase, leading to the production of cyclic guanosine monophosphate. Clearance of NPs is mediated through NPR-C, degradation by neutral endopeptidase, and direct renal clearance.

Patients with HF are in a state of BNP insufficiency resulting from a deficiency of the active BNP form plus molecular resistance to its effects [6]. Studies have demonstrated that the BNP detected in acute HF is primarily the high-molecular-weight proBNP rather than the biologically active form [7]. Some have suggested that abnormal cellular processing of BNP is a factor in the relative BNP deficiency state in HF [8]. Additionally, upregulation of phosphodiesterases leads to rapid clearance of the secondary messenger, cyclic guanosine monophosphate, despite high activation of the NPRs by NPs [9].

What constitutes a normal NP level depends on the specific clinical setting. Two studies found that BNP levels in normal adults without cardiovascular disease increase with age and appear to be higher in women, with NT-proBNP levels showing greater age dependence than BNP levels [10, 11]. General guidelines are that in young, healthy adults, 90% will have BNP <25 pg/ml

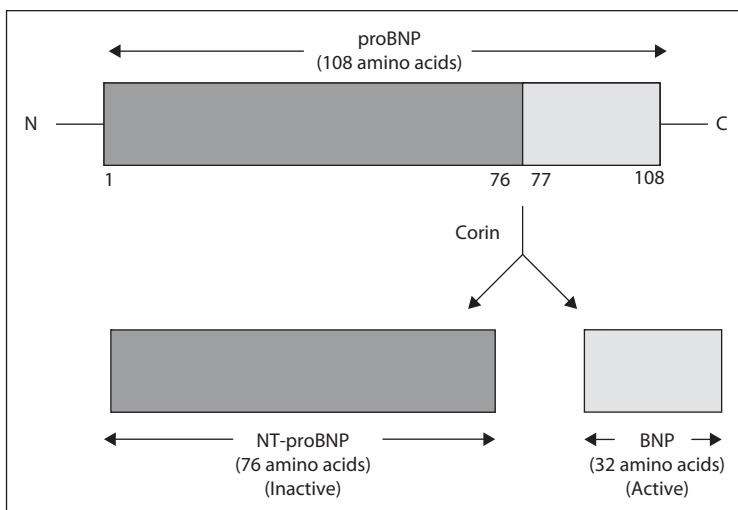


Fig. 1. Synthesis and processing of BNP.

and NT-proBNP ≤ 70 pg/ml [12]. In patients presenting with acute dyspnea, cutoffs of BNP < 100 pg/ml, and NT-proBNP < 300 pg/ml should be used to exclude HF [13, 14].

Natriuretic Peptides in Acute Heart Failure

BNP and NT-proBNP have become powerful diagnostic tools in the evaluation of patients presenting with dyspnea in a variety of clinical settings. In the Breathing Not Properly Multinational Study, BNP levels were measured in 1,586 patients with shortness of breath upon arrival in the Emergency Department (ED). Use of BNP resulted in a higher diagnostic accuracy, with an area under the receiver-operating characteristic curve (AUC) of 0.91 [13]. A BNP cut-point of 100 pg/ml was 90% sensitive and 76% specific for the diagnosis of HF as the cause of dyspnea (fig. 2). The data were extended to NT-proBNP in the PRIDE (ProBNP Investigation of Dyspnea in the ED) study, which measured NT-proBNP in 600 ED patients with dyspnea and demonstrated its sensitivity and specificity in the diagnosis of CHF (AUC = 0.94) [14]. The cut-point of NT-proBNP < 300 pg/ml was proposed to rule out HF as the etiology.

The use of NPs has also proved to be significantly cost-effective. In the BASEL (BNP for Acute Shortness of breath Evaluation) study, 452 patients presenting to the ED with dyspnea were randomized to a single measurement of BNP versus no such measurement. The study reported a 10% reduction in the rate of admissions and a 3-day decrease in the median length of stay with the use of BNP, amounting to a total cost savings of USD 1,800/patient without an increase in mortality or rehospitalization [15]. These results were extended to

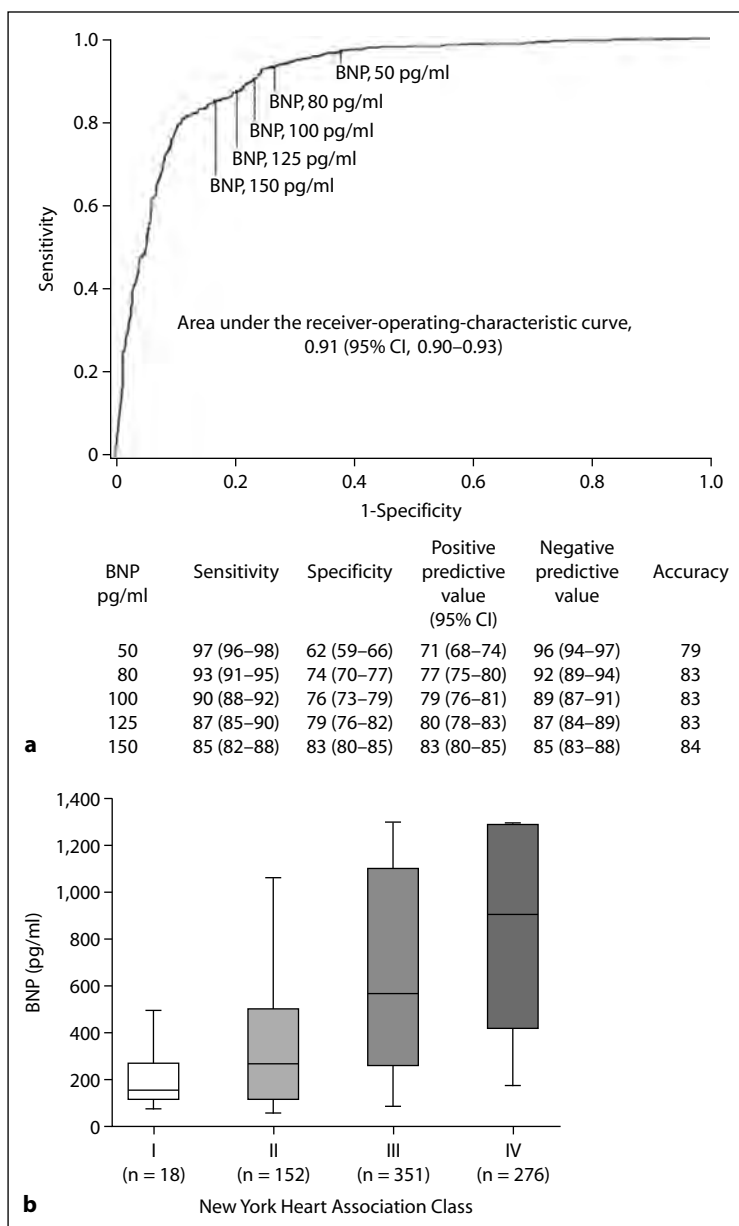


Fig. 2. Receiver-operating characteristic curve from The Breathing Not Properly Trial for the different cutoff values of BNP in differentiating between dyspnea secondary to CHF versus other causes. Reproduced with permission Maisel et al. [13].

NT-proBNP in the IMPROVE-CHF (Improved Management of Patients with Congestive Heart Failure) study [16].

Elevated Natriuretic Peptides in Other Clinical Settings

It is important for clinicians to be aware of clinical scenarios other than acute HF that can cause NP levels to rise. Patients with a history of HF but without an acute exacerbation can have intermediate BNP levels, as shown in the Breathing Not Properly trial [13]. Acute coronary syndrome (ACS) is also associated with elevated levels of NPs: acute ischemia causes transient diastolic dysfunction resulting in increased left ventricular end-diastolic pressure, a rise in wall stress, and increased synthesis of BNP [17]. Although NP values can be elevated to intermediate levels in patients with underlying lung disease, they tend to remain significantly lower than in patients presenting with CHF [18]. The Breathing Not Properly trial demonstrated that NP levels were useful in diagnosing HF, which was present in 87 out of the 417 patients with a history of chronic obstructive pulmonary disease or asthma (BNP levels 587 vs. 109 pg/ml, $p < 0.0001$) [13]. In addition, right heart dysfunction from hemodynamically significant pulmonary embolism, severe lung disease, and pulmonary hypertension can lead to elevated levels of NPs [19–22]. Therefore, when intermediate levels of NPs are encountered in an acutely dyspneic patient, it is important to consider other life-threatening etiologies of dyspnea.

Hyperdynamic states of sepsis, cirrhosis and hyperthyroidism can also be associated with elevated NPs [23–25]. NP levels also are increased in the setting of atrial fibrillation (AF) [26]. The Breathing Not Properly trial demonstrated that BNP still performed well in patients with AF, with an AUC of 0.84 as compared to 0.91 for the entire cohort. Increasing the cutoff to 200 pg/ml in these patients improved specificity and the positive predictive value for diagnosing HF [27].

Caveats in Using Natriuretic Peptide Levels

In addition to wall stress, other factors have been associated with elevated NP levels. Aging appears to be associated with elevated levels of BNP independent of the degree of diastolic dysfunction [10, 11]. Possible mechanisms may include altered renal function, changes in the biosynthesis and processing of NPs on a cellular level, or a reduction in the clearance receptor, NPR-C [28]. Women appear to have higher NP levels than their age-matched counterparts [10, 11]. Although the reasons for this sex difference are unclear, some have proposed that differences in estrogen or testosterone may be responsible [10, 29].

The association between NP levels and renal function is complex. In the setting of renal dysfunction, increased concentrations of NPs may stem from elevation in atrial pressure, systemic pressure or ventricular mass. Patients with renal disease often have hypertension that results in significant left ventricular

hypertrophy, and cardiac comorbidities are also common. This interplay between the heart and kidney in patients with reduced renal function accounts for one component of the increase in NP levels, reflecting elevated 'true' physiologic NP levels [30]. The Breathing Not Properly study found a weak but significant correlation between glomerular filtration rate (GFR) and BNP, and suggested higher cut-points for patients with GFR <60 ml/min/1.7 m² [31].

Interpretation of NT-proBNP in the setting of renal dysfunction is more challenging given that clearance is not mediated by NPR-C or neutral endopeptidase and is more renally dependent. GFR seems to be more strongly correlated with NT-proBNP ($r = -0.55$) than with BNP, though the discrepancy may be somewhat less prominent in patients with acute CHF ($r = -0.33$ for NT-proBNP, and $r = -0.18$ for BNP) [32, 33]. An analysis from the PRIDE study demonstrated that NT-proBNP levels in patients with GFR <60 ml/min/1.7 m² were still the strongest predictors of outcome, and suggested a higher cut-point of >1,200 pg/ml for the diagnosis of HF [33]. In contrast, there is no significant relationship between NT-proBNP levels and GFR in relatively healthy patients with mild renal insufficiency [34]. Despite the relationship between NPs and GFR, both BNP and NT-proBNP still provide important diagnostic and prognostic information in patients with renal dysfunction.

Several studies have demonstrated an inverse relationship between body mass index and BNP levels [11, 35–37]. The reasons for this are not fully elucidated, though some have postulated an increased clearance mediated through elevated levels of NPR-C in adipocytes [38]; data for this are conflicting [34, 39]. A study in postbariatric surgery patients showed an increase in both BNP and NT-proBNP levels after the surgery, suggesting that downregulation of NP production in obesity, rather than increased clearance, may be responsible for the lower levels of NPs in the obese population [40]. Despite lower circulating levels, NPs retain their diagnostic capability in obese patients, albeit at lower cutoff levels [37].

Flash pulmonary edema may occur due to causes upstream of the left ventricle (i.e. acute mitral regurgitation and mitral stenosis), and along with pericardial disease do not lead to substantial elevations in NPs [30]. In flash pulmonary edema, due to the small amount of NPs that are preformed and residing in secretory granules, and to the delay between wall-stress and upregulation of gene expression, the level of NPs is disproportionately low in comparison with symptoms [30]. Patients with constrictive pericardial disease can present with symptoms of right HF; however, since the myocardium is confined from stretching by the stiff pericardium, there are typically normal or minimally elevated NP levels [30, 41].

Prognosis

There has been a tremendous increase in data demonstrating the prognostic power of NPs in a variety of clinical settings. Several studies report that NP

levels in patients presenting to the ED with HF are predictive of future cardiovascular events. Every 100 pg/ml increase is associated with a 35% increase in the risk of death in HF [42]. The prospective, multicenter REDHOT (Rapid ED Heart Failure Outpatient Trial) of 464 patients presenting to the ED with HF showed that BNP was predictive of future HF events and mortality, and was superior to ED physician assessment of severity of illness. In patients with chronic HF, BNP provides powerful prognostic information regarding survival and deterioration of functional status [43]. In over 4,300 outpatients with chronic HF in Val-HeFT (Valsartan Heart Failure Trial), patients with the greatest rise in BNP despite therapy had the highest morbidity and mortality [44].

In addition to HF, both BNP and NT-proBNP have a strong prognostic value in patients with coronary artery disease, ACS, valvular heart disease, and prediction of sudden cardiac death [45–50].

Monitoring Therapy

Inpatient. Several studies have evaluated the relationship between NP levels and pulmonary capillary wedge pressure (PCWP) derived from invasive hemodynamic catheters [51]. Given that in various clinical scenarios, as described above, there can be discordance between NP levels and clinical presentation, NP levels do not always correlate with PCWP [52]. However, in patients with decompensated HF due to volume overload, a treatment-induced drop in PCWP will usually lead to a rapid decrease in BNP levels (35–50 pg/ml/h), especially in the first 24 h of therapy assuming that adequate urine output is maintained [53]. In managing hospitalized patients with HF, it is probably not necessary to measure daily levels of NPs. However, obtaining a level at admission and after the first 1–2 days of therapy can be useful for tailoring appropriate treatment. A predischarge can be useful in tailoring the intensity of therapy, and has been shown to have strong prognostic implications [54, 55]. A study with 114 patients admitted with CHF showed that patients with a predischarge BNP >700 pg/ml had a 15-fold increase in mortality or readmission at 6 months, compared to patients with BNP <350 pg/ml at discharge [56].

Outpatient. Monitoring NP levels in the outpatient setting might improve patient care, at least in patients less than 76 years of age. Potentially, changes in NP levels could help physicians more aggressively and safely titrate neurohormonal blockade agents and diuretics. In the STARS-BNP (Systolic Heart Failure Treatment Supported by BNP) study of 220 patients with HF and left ventricular dysfunction who were randomized to receive therapy guided by NP levels versus standard of care, NP-guided treatment that targeted a BNP <100 pg/ml significantly reduced mortality and hospital stay for HF [57]. The smaller STARBRITE (Strategies for Tailoring Advanced Heart Failure Regimens in the Outpatient Settings: Brain Natriuretic Peptides Versus the Clinical CongesTion Score) study (n = 130) failed to show significant improvement in the primary outcome

Table 3. Non-NP biomarkers of interest in HF

Biomarker	Clinically available?	Elevation in HF indicates
ST2	no	myocardial stretch, elevated PCWP, worse prognosis
MR-proADM	no	myocardial stretch, elevated PCWP, worse prognosis
Troponin	yes	myocardial necrosis, worse prognosis
hsCRP	yes	worse prognosis in acute and chronic HF
NGAL	yes ¹	predictor of AKI

AKI = Acute kidney injury.

¹ Available in Europe.

of nonhospital days alive in patients whose treatment was guided by BNP levels. However, STARBRITE enrolled patients with more severe disease and used a higher cut-point for BNP [58]. In both studies, clinicians who adjusted medical therapy based on NP levels prescribed higher doses of angiotensin-converting enzyme inhibitors and beta-blockers.

In patients followed in clinic, it is important to establish their ‘steady state’ level of NP that corresponds to their optimized fluid status. Significant deviations from this baseline NP allow for rapid diagnosis and institution of therapy, with more aggressive diuresis and follow-up when levels rise substantially [59]. Values that are considerably reduced from baseline can signal overdiuresis and impending prerenal azotemia. Given the significant intraindividual variability in NP levels, a change of at least 50% in the steady-state NP level might be a reasonable mark for triggering a more aggressive evaluation and modification of treatment [30].

Non-Natriuretic Peptide Biomarkers for Heart Failure

Table 3 shows a list of pertinent biomarkers currently under study for HF.

Adrenomedullin

Biology

Adrenomedullin (ADM), like NPs, is produced in the setting of myocardial stress. ADM is a vasoactive peptide consisting of 52 amino acids that shares

homology with calcitonin gene-related peptide [60]. The downstream actions of ADM are mediated by an increase in cyclic adenosine monophosphate levels and nitric oxide, leading to potent vasodilation, an increase in cardiac output, and diuresis and natriuresis [61–65]. This biologically active modulator is produced from the precursor proadrenomedullin, which is produced by the heart, adrenal medulla, lungs, kidneys, and vascular endothelium [66, 67]. ADM levels are increased in endothelial dysfunction, which is common in patients with HF and indicates a poor prognosis. In HF patients, the magnitude of increase in ADM corresponds with the severity of HF, and is inversely related to left ventricular function [66, 68]. ADM levels increase with worsening symptoms of HF and elevated PCWP and are reduced with appropriate therapy [66]. Since ADM combines with complement factor H and is rapidly cleared from the circulation, direct measurements are difficult; however, mid-regional proadrenomedullin (MR-proADM) is another product of the precursor which appears to be more clinically stable and can be readily measured [69, 70].

ADM and Heart Failure

In one of the first studies involving MR-proADM, Kahn et al. [71] evaluated its prognostic capability in 983 patients with postmyocardial infarction. The data showed that MR-proADM is increased in patients who died or developed HF, compared with survivors [median 1.19 nM, (interquartile range 0.09–5.39 nM), vs. 0.71 nM (0.25–6.66 nM), $p < 0.0001$]. In 786 consecutive CHF patients with a mean follow-up of 24 months, Adlbrecht et al. [72] demonstrated that MR-proADM was a significant predictor of death (hazard ratio, HR = 1.77, $p < 0.001$), and was particularly useful in patients with mild-to-moderate symptomatic HF. ADM also has predictive capability in asymptomatic patients with risk factors for CAD. In 121 patients, Nishida et al. [73] reported that patients with elevated ADM levels had higher risk of future cardiovascular events.

MR-proADM has also been evaluated in patients with acute decompensated HF. In 137 patients with acute decompensated HF [74], the AUC for the prediction of 1-year mortality were similar for BNP (0.716; 95% CI 0.633–0.790), mid-regional pro-A-type NP (0.725; 95% CI 0.642–0.798), MR-proADM (0.708; 95% CI 0.624–0.782), and copeptin (0.688; 95% CI 0.603–0.764) [74]. The BACH study compared MR-proADM with BNP and NT-proBNP in predicting mortality at 90 days in patients hospitalized for decompensated HF [75]. Of 1,641 patients recruited, approximately one third ($n = 568$) were ultimately diagnosed with HF. The data showed that MR-proADM was more accurate than BNP or NT-proBNP at predicting outcome at 90 days [75].

Summary of MR-proADM

ADM is a relatively new biomarker that reflects biomechanical stretch and increases with pressure or volume overload. Although there is limited

experience with ADM, based on available data it correlates with NP levels and may provide superior prognostic information in patients with acute and chronic HF.

ST2

Biology

ST2 is a member of the interleukin (IL)-1 receptor family and has 2 primary isoforms, a transmembrane receptor form (ST2L) and a soluble receptor form (ST2), regulated by different promoters [76–78]. Microarray analysis demonstrates marked upregulation of the transcript for ST2 transmembrane and soluble forms, with the soluble form displaying more robust expression in mechanically-stimulated cardiomyocytes [78, 79]. In response to mechanical strain, there is also an increase in the transcription and translation of the ligand, IL-33 [80]. The ST2/IL-33 signaling cascade is thought to serve a critical role in the regulation of myocardial response to pressure overload, inhibiting fibrosis [81–83]. Genetic knockouts of ST2 in mice models demonstrated significant cardiac hypertrophy, interstitial fibrosis and cavity dilation in response to transverse aortic constriction [78, 84]. A similar phenotype is generated by infusion of soluble ST2, which is believed to serve as a decoy receptor, thereby decreasing the beneficial IL-33 interaction with ST2L. In this way, the ratio of soluble ST2 to IL-33 may regulate the IL-33/ST2L system [78].

ST2 and Heart Failure

Weinberg et al. [79] demonstrated that change in ST2 levels over a 2-week period in 161 patients with severe chronic New York Heart Association (NYHA) class III–IV HF was an independent predictor of subsequent mortality or transplantation. ST2 has also proven to be an important biomarker in patients presenting with acute decompensated HF. The PRIDE study measured ST2 concentrations in 593 dyspneic patients in the ED [80]. ST2 levels were higher among patients with acute HF than in patients with other etiologies of dyspnea (0.50 vs. 0.15 ng/ml; $p < 0.001$). An ST2 level ≥ 0.20 ng/ml strongly predicted death at 1 year in the entire cohort (HR = 5.6, 95% CI 2.2–14.2; $p < 0.001$). Patients in the lowest decile of ST2 levels had a 1-year mortality of $<4.5\%$, while those in the highest decile had a mortality rate of 45% (fig. 3). Another study looked at change in ST2 concentrations during the course of a hospitalization in 150 patients with acute HF [81]. Multiple biomarkers were measured including ST2, BNP, NT-proBNP, and BUN at six time points between admission and discharge. Patients whose ST2 values decreased by 15.5% or more during the study period had a 7% incidence of death, whereas those whose ST2 levels failed to decrease by 15.5% had a 33% chance of dying within 90 days [81]. Rehman et al. [82] further examined the

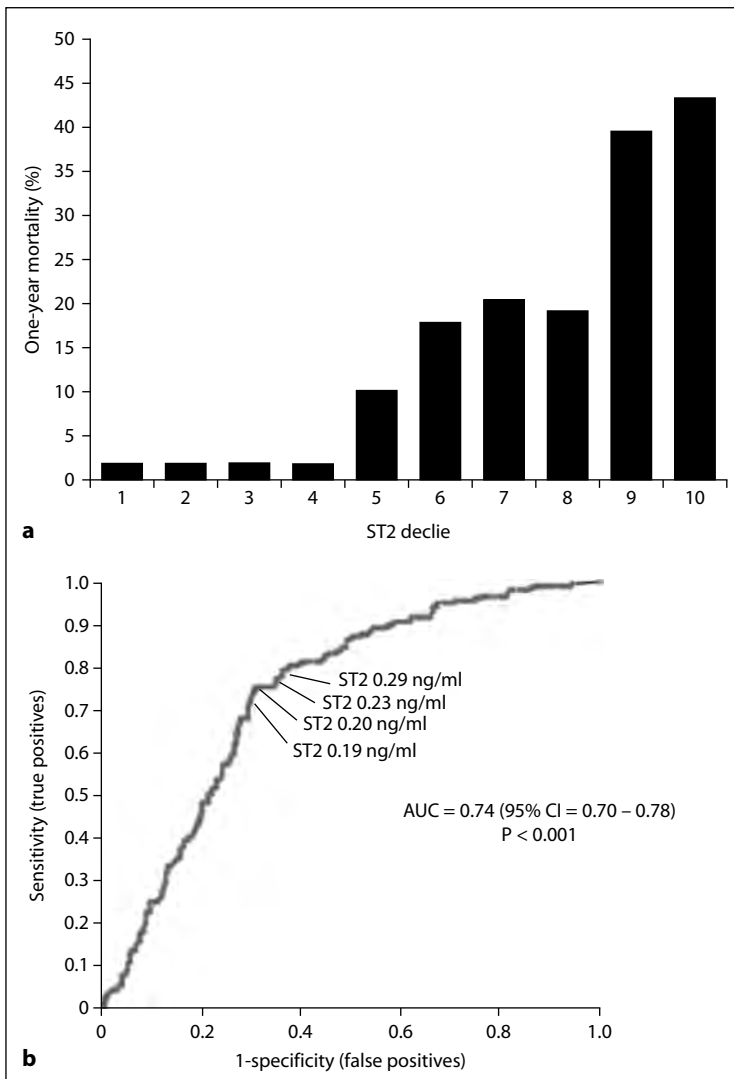


Fig. 3. a PRIDE study analysis demonstrating the rates of death at 1 year as a function of ST2 concentrations in patients with dyspnea. **b** Receiver-operating characteristic analysis with an AUC demonstrated for ST2 and death at 1 year after presentation. Reproduced with permission from Januzzi et al. [80].

patient-specific characteristics of ST2 in 346 patients hospitalized with acute HF, demonstrating that even after controlling for established and clinical characteristics, ST2 remained a predictor of mortality (HR 2.04, CI 1.3–3.24, $p = 0.003$).

Summary of ST2

ST2, induced by myocardial response to pressure or volume overload, has important clinical implications in patients with acute and chronic HF, and ACS. ST2 is a powerful prognosticator of future cardiovascular morbidity and mortality, providing incremental information to NPs [83].

Markers of Inflammation

One possible mechanism for progression and deterioration of HF is an abnormal inflammatory response [84]. Ischemia and other biological insults to the heart trigger an innate immune response leading to the upregulation of proinflammatory cytokines [83]. The activation of these mediators results in apoptosis, hypertrophy and dilation, leading to acceleration of disease progression [83]. Many features of HF, including hemodynamic compromise, vascular abnormalities, and other features can be explained through effects of proinflammatory cytokines including C-reactive protein (CRP), tumor necrosis factor- α , IL-6 and IL-18 [85–88].

C-Reactive Protein

Biology

CRP is an acute-phase reactant, reaching significantly elevated levels shortly within the onset of an inflammatory process, and is synthesized by hepatocytes in response mainly to IL-6 [89]. It is a nonspecific marker, commonly increased in the settings of infection, inflammatory diseases, ACS, smoking, and neoplastic processes [90]. CRP reduces the release of nitric oxide, and increases expression of endothelin-1 and of endothelial adhesion molecules [91]. These features suggest mechanisms by which CRP plays an important role in vascular diseases.

High-Sensitivity C-Reactive Protein and High-Risk Patients

There is a large volume of data examining the relationship between high-sensitivity CRP (hsCRP) and development of HF in high-risk patients, particularly those admitted with ACS (table 4) [90, 92–102]. An early study of 188 patients with acute myocardial infarction (MI) followed for 2 years reported that patients with higher peak CRP levels within the immediate post-MI period had increased risk of death and development of HF [92]. Subsequently, analysis of over 10,000 patients confirmed that elevated levels of CRP or hsCRP within 24 h of acute MI predict short and long-term development of HF.

hsCRP and Prognosis in HF

The prognostic impact of hsCRP in chronic HF patients has been evaluated in multiple studies with a combined total of over 6,600 patients (table 5) [90, 103–111]. There is a significant association between increasing level of hsCRP and

Table 4. hCRP value to predict HF after MI

Reference	Study, country	Patients	Age, years	Males, %	Follow-up	HF	hsCRP comparisons	HR (95% CI)	Adjusted for
Berton et al., [95]	CRP in AMI: association with HF. Italy	220	66.7 (mean)	74	1 year	86 (39.1%)	≥15 mg/l vs. <15 mg/l (optimal cutoff)	4.3 (–)	Age, gender, hypertension, diabetes, BMI, CK, previous MI or angor, thrombolytic therapy, LVEF
Suleiman et al., [96]	Admission CRP levels and 30-day mortality in AMI. Israel	448	60 ± 12	78	30 days	121 (27.0%)	>23.3 mg/l vs. <6.9 mg/l (3rd vs. 1st tertile)	2.60 (1.50–4.60)	Age, gender, smoking, diabetes, hypertension, Killip class, BP, creatinine, aspirin, statin, anterior and ST-elevation MI, thrombolysis vs. primary angioplasty, wall motion score index
Suleiman et al., [97]	Early inflammation and risk of long-term development of HF and mortality in survivors of AMI. Predictive role of CRP. Israel	1,044	60 ± 13	89	23 months (median)	112 (10.7%)	≥37.9 mg/l vs. ≤5.0 mg/l (4th vs. 1st quartile)	2.80 (1.40–5.90)	Age, gender, smoking, hypertension, diabetes, BB, previous HF, Killip class, anterior MI, BP, heart rate, peak CK, LVEF
Scirica et al., [93]	Clinical application of CRP across the spectrum of acute coronary syndromes. USA	1,992	61.1 (mean)	70	30 days and 10 months	–	>25.4 mg/l vs. <3.4 mg/l (4th vs. 1st quartile)	8.20 (–) (30 days) 3.60 (–) (10 months)	Age, gender, smoking, diabetes, prior MI, peripheral arterial or cerebrovascular disease, hypercholesterolemia, BMI, Killip class, statin, aspirin, treatment with orbofiban

Table 4. Continued

Reference	Study, country	Patients	Age, years	Males, %	Follow-up	HF	hsCRP comparisons	HR (95% CI)	Adjusted for
Bursi et al., [98]	CRP and HF after MI in the community. USA	329	69 ± 16	52	1 year	92 (28.0%)	>15 mg/l vs. <3 mg/l (3rd vs. 1st tertile)	2.83 (1.27–4.82)	Age, sex, comorbidities, previous MI, Killip class, troponin T
Kavsak et al., [99]	Elevated CRP in acute coronary syndrome presentation is an independent predictor of long-term mortality and HF. USA	446	62 ± 14	59	2 and 8 years	–	>7.44 mg/l vs. <3 mg/l (arbitrary cutoff)	4.14 (–) (2 years) 3.69 (–) (8 years)	Age, sex, presentation and peak troponin I
Hartford et al., [100]	CRP, IL-6, secretory phospholipase A2 group IIA and intercellular adhesion molecule-1 in the prediction of late outcome events after acute coronary syndrome. Sweden	757	65	73	2 years for morbidity (median)	76 (10.0%)	>16 mg/l vs. <2 mg/l (4th vs. 1st quartile)	1.40 (1.10–1.90)	Age, sex, smoking, diabetes, hypertension, hypercholesterolemia, obesity, previous MI, Killip class, creatinine, aspirin, statin, BB, ACE inhibitor
Mielniczuk et al., [94]	Estimated glomerular filtration rate, inflammation, and cardiovascular events after an acute coronary syndrome. A to Z study. Canada	4,178	60.4	75	2 years	166 (4.0%)	>45.2 mg/l vs. <8.0 mg/l (4th vs. 1st quartile)	2.89 (1.70–4.80)	Age, sex, race, smoking, diabetes, hypertension, prior MI, cholesterol, triglycerides, LVEF, GFR

Table 4. Continued

Reference	Study, country	Patients	Age, years	Males, %	Follow-up	HF	hsCRP comparisons	HR (95% CI)	Adjusted for
Sabatine et al., [101]	Prognostic significance of the Centers for disease control/American Heart Association hsCRP cut points for cardiovascular and other outcomes in patients with stable CHD. Multicentric	3,771	63.7 (mean)	81.1	4.8 years (median)	106 (2.8%)	>3 mg/l vs. <1 mg/l (arbitrary cutoff)	2.83 (1.54–5.22)	Age, sex, smoking, diabetes, hypertension, previous MI, SBP, DBP, BMI, cholesterol, GFR, BB, statin
Williams et al., [102]	CRP, diastolic dysfunction and risk of HF in patients with coronary disease: Heart and Soul Study. USA	985	67 ± 11	81.4	3 years	99 (10.0%)	>3 mg/l vs. ≤3 mg/l (arbitrary cutoff)	2.10 (1.20–3.60)	Sex, smoking, physical activity, BMI, statin, aspirin, LDL and HDL cholesterol, creatinine clearance, MI events, LVEF

ACE = Angiotensin-converting enzyme; BB = beta-blocker; BMI = body mass index; BP = blood pressure; CHD = coronary heart disease; CK = creatine kinase; DBP = diastolic blood pressure; LDL = low-density lipoproteins; HDL = high-density lipoproteins; LVEF = left ventricular ejection fraction; SBP = systolic blood pressure.

worse mortality, lower left ventricular systolic function, higher prevalence of NYHA class III or IV symptoms, and poorer quality of life [98, 115–123].

In contrast, there is a paucity of data evaluating the prognostic significance of hsCRP in acute HF. Alonso-Martínez et al. [112] prospectively studied the role of hsCRP in 76 patients admitted with acute HF. The data showed that elevated hsCRP levels were associated with increased rates of readmission at 18 months. In another 214 patients with acute HF, patients in the highest tertile of CRP had significantly higher in-hospital and all-cause mortality at 24 months [113]. Although the role of CRP as a prognostic biomarker in patients hospitalized with HF is yet to be firmly established, limited data suggest that it may complement other biomarkers in predicting mortality in this clinical setting.

Table 5. Prognostic value of hsCRP in HF

Refer- ence	Study, country	Pat- ients	Age, years	Males, %	Follow- up	Readmis- sion for wor- sening HF/death	hsCRP com- parisons	HR (95% CI)	Adjusted for
Anand et al., [44]	CRP in HF, Prognostic value and the effect of valsartan, Val-HeFT, Multicentric	4,202	63 ± 11	80	36 months	1,255 (29.9%)	≥7.3 mg/l vs. <1.4 mg/l (4th vs. 1st quartile)	1.53 (1.28– 1.84)	Age, sex, CHD, NHYA, LVEF, hemoglobin, GFR, uric acid, BNP, aldo- sterone, renin, norepinephrine, statin, aspirin, BB, valsartan vs. placebo
Yin et al., [103]	Independent prognostic value of elevated hsCRP in chronic HF. Taiwan	108	62 ± 16	66	403 days (median)	35 (32.4%)	>2.97 mg/l vs. <2.97 mg/l (optimal cutoff)	3.50 (1.15– 8.05)	Age, sex, CHD, LVEF, left ventri- cular filling pressure, TNF-α, statin
Xue et al., [104]	Prognostic value of hsCRP in patients with chronic HF. China	128	62 ± 15	79	378 days (mean)	42 (32.8%)	>3.2 mg/l vs. <3.2 mg/l (optimal cutoff)	3.81 (2.14– 9.35)	Age, sex, CHD, LVEF, troponin T, statin
Windram et al., [105]	Relationship of hsCRP to prognosis and other prognostic markers in outpatients with HF. UK	957	71 ± 10	71	36 months	163 (17.0%) Only death	>11 mg/l vs. <2.8 mg/l (4th vs. 1st quartile)	3.00 (2.1– 4.1)	Age, sex, smoking diabetes, white blood cell count, BB, statin, NSAID
Yin et al., [106]	Multimarker approach to risk stratification among patients with advanced chronic HF. Taiwan	152	56 ± 14	77	186 days (median)	63 (41.4%)	>4.92 mg/l vs. <4.92 mg/l (median)	2.16 (1.17– 3.99)	Age, sex, etiology, SBP, LVEF, sodium, creatinine clearance, troponin I, NT- proBNP

Table 5. Continued

Reference	Study, country	Patients	Age, years	Males, %	Follow-up	Readmission for worsening HF/death	hsCRP comparisons	HR (95% CI)	Adjusted for
Tang et al., [107]	Usefulness of CRP and left ventricular diastolic performance for prognosis in patients with left ventricular systolic HF. USA	136	57 ± 14	76	33 months (mean)	36 (26.5%)	>5.96 mg/l vs. <5.96 mg/l (optimal cutoff)	2.26 (1.11–4.63)	LVEF, echocardiographic indexes of diastolic dysfunction, BNP
Lamblin et al., [108]	HsCRP: potential adjunct for risk stratification in patients with stable HF. France	546	56 ± 12	82	972 days (median)	113 (20.7%)	>3 mg/l vs. <3 mg/l (optimal cutoff)	1.78 (1.17–2.72)	Age, sex, etiology, hypertension, diabetes, BMI, NHYA, LVEF, BNP
Chirinos et al., [109]	Usefulness of CRP as an independent predictor of death in patients with ischemic cardiomyopathy. USA	123	64 ± 10	100	3 years	Only death	For each 10 mg/l increase	1.26 (1.02–1.55)	Age, number of vessels involved with coronary disease, LVEF, sodium, creatinine, hemato-crit, ACE inhibitor, BB
Ronnow et al., [110]	CRP predicts death in patients with nonischemic cardiomyopathy. USA	203	62 ± 13	59	2.4 years (mean)	40 (19.7%)	>23.3 mg/l vs. <23.3 mg/l (3rd tertile vs. 1st and 2nd tertiles)	2.00 (1.04–3.80)	Age, sex, smoking, family history, hypertension, hyperlipidemia, diabetes, renal failure, BMI, LVEF

Table 5. Continued

Refer- ence	Study, country	Pat- ients	Age, years	Males, %	Follow- up	Readmis- sion for wor- sening HF/death	hsCRP com- parisons	HR (95% CI)	Adjusted for
Ishikawa et al., [111]	Prediction of mortality by hsCRP and BNP in patients with dilated cardiomyo- pathy. Japan	84	56 ± 2	81	42 months (mean	–	>1 mg/l vs. <1 mg/l (arbitr- ary cutoff)	3.30 (1.2– 9.0)	Age, sex, NHYA, LVEF, cardiac index, hemo- globin, creati- nine, BNP, IL-6, endothelin, norepinephrine

Reprinted with permission from Araújo et al. [90]. ACE = Angiotensin-converting enzyme; BB = beta-blocker; BMI = body mass index; BP = blood pressure; CHD = coronary heart disease; COPD = chronic obstructive pulmonary disease; DBP = diastolic blood pressure; LVEF = left ventricular ejection fraction; MBP = mean blood pressure; NSAID = non-steroidal anti-inflammatory drug; SBP = systolic blood pressure; TNF = tumor necrosis factor-α.

Summary of CRP

CRP is perhaps the most important single marker of inflammation and is routinely used in clinical practice. It has validated utility in predicting the development of HF in low- and high-risk populations, as well as prognostic value in patients with chronic HF. In practice, interpretation of CRP levels is somewhat hampered by the fact that most studies used different cut-points, making individual CRP levels difficult to interpret. The real-world clinical utility of hsCRP requires further investigation with uniform studies that use similar assays and cut-points.

Markers of Myocardial Cell Death

Troponin

Biology

Myocardial cell death occurs commonly in HF and may represent the common final pathway leading to the patient’s demise. Although cardiac troponin levels (cTnI or cTnT) are well-validated markers of myocyte injury during MI, the pathophysiology leading to troponin elevations in HF probably is distinct

from that seen during ACS [114]. Multiple mechanisms including inflammation, interstitial fibrosis, increased wall stress, oxidative stress and neurohormonal activation are responsible for adverse cardiac remodeling leading to progressive HF [115–117]. Troponin is a cardiac structural protein that is part of the troponin-tropomyosin complex, with a small amount present in the cytosol, and mild elevations in troponin have been documented in a number of cardiovascular diseases, including HF. Hypotheses for why troponin levels may be elevated in the setting of HF even in the absence of overt ischemia include: myocardial injury, loss of cell membrane integrity, excessive wall tension leading to subendocardial ischemia, apoptosis, or some combination [118–119].

Troponin and Acute HF

Several small studies have reported that elevated cardiac troponin levels in patients with decompensated HF are associated with a poor prognosis [120–123]. La Vecchia et al. [124] evaluated the clinical associations and prognostic implications of detectable cardiac troponin I (cTnI). In 34 patients with severe HF, modest elevations of cTnI (0.7 ± 0.3 ng/ml) were associated with lower left ventricular ejection fraction, and there was a trend towards higher pulmonary artery pressures. In patients who clinically improved after admission, cTnI became undetectable after a few days. However, in patients with refractory HF who ended up dying in the hospital, detectable levels of cTnI persisted throughout the observation period [139]. The Acute Decompensated Heart Failure National Registry (ADHERE) evaluated the association between cardiac troponin and adverse events in 84,872 patients with acute decompensated HF [140]. Patients with positive troponin (6.2%) had lower systolic blood pressure on admission, a lower ejection fraction, and higher in-hospital mortality (8.0 vs. 2.7%, $p < 0.001$) in comparison to those with undetectable troponin (odds ratio for death 2.55, 95% CI 2.24–2.89; $p < 0.001$). The study confirmed the powerful prognostic utility of elevated troponin levels in predicting mortality in patients hospitalized with decompensated HF (fig. 4).

Troponin and Chronic HF

The role of myocyte injury in prognosis of stable outpatients with HF was evaluated in 136 stable, ambulatory patients. Patients with elevated cTnT levels had an increased risk of death or HF hospitalization (RR 2.7, 95% CI 1.7–4.3, $p = 0.001$) and of death alone (RR 4.2, 95% CI 1.8–9.5, $p = 0.001$) at 14 months [126]. In a larger outpatient data set from the Val-HeFT study, cTnT was detectable in 10.4% of the population with the cTnT assay (lower limit of detection 0.01 ng/ml) compared with 92.0% with the new high-sensitivity troponin T (hsTnT) assay (lower limit of detection 0.001 ng/ml). Patients with cTnT elevation or with hsTnT above the median (0.012 ng/ml) had more severe HF, and worse prognosis [127]. Increased concentration of cTnT (cTnT >0.01) was associated

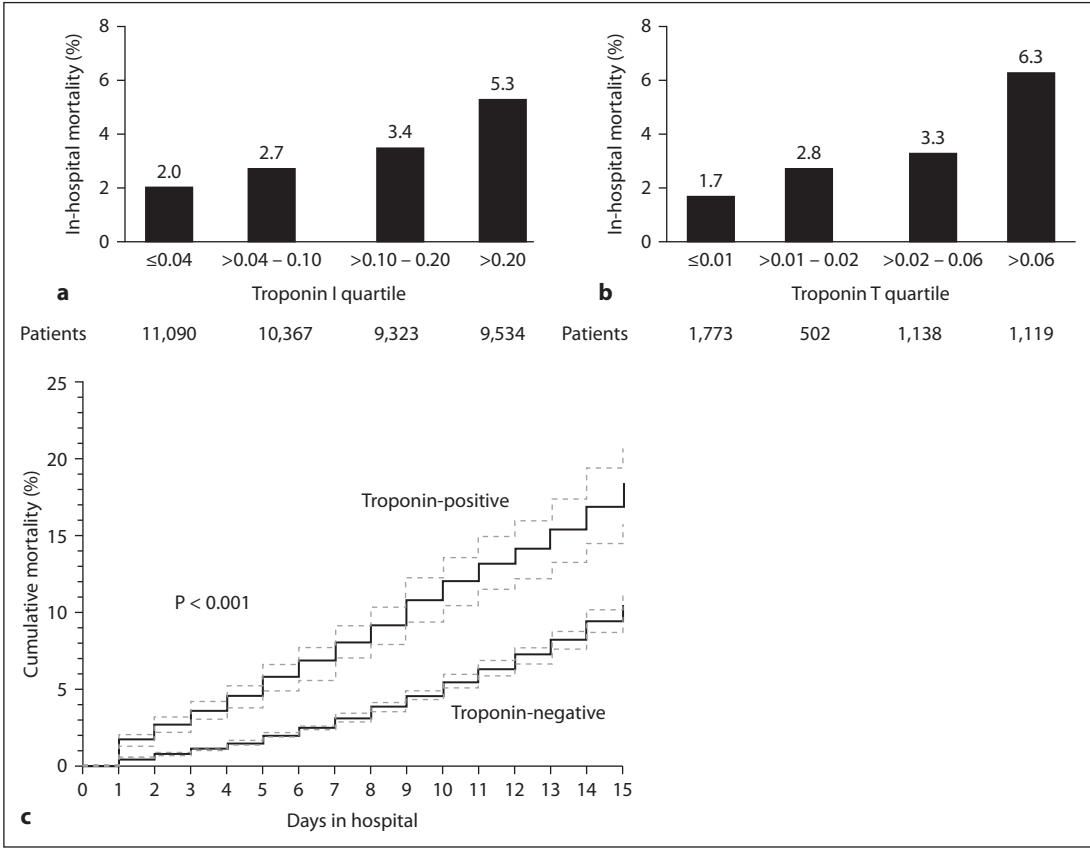


Fig. 4. In-hospital mortality according to troponin I (**a**) or troponin T (**b**) quartiles in patients hospitalized for acute decompensated HF. **c** Mortality based on the number of days in the hospital and troponin status on presentation ($p < 0.001$, dashed lines represent 95% CIs). Reproduced with permission from Peacock et al. [125].

with an increased risk of death (HR 2.08; 95% CI 1.72–2.52; $p < 0.0001$) and of first hospitalization for HF (HR 1.55; 95% CI 1.25–1.93; $p < 0.0001$) in multi-variable models. For each 0.01 ng/ml increase in hsTnT, there was a 5% increase in risk of death (95% CI 4–7%).

Troponin Summary

Cardiac troponin, an indicator of myocardial necrosis, is an established biomarker in the evaluation and management of ACS. Substantial evidence exists that even low levels of detectable troponin in patients with HF has significant prognostic implications in terms of morbidity and mortality.

Neutrophil Gelatinase-Associated Lipocalin

Managing patients with HF who develop concurrent renal dysfunction is challenging, requiring a careful balance between diuretic and vasodilator therapy. The cardiorenal syndrome is a well-documented phenomenon and is common among acute HF patients, with approximately 60% manifesting at least a 0.1 mg/dl rise in creatinine during hospitalization [128]. However, nephrotoxic insult as manifested by an increase in serum creatinine level usually takes 24–48 h to show up. A biomarker that rapidly increases with acute kidney injury could prove to be very powerful in guiding therapy in these complex clinical scenarios.

Biology

Neutrophil gelatinase-associated lipocalin (NGAL) is a small 25-kDa molecule that belongs to a superfamily of lipocalins, and is normally secreted in low amounts in lung, kidney, trachea, stomach and colon [129, 130]. Cellular action of NGAL is mediated by binding to 2 types of cellular receptors, 24p3R, a brain-type organic cation transporter, and the megalin multiscavenger complex found on the brush-boarder surface of renal tubular cells [131, 132]. NGAL interacts with these receptors and forms a complex with its ligand, iron siderophores, leading to receptor-mediated endocytosis, and inter- and intracellular iron trafficking [129]. By depleting iron and iron-binding molecules critical to bacterial survival, NGAL exerts bacteriostatic effects [130]. In addition to its antimicrobial properties, in-vitro experiments demonstrate that NGAL is a stress-induced renal biomarker. In renal tubules, NGAL mRNA is upregulated within a few hours of harmful stimuli [129]. NGAL is rapidly induced and expressed in mice upon intraperitoneal injection of cisplatin, and the subsequent rise in levels of NGAL precedes the rise in serum creatinine or urine N-acetyl glucosaminidase levels [133].

NGAL and Acute Kidney Injury

The promise of NGAL as an early marker of acute kidney injury has been demonstrated in small clinical studies [134–137]. In 71 children undergoing cardiopulmonary bypass, both serum (sNGAL) and urine (uNGAL) levels at baseline and 2 h after procedure were found to be predictive of renal injury [132]. uNGAL, with a cut-point of 50 µg/l demonstrated excellent prediction of acute kidney injury onset (AUC 0.99, sensitivity 100%, specificity 98%). Hirsch et al. [135] evaluated the utility of NGAL in predicting contrast-induced nephropathy (CIN) in 91 children with congenital heart disease undergoing cardiac catheterization. In patients who subsequently developed CIN, there was a significant increase in uNGAL and sNGAL 2 h after procedure, using a cut-point of 100 ng/ml (uNGAL 0.92, sNGAL 0.91, sensitivity 73%, specificity 100% for both).

NGAL and Heart Failure

There are limited data on the utility of NGAL in HF. A small study of 90 patients showed that, compared to age and sex-matched healthy control, patients with left ventricular dysfunction, as expected, had a lower GFR and higher NT-proBNP levels and urine albumin excretion [138]. The median uNGAL levels were significantly higher in the group with left ventricular dysfunction (175 vs. 37 $\mu\text{g/gCr}$, $p = 0.0001$). Both serum creatinine and estimated GFR were significantly correlated with uNGAL levels. Another cohort of 46 elderly patients with CHF confirmed higher levels of NGAL in patients with HF than in healthy age-matched controls (458 vs. 37.8 ng/ml, $p = 0.0001$) [139]. Moreover, NGAL was found to increase in parallel with severity of HF and proved to be prognostic, as patients with baseline NGAL >783 ng/ml had significantly higher mortality (HR 4.08, $p = 0.001$). In HF, reduction in GFR arises in large part from reduced renal perfusion, which serves as a hypoxic trigger for acute tubular necrosis [140].

NGAL Summary

NGAL is a renal stress biomarker that appears to identify kidney injury at an early stage. Future studies may further define the role of NGAL in assisting clinicians to achieve a proper balance between diuretics, vasodilators and inotropes when treating acute HF patients.

Conclusion

The era of biomarker use is in full swing. NPs, due to their low cost and rapid and accurate ability to provide additional information not surmised from clinical evaluation, are the standard bearer for the newer 'players' on the block. But work with NPs has also shown that they are not to be used as 'stand-alone' tests; rather they are best used as adjuncts to everything else the health care provider brings to the table. There are many caveats to using NPs, as there will be with all future biomarkers; thus, learning curves will always be present. Finally, since we live in an age where complex patients are the rule of the day, panels of multiple biomarkers will be needed in evaluation, risk stratification, and ultimately treatment initiation and follow-up.

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Oliguria, Creatinine and Other Biomarkers of Acute Kidney Injury

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Abstract

Acute kidney injury (AKI) and fluid overload are conditions that require an early diagnosis and a prompt intervention. The recognition of these pathologic conditions is possible in the early stages if specific signs and symptoms are taken into account. Among them, oliguria represents an important sign. Reduced urine output for a certain number of hours may be an important sign of kidney dysfunction. This must be evaluated in conjunction with other factors such as hydration status and use of drugs. At the same time, traditional markers of kidney function such as urea nitrogen and creatinine must be evaluated in light of a possible altered balance. Increased levels may be due to reduced kidney function but also increased generation or altered solute distribution space due to non-optimal hydration status. Finally, novel biomarkers for renal tissue damage are becoming popular. Molecules such as NGAL or cystatin C may become altered well before creatinine or oliguria signal a condition of reduced kidney function. Here, the difference between insult and dysfunction becomes evident. Novel biomarkers seem to enable the clinician to make early diagnosis of kidney damage, distinguishing between AKI and acute kidney failure. Reduced glomerular filtration rate is, in fact, a late event in the continuum of the AKI syndrome.

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The diagnosis of AKI is generally made using two markers: urine output and creatinine. More recently, newer early biomarkers of AKI have appeared and novel opportunities for an early diagnosis become a reality in clinical practice. The use of urine output and creatinine has, however, dominated the clinical scenario for many years. They represent important tools since they are the

foundations of the criteria for diagnosing AKI in both the RIFLE and the AKIN classification systems [1, 2].

Oliguria

A number of definitions for oliguria can be found in the literature, generally describing a urine output lower than 200–500 ml in 24 h. In order to standardize the use of the term across different studies and populations, the Acute Dialysis Quality Initiative has recently adopted a definition of oliguria as urine output of less than 0.3 ml/kg/h for at least 24 h (www.ADQI.net). The incidence of oliguria has been estimated to be as high as 18% of ICU admissions [3]. Further, 69% of ICU patients who develop acute kidney injury (AKI) are oliguric [4]. Oliguric AKI is associated with worse outcome compared to nonoliguric AKI. Oliguria generally indicates either a dramatic reduction in GFR or a mechanical obstruction to urine flow. In the first case, oliguria can be functional (extreme success of the kidney in retaining fluid) or pathological (inability to maintain urine flow in presence of adequate renal perfusion).

Functional oliguria may be secondary to absolute decrease in intravascular volume (e.g. hemorrhage, diarrhea or sequestration of fluid after abdominal surgery), relative decrease in renal perfusion pressure (sepsis, hepatic failure, nephrotic syndrome, and use of vasodilatory drugs), and decreased renal perfusion due to structural causes such as thromboembolism, atherosclerosis, dissection, and inflammation affecting the renal circulation. In this case, renal function may be preserved and oliguria is a sign of extreme tubular fluid reabsorption. Pathological oliguria may be due to AKI and acute tubular necrosis due to direct nephrotoxicity or ischemic conditions. Oliguria is associated with considerable morbidity and mortality. However, merely reversing oliguria, particularly by use of diuretic agents, does not improve outcome. Thus, rapidly determining the cause of oliguria is essential. The initial step in diagnosis is to rule out urinary obstruction prior to embarking on a lengthy workup for prerenal vs. intrarenal causes of renal insufficiency. Renal ultrasonography is usually the test of choice to exclude obstruction, although a dilatation of the urinary tract is not always present even in anuric obstructed patients [5]. Examination of the urine sediment shows hyaline and fine granular casts in prerenal oliguric states, while acute tubular necrosis usually is associated with coarse granular casts and tubular epithelial casts. Red cell casts usually indicate glomerular disease. Laboratory values are used in distinguishing prerenal from intrarenal causes of ARF. A fractional excretion of sodium <1 has traditionally been used as a marker for a prerenal cause of oliguria. These indices are unreliable once the patient has received diuretic agents. Another important and often overlooked reason for acute oliguria is abdominal compartment syndrome (ACS). ACS leads to ARF and acute oliguria mainly by directly increasing renal outflow pressure, thus reducing renal perfusion. Other mechanisms include direct parenchymal compression and

arterial vasoconstriction mediated by stimulation of the sympathetic nervous and renin-angiotensin systems by the fall in cardiac output related to decreased venous return. These factors lead to decreased renal and glomerular perfusion and hence manifest as acute oliguria. Intra-abdominal pressures >15 mm Hg can lead to oliguria and pressures >30 mm Hg can cause anuria [6].

Treatment of oliguria includes identification and correction of the precipitating factors, supportive measures such as avoidance of nephrotoxic agents and dose adjustment of renally excreted drugs, ensuring adequate renal perfusion and correcting potentially obstructive conditions. The use of diuretic agents in oliguric renal failure is widespread despite the convincing lack of evidence supporting their efficacy. While loop diuretics often result in a significant increase in diuresis, there is generally no difference in the clinical outcomes compared to placebo patients [7–9].

In oliguric states leading to hyponatremia as in the case of acute decompensated heart failure, given the central role of arginine vasopressin (AVP) activation, new therapeutic approaches have been tried using AVP receptor antagonists [10]. In these clinical conditions, an increased free water excretion is expected with a mechanism called ‘aquaresis’.

The presence of oliguria should alert the clinician to undertake a diligent search for any correctable underlying causes. The mainstay of treatment is to ensure adequate renal perfusion through optimization of cardiac output and volume status. The use of diuretics and vasoactive agents, while still fairly common, is not supported by the evidence, and emerging data actually suggest harm. In general terms, we may say that fluid balance can be considered a biomarker of AKI allowing to determine the presence of the syndrome, its severity and its prognosis [11].

Creatinine and Urea

The diagnosis and etiological classification of AKI, at present, largely depend on the detection of changes in conventional endogenous surrogate markers of kidney function, specifically serum levels of creatinine (SCr) and urea. These tests are familiar to clinicians and have long been used at the bedside. Regrettably, however, these markers are not ideal, each has limitations, none reflect real-time dynamic changes in GFR, and none reflect genuine kidney injury. Moreover, these endogenous markers require time to accumulate before being detected in serum as abnormal, thus contributing to a potential delay in the diagnosis of AKI. Although there are other established exogenous serum markers to estimate GFR (e.g. inulin, iothalamate, EDTA, iohexol), their use is complex, expensive, and impractical for routine use in ICU patients.

Creatinine is an amino acid compound derived from the nonenzymatic conversion of creatine to phosphor-creatinine in skeletal muscle and subsequent liver metabolism of creatine through methylation of guanidine aminoacetic acid to

form creatinine. Creatinine has a molecular weight of 113 Da, is released into the plasma at a relatively constant rate, is freely filtered by the glomerulus, and is not reabsorbed or metabolized by the kidney. The clearance of creatinine is the most widely used means for estimating GFR, and SCr levels generally have an inverse relationship to GFR [12]. Thus, a rise in SCr is associated with a parallel decrease in GFR and generally implies a reduction in kidney function, and vice versa. There are limitations to the use of SCr as a marker of kidney function. The production and release of creatinine into the serum can be highly variable. Differences in age, sex, dietary intake and muscle mass can result in significant variation in baseline SCr. In pathological states such as rhabdomyolysis, SCr levels may rise more rapidly due to release of preformed creatinine from damaged muscle or peripheral metabolism of creatine phosphate to creatinine in extracellular tissue.

An estimated 10–40% of creatinine is cleared by tubular secretion into the urine. This effect has the potential to hide a considerable initial decline in GFR. Several drugs are known to impair creatinine secretion and thus may cause transient and reversible increases in SCr levels. Finally, as mentioned previously, SCr levels do not depict real-time changes in GFR that occur with acute reductions in kidney function or ‘acute’ injury. Rather, SCr requires time to accumulate before being detected as abnormal, thus leading to a potential delay in the diagnosis of acute changes to GFR or AKI, which are vital to recognize. Nevertheless, SCr has been and still is the cornerstone of the definition of AKI both in RIFLE and AKIN classification systems [1, 2].

Urea is a water-soluble, low-molecular-weight (60 Da) by-product of protein metabolism that is used as a serum marker of uremic solute retention and elimination. For chronic hemodialysis patients, the degree of urea clearance has clearly shown correlation with clinical outcome and is used to model renal replacement therapy over time. Acute and large rises in serum urea concentration are characteristic of the development of the uremic syndrome and retention of a large variety of uremic toxins. The accumulation of urea itself is believed to predispose to adverse metabolic, biochemical, and physiologic effects, such as increased oxidative stress, altered function of Na/K/Cl cotransport pathways important in regulation of intracellular potassium and water, and alterations in immune function. In addition, retention of uremic toxins may contribute to secondary organ dysfunction, such as acute lung injury. Similar to SCr, urea levels exhibit a nonlinear and inverse relationship with GFR [13]. However, the use of urea levels to estimate GFR is problematic due to the numerous extrarenal factors that influence its endogenous production and renal clearance independent of GFR. The rate of urea production is not constant. Urea values can be modified by a high protein intake, critical illness gastrointestinal hemorrhage, or drug therapy, such as use of corticosteroids or tetracycline.

Relative adrenal insufficiency in septic shock is common, and clinical trials and meta-analyses have suggested that physiologic replacement with low-dose corticosteroid therapy leads to improved surrogate outcomes (e.g. vasopressor therapy withdrawal, shock reversal) and survival. Accordingly, in ICU patients

with septic shock, corticosteroid replacement has become more widely practiced. ICU patients with AKI receiving corticosteroids may show large increases in serum urea consistent with uremic solute retention in the absence of a similar rise in SCr. The rate of renal clearance of urea is also not constant. An estimated 40–50% of filtered urea is passively reabsorbed by proximal and distal renal tubular cells. Moreover, in states of decreased effective circulating volume (i.e. volume depletion, low cardiac output), there is enhanced resorption of sodium and water in the proximal renal tubular cells along with a corresponding increase in urea resorption. Consequently, the serum urea concentration may increase out of proportion to changes in SCr and be underrepresentative of GFR. The ratio of serum urea to SCr concentration has traditionally been used as an index to discriminate so-called prerenal azotemia from more established AKI (i.e. acute tubular necrosis). Overall, urea concentration is a poor measure of GFR. It does not represent real-time changes in GFR and requires time to accumulate. Likewise, urea does not reflect true ‘acute’ kidney injury. As such, reliance on urea can lead to potential delays in diagnosis of acute changes to GFR or detection of AKI.

Novel Biomarkers and Early Acute Kidney Injury Diagnosis

Novel biomarkers beyond urine output and creatinine can help to make the diagnosis of AKI easier and earlier. An ideal biomarker should be sensitive (early sign of organ injury) and specific (typical of the organ damage). Measurement should be technically easy with good reproducibility. Biomarker levels should change in parallel with the degree of organ injury even in the absence of typical clinical signs and should enable early intervention. Finally, the level of an ideal biomarker should correlate with both prognosis and response to treatment.

The important question for any chosen biomarker is whether it is merely *associated* with the syndrome or whether it has a *causal* role in syndrome’s pathophysiology. Various biomarkers display different characteristics and several of them can play both roles.

Using cDNA microarray as a screening technique, a subset of genes whose expression is upregulated within the first few hours after renal injury has been discovered [14–15]. An ideal AKI biomarker should help in identifying the primary location of injury (proximal tubule, distal tubule, interstitium, or vasculature), address the duration of kidney failure (AKI, chronic kidney disease – CKD, or ‘acute-on-chronic’), discern the AKI subtype (prerenal, intrinsic renal, or postrenal), identify the etiology of AKI (ischemia, toxins, sepsis, or a combination), differentiate AKI from other forms of acute kidney disease (urinary tract infection, glomerulonephritis, interstitial nephritis), stratify risk and prognosis (duration and severity of AKI, need for renal replacement therapy, length of hospital stay, mortality), define the course of AKI, and finally, allow the monitoring of response to interventions.

Human neutrophil gelatinase-associated lipocalin (NGAL) was originally identified as a 25-kDa protein covalently bound to gelatinase from neutrophils. NGAL is normally expressed at very low levels in several human tissues, including kidney, lungs, stomach, and colon. NGAL expression is markedly induced in injured epithelia, and it is elevated in the serum of patients with acute bacterial infections [16]. NGAL seems to be one of the earliest markers in the kidney after ischemic or nephrotoxic injury in animal models, and it is detected in the blood and urine of humans soon after AKI [17–21]. Several studies have confirmed these findings; in intensive care adult patients with AKI secondary to sepsis, ischemia, or nephrotoxins, NGAL is significantly increased in plasma and urine when compared to normal controls [22]. Human kidney biopsies in these settings show intense accumulation of immunoreactive NGAL in 50% of the cortical tubules [17]. In children undergoing cardiopulmonary bypass, NGAL increases significantly in plasma and urine 2–6 h after surgery in those patients who subsequently developed AKI with the rise in creatinine seen only 48–72 h later. In this setting, both urine and plasma NGAL are powerful independent predictors of AKI, with an outstanding area under the curve (AUC) of 0.998 for 2-hour urine NGAL levels and 0.91 for 2-hour plasma NGAL measurement [23]. Similar findings have been reported in adults who develop AKI after cardiac surgery, with NGAL elevation 1–3 h after surgery [24].

NGAL has also been evaluated as a biomarker of delayed graft function in kidney transplantation [25]. The receiver-operating characteristic curve for prediction of delayed graft function based on urine NGAL at day 0 was 0.9, indicative of an excellent predictive biomarker [26]. Urine NGAL also predicts the severity of AKI and dialysis requirement in children [27]. Elevated plasma and urine NGAL levels also predict AKI caused by contrast media [28–30] and AKI in critically ill patients admitted to intensive care [31].

A note of caution in the interpretation of NGAL value is that its level may be influenced by a number of coexisting variables such as pre-existing renal disease [32] and systemic or urinary tract infections [16].

Cystatin C is a cysteine protease inhibitor that is synthesized and released into the blood at a relatively constant rate by all nucleated cells. It is freely filtered by the glomerulus, completely reabsorbed by the proximal tubule, and not secreted into urine. Its blood levels are not affected by age, gender, race, or muscle mass; thus, it appears to be a better predictor of glomerular function than serum creatinine in patients with CKD. In AKI, urinary excretion of cystatin C has been shown to predict the requirement for renal replacement therapy earlier than creatinine [33]. In the intensive care setting, a 50% increase in serum cystatin C predicted AKI 1–2 days before the rise in serum creatinine, with an AUC of 0.97 and 0.82, respectively [34]. Serum cystatin C has been compared to NGAL in cardiac surgery-mediated AKI [35]. Both biomarkers predicted AKI at 12 h, but NGAL outperformed cystatin C at earlier time points. Considering them together, they may represent a combination of structural and functional damage of the kidney.

Table 1. Protein biomarkers for early detection of AKI

Biomarker	Associated Injury
Crystatin C	Proximal tubule injury
KIM-1	Ischemia and nephrotoxins
NGAL (lipocalin)	Ischemia and nephrotoxins
NHE3	Ischemia, prerenal, postrenal AKI
Cytokines (IL-6, -8, -18)	Toxic, delayed graft function
Actin-actin depolymerizing F.	Ischemia and delayed graft function
α -GST	Proximal T. injury, Cy-A toxicity
π -GST	Distal tub. injury, acute rejection
L-FABP	Ischemia and nephrotoxins
Netrin-1.	Ischemia and nephrotoxins, sepsis
Keratin. Der. Chemokine	Ischemia and delayed graft function

GST = Glutathione S transferase; L-FABP = liver fatty acid-binding protein.

Kidney injury molecule-1 (KIM-1) is a protein detectable in urine after ischemic or nephrotoxic insults to proximal tubular cells [36–38]. Urinary KIM-1 seems to be highly specific for ischemic AKI and not for prerenal azotemia, CKD or contrast-induced nephropathy [36]. KIM-1 has been shown to be predictive of AKI in adults and children undergoing cardiopulmonary bypass in a time frame between 2 and 24 h after surgery. KIM-1 seems to represent an interesting additional marker for AKI, adding specificity to the high sensitivity displayed by NGAL in the early phases of AKI.

NAG [N-acetyl- β -(D)glucosaminidase] activity has also been shown to function as a marker of kidney injury, reflecting particularly the degree of tubular damage, with adverse outcomes in acute kidney failure [39].

Interleukin-18 (IL-18) is a proinflammatory cytokine detected in the urine after acute ischemic proximal tubular damage [40]. It displays sensitivity and specificity for ischemic AKI with an AUC >90% [41] with increased levels 48 h prior to increase in serum creatinine. Urinary NGAL and IL-18 have been studied as tandem biomarkers for delayed graft function following kidney transplantation [26].

In conclusion, serum cystatin C, urine NGAL and IL-18 appear to perform best for the early diagnosis of AKI. Serum cystatin C, urine IL-18, and urine KIM-1 appear to perform best for the differential diagnosis of established AKI. Urine NAG, KIM-1, and IL-18 appear to perform best for risk prediction after AKI. Other biomarkers have been studied and represent an interesting and promising contribution to future diagnostic approaches to AKI and progression of CKD. They are summarized in table 1. The most likely evolution will be a ‘panel’ of biomarkers that include several molecules both in serum and urine which combine their best characteristics in terms of specificity and sensitivity of each marker

molecule [42–48]. This approach brings a new hope for an early diagnosis of AKI and the timely institution of measures for prevention and protection.

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Current Techniques of Fluid Status Assessment

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Abstract

The estimation of volume status is of critical importance in the early management of acute illness. Inappropriate therapy, given when errors in volume assessment go unrecognized, is associated with increased acute mortality rates. Unfortunately, the gold standard of radioisotopic volume measurement is neither rapid nor inexpensive, thus leaving the clinician to rely on less accurate measures. This chapter reviews the available methods of volume assessment in the acute care environment. In addition to the history, physical exam, and standard radiographic techniques for volume assessment, the newer technologies of acoustic cardiography, bedside ultrasound, and bioimpedance are presented.

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Patients may present to the acute care environment with a wide range of symptoms indicative of volume perturbations. Volume abnormalities occur across a spectrum of pathologies, and wide range of presentations. At one extreme, volume deficits may reflect severe intravascular hypovolemia secondary to blood loss in the setting of hemorrhagic shock, or a crystalloid deficit for many reasons (e.g. GI losses, diabetes insipidus). Conversely, volume excess may result in a clinical presentation of organ failure (cardiac, renal, or hepatic), excessive oral intake, or iatrogenic error. Because the differential diagnosis is long and complicated, the physiologic responses nonspecific and varied, and the consequence of therapeutic intervention critical, accurate volume assessment is mandatory.

Implementation of the wrong therapy as a consequence of inaccurate volume assessment may be fatal. This has been shown in a number of studies. Wuerz and Meador [1] reported outcomes from 8,315 ambulance patients. Of these, 499 were thought to suffer acute decompensated heart failure (ADHF). Based on a prospectively established protocol, volume-overloaded HF patients with an elevated systolic blood pressure were treated with bolus furosemide,

sublingual nitroglycerin, and intravenous morphine before ambulance transfer. While this intervention increased scene times by a mean of 1.1 min, patients received therapy 36 min earlier than if administration was delayed until hospital arrival. While 36 min seems a short therapeutic delay, in this high severity of illness population (calling an ambulance suggests greater acuity of illness), early treatment was associated with a mortality benefit. In the 241 (48.3% of ADHF) patients ultimately confirmed with ADHF, early treatment conferred a 251% increase in survival probability ($p < 0.01$) versus the 252 ADHF patients who did not receive prehospital therapy. A reasonable conclusion would be that in all patients in whom the clinical impression was volume overloaded ADHF, immediate furosemide, nitroglycerin, and morphine should be given.

Unfortunately in this analysis, errors in the assessment of volume status were costly. Outcomes in patients receiving HF therapy, but ultimately found to not have HF, were dismal. Mortality in the non-HF cohort receiving bronchodilators was 3.6% compared to 13.6% in non-HF patients receiving HF therapy (a 358% mortality increase). In fact, it was better to receive no treatment than erroneous treatment, as the non-HF group who received no therapy at all had a mortality of only 8.2%.

In acutely ill patients, accurate volume status assessment predicates appropriate therapy. Errors of volume assessment can result in the absence of necessary treatment, or the administration of unneeded therapy, both associated with increased mortality in critically ill patients. This is also true in chronic illness where blood volume assessment can be challenging. For example, in a study of 43 nonedematous apparently normovolemic ambulatory congestive heart failure patients, blood volume analysis found 5% were hypovolemic (mean deviation from normal values $-20 \pm 6\%$), 30% were normovolemic (mean deviation from normal values $-1 \pm 1\%$), and 65% were hypervolemic (mean deviation from normal values $+30 \pm 3\%$). While physical findings of congestion were infrequent and not associated with blood volume status, increased blood volume was associated with increased pulmonary capillary wedge pressure (PCWP; $p = 0.01$) and with a markedly increased risk of death or urgent cardiac transplantation during a median follow-up of 719 days (1-year event rate 39 vs. 0% in the normovolemic cohort, $p < 0.01$). Unfortunately, clinically unrecognized hypervolemia is frequently present in nonedematous HF patients, and is associated with increased cardiac filling pressures and worse outcomes [2].

Some promote the early use of pulmonary artery catheterization for volume assessment. The pulmonary artery catheter is a common hemodynamic monitoring tool, but it is important to recognize that it does not measure volume; rather, it measures pressures and calculates flow. While these parameters may be clinically useful, they have poor correlation to overall volume status [3]. This is suggested by obvious clinical examples; although volume overload occurs in both sepsis and HF, septic patients may have markedly increased cardiac output

and low filling pressures, while HF patients will have the exact opposite parameters. Thus, an objective measure of volume status is needed.

As volume assessment is a critical intervention for determining appropriate therapy, the tools of its evaluation should be considered. The gold standard for determining blood volume is radioisotopic measurement [4, 5]. This calculates red cell mass with injected Cr-51-labeled autologous red cells, and plasma volume with I-125-labeled human serum albumin. Alternative technology may use an I-131 kit (Volumex, Daxor Corporation) for these measurements. Although volume evaluation is a difficult clinical challenge, and accuracy early after presentation is critical, objective radioisotopic blood volume analysis is neither rapid nor inexpensive. While it has been proven useful in subacute and chronic presentations, no study has evaluated radioisotopic blood volume analysis in the emergency evaluation of patients suspected to have clinically significant volume perturbations. Thus, in acutely decompensated or unstable patients, where the consequences of errors may be greatest, volume assessment currently relies on a group of fairly inaccurate diagnostic testing procedures.

History

Several studies have examined the accuracy and reliability of the history and physical examination findings associated with excessive volume. Using HF as a diagnostic model, Wang et al. [6, 7] performed a meta-analysis of 18 studies published from 1966 to 2005 that evaluated clinical history and physical exam for the impression of circulatory congestion (table 1). Of the historical parameters, they concluded a prior history of HF was predictive of volume overload. Risk factors considered helpful in the assessment of potential volume overload included hypertension, diabetes, valvular heart disease, advanced age, male sex, and obesity; unfortunately, in specific patients risk factors have limited utility for the diagnosis of an event resulting in an urgent presentation [8–11].

When considering symptoms, dyspnea on exertion had the highest sensitivity for circulatory congestion, and edema was also useful [6, 7]. The most specific symptoms were paroxysmal nocturnal dyspnea, orthopnea, and edema [6, 7], any of which increased the probability that volume overload was present. While Wang et al. [6], found the overall clinical gestalt of the emergency physician was associated with high sensitivity and specificity for the presence of volume overload from HF, others have found that an initial impression, based only on history and physical examination is accurate approximately half the time [12].

Conversely, the possibility that low volume status is present must be considered when taking the patient's history. In a study examining 38 clinical indicators of dehydration in elderly patients [13], those findings that best correlated with the severity of volume deficit, and unrelated to the patient's age, included tongue dryness, longitudinal tongue furrows, dryness of the mouth mucous

Table 1. Summary of diagnostic accuracy of history and physical findings for the presence of volume overload in ED patients presenting with dyspnea [6]

Finding	Sensitivity	Specificity	Positive LR	Negative LR
<i>Symptoms</i>				
Paroxysmal nocturnal dyspnea	0.41	0.84	2.6	0.70
Orthopnea	0.50	0.77	2.2	0.65
Edema	0.51	0.76	2.1	0.64
Dyspnea on exertion	0.84	0.34	1.3	0.48
Fatigue and weight gain	0.31	0.70	1.0	0.99
Cough	0.36	0.61	0.93	1.0
<i>Physical exam</i>				
Third heart sound	0.13	0.99	11	0.88
Abdominal jugular reflux	0.24	0.96	6.4	0.79
JVD	0.39	0.92	5.1	0.66
Rales	0.66	0.78	2.8	0.51
Any murmur	0.27	0.90	2.6	0.81
Lower extremity edema	0.50	0.78	2.3	0.64
SBP <100 mm Hg	0.06	0.97	2.0	0.97
Fourth heart sound	0.05	0.97	1.6	0.98
SBP >150 mm Hg	0.28	0.73	1.0	0.99
Wheezing	0.22	0.58	0.52	1.3
Ascites	0.01	0.97	0.33	1.0

membranes, upper body muscle weakness, confusion, speech difficulty, and sunken eyes. Other indicators had only weak associations with dehydration severity or were related to the patient's age. Unfortunately, the presence of thirst was not related to dehydration severity.

In more severe presentations, orthostatic symptoms and hypotension may suggest hypovolemia, although pump failure and excessive vasodilation may confound the differential diagnosis. Orthostatic symptoms may include dizziness, shortness of breath, weakness, malaise, or when severe, syncope. Orthostatic symptoms should worsen when the patient is upright and improve or resolve when supine. Of note, orthostatic symptoms can be confounded by neurologic events; however, careful examination is usually able to discern these presentations.

Physical Exam

The physical exam assists in evaluating volume status. Lung sounds, peripheral edema, jugular venous distention (JVD), hepatojugular reflux (HJR), and the

presence of extra heart sounds may all be helpful to help detect fluid overload. Skin mottling, indicative of poor peripheral perfusion secondary to pump failure, is ominous and has an OR of 17.5 for acute in-hospital mortality [14].

Importantly, the physical exam has significant limits when assessing the potential for volume overload. JVD, rales, and lower extremity edema are useful findings that should be ascertained. While JVD is reported to correlate with an elevated right atrial pressure [15–18], studies of the correlation between the physical exam and more invasive measures (e.g. PCWP) have produced variable results. While Butman et al. [19] found JVD was specific and sensitive for an elevated PCWP, another study (defining volume overload as a PCWP >18 mm Hg) reported JVD and HJR had a predictive accuracy of only 81%. In this same analysis, the presence of rales had a positive predictive value of 100% for volume overload, but their absence had a negative predictive value of only 35%. Finally, a different study showed HJR had a sensitivity of 24%, but a specificity of 94% [20].

In one prospective study of 50 chronic HF patients with low ejection fraction, Stevenson and Perloff [21] compared the physical exam and hemodynamics. They found that rales, edema, and elevated JVD were absent in almost half of patients with increased PCWP. Chakko et al. [22] examined 52 patients with congestion and found that physical and radiographic findings were more common with elevated PCWP, but positive findings had poor predictive power.

Other exam findings may suggest hypovolemia in patients with vomiting, diarrhea, or decreased oral intake. In one study, the presence of a dry axilla supported the diagnosis of hypovolemia (positive likelihood ratio – LR, 2.8; 95% CI, 1.4–5.4), while moist mucous membranes and a tongue without furrows argued against it (negative LR, 0.3; 95% CI, 0.1–0.6 for both findings) [23]. In this analysis of adult patients [23], capillary refill time and poor skin turgor had no proven diagnostic value, a finding also supported by others. In a prospective analysis of patients undergoing a 450-ml blood donation [24], mean capillary refill time decreased from 1.4 to 1.1 s, and had a sensitivity of 6% for identifying this amount of blood loss. They concluded that the accuracy of capillary refill in a patient with a 50% prior probability of hypovolemia was 64%.

Orthostatic Vital Signs

Orthostatic vital signs refer to the technique of evaluating the differences in pulse and blood pressure that result with postural change. They are easily obtained, rapidly performed, commonly used, and noninvasive. To provide the greatest accuracy, the baseline heart rate and blood pressure are measured after the patient has been recumbent for at least 3 min. The patient is then placed in the standing position for an additional 3 min and the vital sign measures are repeated. Significant changes are defined as a blood pressure decrease in excess of 10 mm Hg, or a heart rate increase exceeding 20 beats per min.

Long considered an indicator of hypovolemia, the accuracy of this technique does not withstand scientific validation. In a prospective study of 132 euvolemic patients, statistically normal (mean $\pm$ 2 SD) orthostatic vital sign changes had excessively wide ranges. Heart rate changes ranged from -5 to $+39$ beats per minute, and systolic blood pressure fluctuated from -20 to $+26$ mm Hg. Using the conventional definition of a significant orthostatic vital sign change, 43% of the patients would have been considered 'positive' [25]. In another study of 502 hospitalized geriatric patients with orthostatic vital signs obtained three times daily, 68% had significant changes documented at least daily [26]. These studies suggest inadequate specificity of orthostatic vital signs for diagnosing hypovolemia.

Conversely, in a systematic review [23] performed to evaluate adults with suspected blood loss, the most helpful physical findings were postural dizziness to the extent that it prevented the measurement of upright vital signs, or a postural pulse increase greater than 30 beats/min. Unfortunately, the sensitivity for moderate blood loss with either of these predictors was only 22%. Only when blood loss exceeded 1 l, did the sensitivity and specificity improve to 97 and 98%, respectively. The authors concluded that supine hypotension and tachycardia are frequently absent, even after 1,150 ml of blood loss (sensitivity, 33%; 95% CI, 21–47, for supine hypotension) and the finding of mild postural dizziness had no proven value.

Auscultation as a Predictor of Volume Status

Cardiac sounds are commonly used to evaluate the potential for volume overload. A third heart sound (S3) is related to the rapid filling of a poorly compliant ventricle in the setting of increased filling pressure [16] and is indicative of an unfavorable prognosis in HF. In fact, Drazner et al. [15] found that, even after adjusting for other signs of severe HF, JVD and an S3 were independently associated with an increased risk of HF hospitalization, death, rehospitalization for HF, and death from pump failure.

When present, the S3 is highly specific for ventricular dysfunction and elevated left-sided ventricular filling pressures [6, 27–28]. In one report on the physical exam, the presence of an S3 had the highest positive LR (11.0) but was not valuable as a negative predictor (LR 0.88) for diagnosing volume overload [6]. The poor sensitivity of the S3 is commonly attributed to the fact that it is difficult to detect in patients with confounding diseases (e.g. COPD and obesity). Accurate auscultation can also be challenging, especially in a noisy emergency department (ED), or when tachypnea obscures the heart sounds. Finally, the inter-rater reliability of the S3 is commonly found to be only low to moderate [29–32].

Unfortunately, while history and physical are the earliest diagnostic tools, both suffer significant limitations in accuracy. In the most critical patients,

where early therapeutic interventions are needed, clinical decision must be made before extensive testing. Further challenges exist when patients present with multiple potential comorbidities, e.g. simultaneous HF and sepsis. In these difficult cases, rapid objective measurement of volume status is needed.

Rapid Objective Measures of Blood Volume

The gold standard for blood volume analysis is measurement by radioimmunoassay. While accurate, it requires injection of radioisotope, extensive time, and intermittent measures before the final assessment is complete. Besides taking too long to be practical in the ED, the need to transfer patients for imaging outside the acute care environment makes it challenging in the critically ill. Finally, its significant cost has resulted in few patients actually receiving this diagnostic test. Thus, there is an important need for a rapid, objective, portable or bedside technology that can accurately determine volume status.

Acoustic Cardiography

Recent technologic advances have made it possible to digitally capture heart sound data by recording microphone ECG leads. Studies suggest that acoustic cardiographic S3 detection may overcome the limitations of standard auscultation. Even in ideal settings, acoustic cardiography has been shown to be superior to auscultation for the detection of the S3, and can be performed within 10 min of presentation at ED, concurrent with the initial ECG [33]. Acoustic cardiography may offer a rapid, objective test for the presence of an S3 in patients with undifferentiated dyspnea [34]. However, in one study, while the acoustic cardiography S3 was specific for ADHF and affected physician confidence in undifferentiated ED patients presenting with acute dyspnea, it did not improve overall diagnostic accuracy, largely because of its low sensitivity [35].

Chest Radiography

Historically, the chest radiograph has been one of the earliest obtainable tests to estimate volume status. While not helpful in the setting of hypovolemia, it may be useful in determining the ultimate diagnosis that leads to the patient's presentation. Furthermore, they can be of value in the setting of hypervolemia. When present, radiographic signs of volume overload are highly specific and are, in descending order of frequency: dilated upper lobe vessels, cardiomegaly, interstitial edema, enlarged pulmonary artery, pleural effusion, alveolar edema, prominent superior vena cava, and Kerley lines [36].

However, since abnormalities lag the clinical appearance by hours, it is important to not withhold therapy pending a film. In the setting of suspected volume overload, negative films do not exclude abnormal left ventricular function, but can eliminate other diagnoses (e.g. pneumonia). Collins et al. [37, 38] found that up to 20% of patients subsequently diagnosed with HF had negative chest radiographs at initial ED evaluation. In patients who have late-stage HF, radiographic signs of HF can be minimal despite an elevated PCWP.

In chronic HF patients, chest X-ray signs of congestion have unreliable sensitivity, specificity, and predictive value for identifying patients with high PCWP [39]. In one study, radiographic pulmonary congestion was absent in 53% of mild to moderately elevated PCWPs (16–29 mm Hg) and in 39% of those with markedly elevated PCWP (>30 mm Hg) [39].

An enlarged heart is a useful finding in a suspected HF patient, and a cardiothoracic ratio >60% correlates with increased 5-year mortality [40]. Unfortunately, the chest X-ray has poor sensitivity for cardiomegaly. In echocardiographically proven cardiomegaly, 22% of patients had a cardiothoracic ratio <50% [41]. Poor X-ray detection of cardiomegaly is explained by intrathoracic cardiac rotation.

The technique of obtaining the X-ray and the clinical status of the patient both impact radiographic performance for detecting volume overload. When the chest X-ray is obtained portably, the sensitivity for findings of volume overload is poor. In one study of mild HF, only dilated upper lobe vessels were found in >60% of patients. However, the frequency of volume overload findings increase with the severity of presentation. In severe HF, X-ray findings of volume overload occurred in at least two thirds of patients, except for Kerley lines (occur in only 11%) and a prominent vena cava (found in only 44%) [42]. Finally, pleural effusions can be missed, especially if the patient is intubated, as the film is performed supine. In patients with pleural effusions, the sensitivity, specificity, and accuracy of the supine chest X-ray was reported to be 67, 70, and 67%, respectively [43].

Thus, when the chest X-ray has positive findings of volume overload, or of an alternative diagnosis, it is clinically of use. However, it has poor performance in hypovolemia, and is insensitive in chronic or mild acute presentations of volume overload.

Natriuretic Peptides

The B-type natriuretic peptide (BNP), its synthetic byproduct NTproBNP, and the mid-regional prohormone of atrial natriuretic peptide are elevated with myocardial stress, and levels of these molecules may be increased with volume overload. However, as there are many causes of myocardial stress unrelated to volume status (e.g. myocardial infarction, pulmonary embolus, etc.), the natriuretic peptide (NP) level must be considered within the context of the clinical

presentation. Furthermore, NP interpretation must be considered in light of their well-known confounders of obesity (associated with lower NP levels) and renal failure (associated with elevated NPs). Finally, patients with chronic HF may have persistently elevated NP levels at their baseline dry weight, so knowledge of the patient's historical trend is necessary to appropriately interpret the NP measurement.

Ultimately, while NPs can be performed rapidly as a bedside test and thus satisfy the need for objective assessment in critically ill presentations, in patients in whom knowledge of prior NP test results are unknown, their greatest utility is in the absence of elevation. Except in obesity, a low NP level has a high negative predictive value for excluding an HF diagnosis. Conversely, a high NP level can be nonspecific for volume overload.

Bioimpedance

Historically, determination of hemodynamic status required the insertion of a catheter directly into the heart. As a result of the significant morbidity and mortality associated with this invasive procedure, noninvasive techniques are now being considered as an acceptable alternative [44]. One of the most researched of these technologies is impedance cardiography (ICG). ICG measurement is based on the concept that the human thorax is an inhomogeneous electrical conductor [45, 46]. If a high-frequency current is injected across the thorax, impedance can be measured by pairs of electrodes at the edge of the chest. Voltage perturbations (ΔZ) arise from alterations in the intra-alveolar and interstitial thoracic compartments as a result of fluid, and dynamic changes occur from volumetric and velocity changes within the aorta. By integrating these changes with ECG-derived timing measures, hemodynamic parameters can be approximated. The accuracy of the cardiac output measurements obtained with ICG has been compared to the invasive measures acquired by thermodilution techniques. A recent meta-analysis of over 200 studies found a correlation of 0.81 for ICG-determined stroke volume and cardiac output when compared to traditional measurements. In general, ICG assessments are considered less variable and more reproducible than many other techniques used to evaluate volume status. Apart from being noninvasive, the major advantage of ICG technology is that it can also be utilized for continuous monitoring and trend identification.

Limitations to obtaining accurate impedance measures include the following: (1) severe cutaneous alterations (great ulcers/wounds/eschars, crusting skin); (2) excessive diaphoresis, inadequate cutaneous cleaning with alcohol, or excessive unshaven hair preventing inadequate electrode adherence; (3) erroneous electrode position; (4) incapacity to maintain temporally a stable body position (dementia and severe psychiatric disease); (5) contact with an

electrical ground (e.g. metal bed frame) or electrical interference; (6) severe obesity.

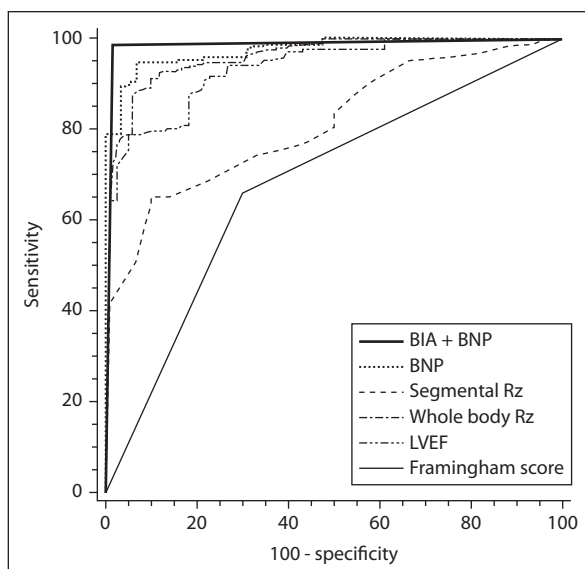
Bioimpedance Vector Analysis

A newer volume assessment technique is bioimpedance vector analysis (BIVA). Whole body impedance is a combination of resistance, R (the opposition to flow of an alternating current through intra- and extracellular electrolytic solutions), and reactance, X_c (the capacitance produced by tissue interfaces and cell membranes). The arc tangent of X_c/R is termed the phase angle, and represents the phase difference between voltage and current, determined by the reactive component of R . For a constant signal frequency, electrical impedance is proportional to the product of specific impedivity and length, divided by the cross-sectional area ($\text{ohm} \cdot \text{m}/\text{m}^2$). In conductors without cells (e.g. saline), no capacitance exists, and thus X_c cannot be measured. By including X_c , the accuracy of volume assessment is improved over conventional bioimpedance measurements. BIVA thus measures whole-body fluid volume [47, 48], has a correlation coefficient of 0.996, and a measurement error that ranges from 2 to 4%. BIVA provides data on volume status and has been validated in kidney [49], liver, and heart disease [50–52]. In one study using BIVA as a proxy for the adequacy of ultrafiltration in over 3,000 hemodialysis patients, BIVA indices reflecting greater soft tissue hydration (less adequate ultrafiltration) were associated with a significant increase in mortality [53]. BIVA is also complementary with existing myocardial stress measures. In a prospective study of the value of BIVA with BNP in 292 patients [54], the combination of BNP and BIVA resulted in the most accurate volume status determination (fig. 1).

There are some limitations that must be considered in the application of BIVA. Because total body resistance is calculated with BIVA, accurate body position is required (limb abduction with arms separated from trunk by about 30° and legs separated by about 45°). Another limitation of BIVA is its failure to distinguish compartmentalized edema such as pericardial, pleural, or abdominal effusion. Lastly, BIVA is standardized for western Europeans, and as of yet normal values for patients of African heritage have not been established [55]. BIVA offers the advantage of requiring measurement on only one side of the body, so where bioimpedance may be limited in patients with unilateral abnormalities, BIVA can simply be measured on the contralateral side.

Thoracic Ultrasound

Thoracic ultrasound, increasingly available in the ED, can detect pulmonary water. The presence of sonographic artifacts, known as B-lines, suggests



Diagnostic strategy	Area under the receiver operator characteristic curve (SE)	95% CI
BIA + BNP	0.989 (0.005)	0.965–0.996
BNP alone	0.970 (0.008)	0.952–0.990
Segmental Rz BIA Rz, Ω	0.963 (0.012)	0.965–0.982
Whole body BIA Rz, Ω	0.934 (0.016)	0.902–0.961
Left ventricular ejection fraction	0.814 (0.027)	0.764–0.857
Framingham score	0.681 (0.031)	0.625–0.734
BIA = Blood impedance analysis using BIVA; SE = standard error.		

Fig. 1. Comparison of various strategies for diagnosis of volume overload.

thickened interstitia or fluid-filled alveoli [56]. B-lines are seen most commonly in patients with congestive heart failure [56–58] and have been correlated with both PCWP and extravascular lung water [59–61]. B-lines have been specifically studied in emergency patients [62] and demonstrate high sensitivity and

specificity for alveolar interstitial syndrome. In a study of 94 ED patients evaluated for HF, B-lines had a positive LR of 3.88 (99% CI, 1.55–9.73) and a negative LR of 0.5 (95% CI, 0.30–0.82) [63].

Vena Cava Diameter Ultrasound

A second application of ultrasound to evaluate volume status is the measurement of the inferior vena cava diameter. Evaluated in an experimental model using 31 volunteers undergoing a 450-ml phlebotomy, the inferior vena cava decreased in diameter after blood donation by >5 mm, after either inspiration or expiration ($p < 0.0001$) [64]. In another study using radioisotopic analysis as the gold standard volume assessment in patients undergoing hemodialysis, Katzarski et al. [65] reported that blood volume and inferior vena cava diameter decreased in parallel during hemodialysis and increased during 2 h after due to refilling of the intravascular space, indicating that changes in inferior vena cava diameter reflect changes in blood volume.

Conclusions

Objective, rapid and accurate volume assessment is important in undiagnosed patients presenting with critical illness, as errors may result in interventions with fatal outcomes. The historical tools of history, physical exam, and chest radiography suffer from significant limitations. As a gold standard, radioisotopic measurement of volume is impractical in the acute care environment. Newer technologies offer the promise of both rapid and accurate bedside estimation of volume status with the potential to improve clinical outcomes. Blood volume assessment with BIVA, and bedside ultrasound seem to be promising technologies for this unmet need.

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Bioelectric Impedance Measurement for Fluid Status Assessment

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Abstract

Background: Adequacy of body fluid volume improves short- and long-term outcomes in patients with heart and kidney disorders. Bioelectrical impedance vector analysis (BIVA) has the potential to be used as a routine method at the bedside for assessment and management of body fluids. **Methods:** Impedance (Z vector) is a combination of resistance, R (function of intra- and extracellular fluid volume) and reactance, Xc (function of the dielectric material of tissue cells), with the best signal to noise ratio at 50 kHz. BIVA allows a direct assessment of body fluid volume through patterns of vector distribution on the R-Xc plane without the knowledge of the body weight. Reference tolerance ellipses (50, 75 and 95%) for the individual vector were previously calculated in the healthy population. **Results:** We determined the optimal vector distribution in patients undergoing hemodialysis without hypotension or intradialytic symptoms. Most vectors lay within the reference 75% tolerance ellipse of the healthy population indicating full electrical restoration of tissues. We also determined the optimal vector distribution of patients undergoing continuous ambulatory peritoneal dialysis without edema and with a residual urine output. The vector distribution was close to the distribution of both healthy subjects and pre-session distribution of hemodialysis patients. We established the relationship between central venous pressure and BIVA in critically ill patients. Shorter vectors (overhydration) were associated with increasing venous pressure, whereas longer vectors were associated with decreasing venous pressure. The association between BIVA and NT-proBNP has been evaluated in patients with acute cardiac-related dyspnea. In the 'gray zone' of NT-proBNP values between 'ruling out' and 'ruling in' acute heart failure, BIVA detected latent peripheral congestion. **Conclusion:** Simple patterns of BIVA allow detection, monitoring, and control of hydration status using vector displacement for the feedback on treatment.

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Noninvasive assessment of body composition is crucial for the routine evaluation of patients with heart failure (HF), chronic kidney disease, cardiorenal syndrome, and in critically ill patients. In these conditions, adequacy of fluid

volume control improves short- and long-term outcomes. The routine evaluation of hydration status based on body weight and blood pressure changes over time can be misleading, since changes are not uniquely determined by body fluid volume variations. Edema is not usually detectable until the interstitial fluid volume has risen to about 30% above normal (4–5 kg of body weight), while severe dehydration can develop before clinical signs [1].

Hemodialysis (HD) is an excellent model of fluid removal (1–5 l in 4 h) and overload (1–5 l in 2–3 days). HD often results in bringing the patient either to dehydration or to fluid repletion. Dehydration can be symptomatic (decompensated, with hypotensive episodes in the latter part of the session, malaise, washed-out feeling, cramps, and dizziness after dialysis) or asymptomatic (compensated). Fluid overload is mostly symptomatic with pitting edema, worsening of hypertension, and pulmonary congestion during the interdialysis interval. The so-called dry weight is the postdialysis weight at which all or most excess body fluid has been removed [2] (generally as the lowest weight a patient can tolerate without intradialytic symptoms or hypotension).

Treatment with diuretics and ultrafiltration (UF) of decompensated HF patients remove pulmonary and peripheral congestions until a ‘dry weight’ is achieved often resulting in dehydration. Therefore, prescription of treatment for the HF cycle of hydration can take advantage of the observations collected from the HD cycle of hydration.

Tools for Detecting Hydration

Anthropometry

Anthropometry formulas recommended in the literature [2] for estimation of total body water (e.g. Watson, Hume-Weyers, Chertow, Johanssohn) are of limited value because they are functions of body weight [3–6]. It has been shown that these formulas are completely insensitive to fluid overload with apparent edema [7].

Dilutometry

At the top of total body water measurement, utilization of dilutometry (e.g. tritium and deuterium) is implemented in unique centers evaluating plasma activity 3–4 h after isotope ingestion. But estimates are obtained with a relevant within-subject measurement error (up to 10%) even in the absence of delayed gastric emptying. Furthermore, three available isotopes measure different water spaces (by 3–4%). Therefore, dilutometry cannot be considered an optimal method for monitoring hydration in the clinical setting [6].

Bioelectrical Impedance

Bioelectrical impedance analysis (BIA) is a property-based method of body composition specifically detecting soft tissue hydration with a 2–3% measurement error,

which is comparable to routine laboratory tests [8]. The usefulness of body impedance measurement derives from its immediate availability as a noninvasive, inexpensive and highly versatile test that transforms electrical properties of tissues into clinical information [8]. Conventional BIA is based on electric models supporting quantitative estimates of body compartments through regression equations which are not valid in individuals with altered hydration. Bioelectrical impedance vector analysis (BIVA) is based on patterns of the resistance-reactance graph (RXc graph) relating body impedance to body hydration without equations [8–10]. A simple algorithm with few operational rules has been derived for interpreting impedance vector position and migration on the RXc graph at the bedside in any clinical condition. Changes in tissue hydration status below 500 ml are detected and ranked.

Body impedance is generated in soft tissues as an opposition to the flow of an injected alternate current and is measured from skin electrodes that are placed on hand and foot (whole body analysis) or on segments and regions of the body (segmental, regional analysis). Impedance (Z vector, ohm) is represented with a point in the R - X_c plane which is a combination of resistance, R , i.e. the opposition to the flow of an injected alternating current, at any current frequency, through intra- and extracellular ionic solutions and reactance, X_c , i.e. the dielectric or capacitative component of cell membranes and organelles, and tissue interfaces.

The impedance of a cylindrical conductor is proportional to its impedivity (i.e. impedance per meter) and to its length, and is inversely proportional to its transverse area. Hence, whole-body impedance is determined by limbs up to 90% and by trunk up to 10% [11]. Therefore, changes in bioimpedance measurements reflect changes in the hydration of lean and fat soft tissues of limbs, whereas ascites and effusions do not contribute to the measured impedance. Vector normalization by the subject's height (Z/H , in Ω/m) controls for the different conductor length [8–10, 12].

Basic Patterns of BIVA

Clinical information on hydration is obtained through patterns of vector distribution with respect to the healthy population of the same race, sex, class of BMI, and class of age [7–10, 13–23]. Unfortunately, the reference vector distribution may change with different analyzers due to the lack of one universal method of calibration of impedance devices. Our reference distribution and subsequent clinical validation studies were performed using the phase-sensitive analyzers produced by Akern-RJL Systems (Florence, Italy). Although BIVA can be done on R and X_c components at any current frequency, the optimal performance of the method is obtained with the standard, single frequency, 50 kHz current that allows impedance measurements with the best signal to noise ratio [8, 11, 13] (fig. 1). The RXc graph is a probability chart (50, 75, and 95% tolerance ellipses, i.e. bivariate percentiles) that classifies and ranks individual vectors according to the distance

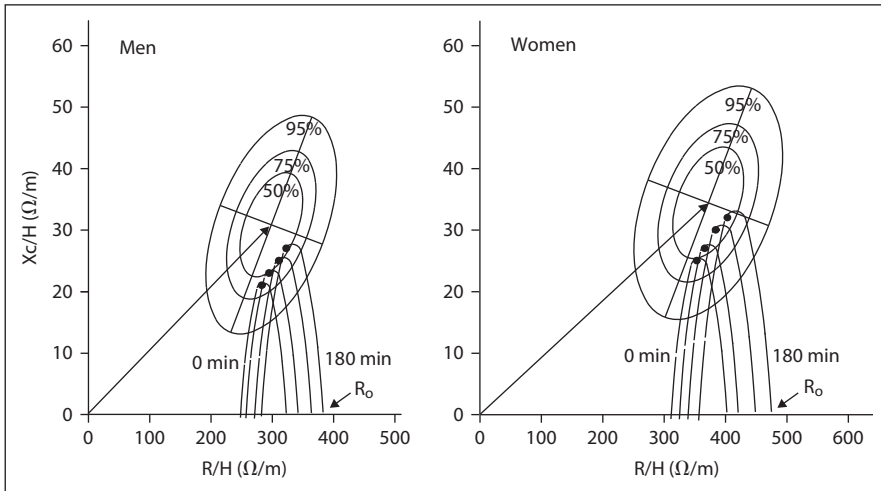


Fig. 1. The 50, 75 and 95% tolerance ellipses indicate sex-specific, reference intervals for an individual vector (Z/H in Ω/m) at 50 kHz, and point vectors represent the mean vectors at 50 kHz of dialysis patients, plotted on their hourly Cole's arc (baseline, 60, 120, 180 min, from R_0 to R_{∞}). Vectors at 50 kHz are close to the vault of the arcs (characteristic frequency; i.e. the mid-point between R_0 and R_{∞}). As progressive tissue dehydration increases tissue impedance, circles enlarge and migrate from the left to the right side. Vector displacement is parallel to the major axis of the tolerance ellipses. BIVA allows tracking of fluid removal with a direct comparison of impedance readings with reference intervals of the healthy population. UF in HF patients causes the same vector displacement. R is resistance, Xc reactance, and H height.

from the mean value of the reference population (fig. 1 and 2). From clinical validation studies in adults, vectors falling out of the 75% tolerance ellipse indicate an abnormal tissue impedance (i.e. abnormal hydration) [7, 14, 17–20, 22].

Vector position on the RXc graph is interpreted following two directions on the R-Xc plane, as depicted in figure 2: (1) Vector displacements parallel to the major axis of tolerance ellipses indicate progressive changes in tissue hydration (dehydration with long vectors, out of the upper poles of the 75 and 95%, and hyperhydration with apparent edema, with short vectors, out of the lower poles of 75 and 95%); (2) Peripheral vectors lying on the left side of the major axis, or on the right side of the major axis of tolerance ellipses indicate more or less cell mass, respectively (i.e. vectors with a comparable R value and a higher or lower Xc value, respectively).

BIVA in Hemodialysis

Figure 2 shows vector trajectories observed in a dialysis session (measurements at the start and every hour) spanning within (solid circles) or out (open circles)

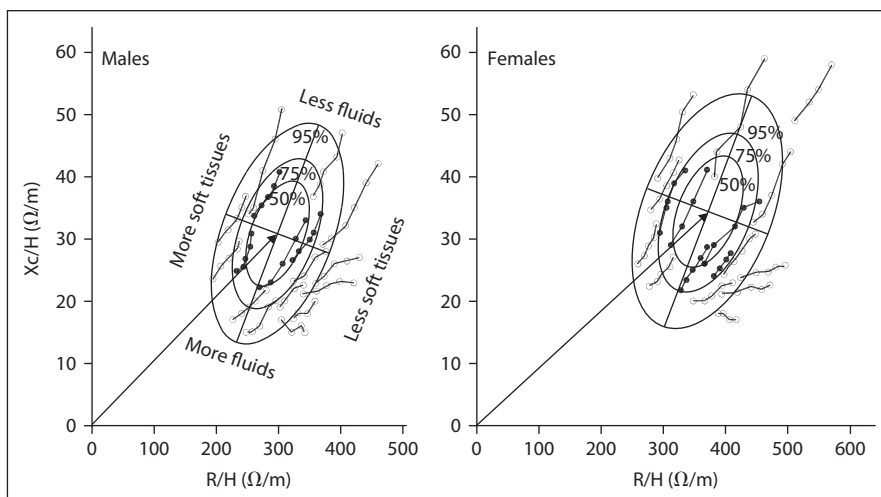


Fig. 2. Solid and open circles indicate vector trajectories that spanned within (normal) or out (abnormal) of the 75% tolerance ellipses, respectively, during 3–4 h of UF in representative HD patients (several with HF). The first and more frequent pattern is a vector displacement parallel to the major axis of the tolerance ellipses. Long vectors overshooting the upper poles indicate dehydration (dry vectors), and short vectors migrating across the lower poles indicate fluid overload (wet vectors). Vector trajectories spanning on the left side versus trajectories on the right side of ellipses are from patients with more versus less soft tissue mass, respectively. The second pattern of UF is a flat vector migration to the right, due to an increase in R/H without a proportional increase in Xc/H due to loss of cells in soft tissue. This pattern is characteristic of patients with severe malnutrition or cachexia, including cardiac cachexia. It is never observed in vectors lying on the left of the ellipses. R is resistance, Xc reactance, and H height.

of the 75% tolerance ellipses during 3–4 h of UF in representative HD patients (several with HF). Vector displacement occurs following fluid volume changes below 500 ml (fig. 1 and 2) [19].

The first and more frequent pattern is a vector displacement parallel to the major axis of the tolerance ellipses. According to the basic patterns, long vectors migrating across the upper poles indicate dehydration (dry vectors), and short vectors migrating across the lower poles indicate fluid overload (wet vectors). Vector trajectories spanning on the left side of ellipses are from obese patients (BMI 31–41) undergoing the same UF as lean patients [17].

The second pattern associated with UF is a flat vector migration to the right side, due to an increase in R/H without a proportional increase in Xc/H caused by severe loss of soft tissue mass. This pattern is characteristic of patients with severe malnutrition or cachexia, in particular with cardiac cachexia following congestive HF. It is never observed in vectors lying on the left of the ellipses.

Better Information from BIVA than BIS

The analysis of the HD cycle highlighted pitfalls in the BIS model [13] (fig. 1). Intra- and extracellular flows of current at any frequency, due to tissue anisotropy, cause equivalence of information based on functions of R and X_c measurements made at 50 kHz versus other frequencies (4–1,024 kHz). With whole-body BIS before and during fluid removal (0, 60, 120, 180 min, 2.5 kg) in HD patients, one can observe that with increasing current frequency, R decreases and X_c moves along the Cole's semicircle on the R - X_c plane (fig. 1). The Cole's semicircles progressively enlarge and move to the right on the R - X_c plane following fluid removal (increase in both R and X_c values at any given frequency). X_c values at 5 kHz (expected values close to 0 Ω) reached 70% of the maximum X_c , indicating an intracellular current flow also at low frequencies. The correlation coefficient between R at 50 kHz and R at other frequencies ranged from 0.96 to 0.99. In the clinical setting, the comparison of vector position and migration with target reference intervals represents an additional advantage of BIVA, which is not allowed with BIS (fig. 1).

BIVA in Peritoneal Dialysis

In continuous ambulatory peritoneal dialysis, peritoneal UF is obtained with 2 l of hypertonic glucose solutions or icodextrin infused within the abdomen and exchanged with 2 l of fresh solution every 6 h. More glucose in the solution drives more UF. The process is continuous rather than cyclical as in HD. Adequate UF should keep hydration of CAPD patients close to normal [2].

With BIVA, we established the optimal tissue hydration in CAPD patients. We studied 200 patients, 149 without edema and asymptomatic, and 51 with pitting edema due to fluid overload. There was no difference in impedance measurements before and after 2 l of fluid infusion in the abdomen. In asymptomatic CAPD patients, we found a vector distribution close to the healthy population and to the distribution of asymptomatic HD patients before the dialysis session [7]. Vectors from patients with edema were displaced downward on the RX_c graph, out of the 75% ellipse and close to vectors from nephrotic patients not undergoing dialysis. Therefore, the pattern of fluid overload with the vector displacement in the direction of the major axis was also observed in CAPD patients. This pattern can be utilized in dialysis prescription using vector displacement for the feedback on glucose solutions in order to keep or achieve a normal hydration without the knowledge of the body weight.

BIVA in Congestive Heart Failure

The clinical validation of BIVA in HD patients allows direct extension of the same BIVA patterns to the congestive HF. Similar to the HD cycle, HF is

characterized by a cyclical fluid overload (pulmonary and peripheral congestion) and removal (diuretics, extracorporeal fluid removal with UF). Despite current therapy, the high rate of readmission indicates that the present criteria for discharge, typically based mostly on subjective impressions, correlates poorly with clinical stabilization.

Current practice uses the biomarker NT-proBNP for interpretation of overhydration in the diagnosis of HF [24]. Values between the lower threshold point for 'ruling out' acute HF and the higher, aged-adjusted cutoff point for 'ruling in' acute HF are referred to as gray zone values. In the situation of a 'gray zone' diagnosis, clinical judgment of congestion is often necessary to ascertain the correct diagnosis. It is possible that the diagnostic and prognostic values of the NT-proBNP depend on the level of congestion (i.e. 'wet' worse than 'dry' NT-proBNP). In 315 patients admitted to the emergency department for acute dyspnea, NT-proBNP was used as biomarker of HF, lung ultrasound was used to detect pulmonary congestion, and BIVA was used to detect peripheral congestion. Peripheral congestion was either apparent with edema or latent without edema (unpubl. obs.). Patients were classified into two categories: cardiac-related dyspnea ($n = 169$) or noncardiac-related dyspnea ($n = 146$).

The mean impedance vector was significantly shorter in patients with cardiac-related dyspnea, with a parallel decrease in both R and Xc components according to the pattern of fluid overload. BIVA was able to detect a 'latent peripheral congestion' in dyspneic patients with NT-proBNP in the 'gray zone'. Ongoing intervention studies are needed to establish the region of the R-Xc plane where the individual vectors should be brought following an adequate fluid removal which is the region where an optimal 'dry' patient will decrease the rate of death and readmission, and also decrease the incidence of acute renal dysfunction.

BIVA in Critically Ill Patients

Determination of fluid volumes in patients in the intensive care unit is neither practical nor reliable. Limitations in the use of tracer dilution methods and violations of the assumption of constant hydration of soft tissues severely diminish the validity of the dilution method and conventional BIA in critically ill patients. In the critical care setting, however, central venous pressure (CVP) values are used as a guide for fluid infusion. Low CVP values are observed with true or relative hypovolemia, once a negative intrathoracic pressure has been excluded. Conversely, high CVP values indicate true or relative hypervolemia and fluid overload.

BIVA was examined as an indicator of fluid status compared to CVP in 121 ICU patients [18]. Both components of the impedance vector were significantly, linearly, and inversely correlated with CVP values. A progressive increase in the CVP corresponded in the R-Xc plane with backward and downward

displacement of the impedance vector to the region of fluid overload out of the lower pole of the 75% tolerance ellipse. Low CVP values were associated with most vectors of normal length or long vectors overshooting the upper pole of the 75% reference ellipse (e.g. BIVA pattern indicating tissue dehydration).

The combined evaluation of peripheral tissue hydration with BIVA and of central filling pressure with CVP provides a useful clinical evaluation tool in the planning of fluid therapy for ICU patients, particularly in those patients with low CVP. Indeed, a different response or tolerance to fluid infusion is expected in patients with peripheral dehydration compared to well-hydrated patients with a same low CVP where BIVA can identify those with reduced, preserved, or increased peripheral tissue fluid content.

BIVA in Localized Edema

Direct measurements of segmental Z can be evaluated with BIVA. Edema localized in one leg frequently follows a femoral-popliteal bypass. Localized edema can bias the interpretation of whole-body impedance [12]. Limbs and trunk contribute to whole-body Z by 90 and 10%, respectively [11]. The R and Xc components of Z vector were measured at 50 kHz in 20 adult male patients without edema, before and 3 days after a femoral-popliteal bypass that induced pitting edema in the leg. Whole-body Z was measured from hand to foot of the right and left side. The impedance of each leg was measured from the pair of electrodes on foot and the other pair on the trochanter.

After surgery, mean whole-body and leg Z vectors from the side without edema did not change position in the R-Xc plane with respect to the position before surgery. In contrast, mean whole-body and leg Z vectors of the body side with edema significantly shortened according to the BIVA patterns of fluid accumulation along a down-sloping trajectory, due to a combined decrease in both vector components (R and Xc).

Because whole-body Z vector from the side of the body without edema was not sensitive to the edema localized in the leg of the opposite side, it can be utilized in the assessment of body composition also in patients with edema in one leg. Furthermore, a complete resolution of the fluid accumulation in the leg is expected to bring Z-leg to the baseline position before surgery. Similar evidence cannot be obtained with other BIA methods.

Conclusions

Tissue hydration changes that are cyclical in HD and HF patients or slow over days in CAPD and ICU patients are detectable as changes in the whole-body impedance, which can be utilized with BIVA patterns in monitoring and

prescribing optimal hydration independent of the body weight. Wet-dry weight prescription based on BIVA indication would bring abnormal vectors back into the 75% reference ellipse, where tissue electrical properties are restored. A simple algorithm with few operational rules is provided for interpreting impedance vector position and migration on the RXc graph at the bedside. Longitudinal and intervention studies are required to establish whether patients with vectors cycling within the normal third quartile ellipse have better outcomes than those cycling out of the target interval.

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Diuretic Therapy in Fluid-Overloaded and Heart Failure Patients

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Abstract

Diuretics are the most commonly used drugs to treat clinically diagnosed fluid overload in patients with heart failure. There is no conclusive evidence that they alter major outcomes such as survival to hospital discharge or time in hospital compared to other therapies. However, they demonstrably achieve fluid removal in the majority of patients, restore dry body weight, improve the breathlessness of pulmonary edema and are unlikely to be subjected to a large double-blind randomized controlled trial in this setting because of lack of equipoise. The effective and safe use of diuretics requires physiological understanding of the pharmacokinetics and pharmacodynamics of diuretic therapy, an appreciation of the clinical goals of diuretic therapy, the application of physiological targeting of dose, an understanding of the effects of hemodynamic impairment on their ability to achieve fluid removal, an appreciation of the effects of combinations of different diuretics in patients refractory to single agents and an understanding of the most common side effects of such therapy. The use of continuous infusions of loop diuretics, sometimes combined with carbonic anhydrase inhibitors and/or aldosterone antagonists and/or thiazide diuretics can prove particularly effective in patients with advanced heart failure. Such therapy often requires more intensive monitoring than available in medical wards. If diuretic therapy fails to achieve its clinical goals, ultrafiltration by semipermeable membranes is reliably effective in achieving targeted fluid removal. The combination of diuretic therapy and/or ultrafiltration can achieve volume control in essentially all patients with heart failure.

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Introduction

An Illustrative Case

A 72-year-old man was admitted to intensive care following drainage of a large pericardial effusion (600 ml) and a large left-sided pleural effusion (800 ml). His immediately relevant medical history was that he had mitral valve repair surgery

16 days earlier for rheumatic heart disease. From the point of view of the intensive care team, his operation had been technically successful, as confirmed by postrepair transesophageal echocardiography. He had been in intensive care for 48 h and had been discharged to the cardiothoracic ward in a stable condition.

On readmission to the intensive care unit, he was breathing spontaneously via an oxygen mask, had a pleural drain in his left chest, a mediastinal drain exiting through his skin immediately below the sternum, a right jugular central line and right radial arterial line. On physical examination, his blood pressure was 100/50 mm Hg, his heart rate was 44 beats/min in sinus rhythm, his respiratory rate was 22 breaths/min, and his temperature was 37.3°C. His right atrial pressure was 22 mm Hg. Air entry was diminished on the right side, and there was dullness on percussion at the right base consistent with a pleural effusion. His cardiac examination revealed a third heart sound and no murmurs. His hands and feet were cool and the extremities slightly cyanosed; his pulse oximetry probe placed on the left ear lobe recorded a hemoglobin saturation of 95%. Drainage from his chest drain was yellow in color and totaled 50 ml for the last hour. His urine output was 20 ml for the last hour. The most remarkable finding, on physical examination, however, was that of marked and *generalized pitting edema, which could be detected all the way to his face*. A set of arterial blood gases on humidified oxygen flow of 30 l/min via a face mask showed a pH of 7.34, a PaCO₂ of 34 mm Hg, a PaO₂ of 73 mm Hg, a serum HCO₃ of 22 mM, and a base excess of -2 mEq/l.

His serum sodium was 134 mM, his chloride was 100 mM, his potassium was 3.8 mM, his blood lactate was 3 mM, his serum albumin was 17 g/l, his plasma urea was 25 mM and his serum creatinine was 154 µM. An echocardiogram performed before his surgery had demonstrated severe mitral regurgitation, a dilated left atrium, normal fractional shortening of the left ventricle, a mean pulmonary artery pressure of 37 mm Hg + RA pressure, a dilated right atrium and mild tricuspid valve regurgitation. His chest X-ray showed a right-sided pleural effusion, a mildly enlarged cardiac silhouette and the chest drains described above. His electrocardiogram showed sinus bradycardia, left axis deviation and evidence of atrial hypertrophy.

Management Issues in Fluid-Overloaded Heart Failure Patients

The above clinical case presents many questions related to fluid overload, cardiac failure and the possible role of diuretics: how should this patient be managed now? Why does he have anasarca? Why was this patient allowed to deteriorate to this level? What is the role of diuretics in his treatment? What are the principles of care in fluid overload and cardiac failure with regard to fluid management? In the following pages, we will try to address some of these issues: to present a case for a particular approach to management and factually describe what happened to this particular individual, drawing some lessons from both the clinical case and the literature.

Diagnostic Challenges

This patient presents many, perhaps all of the challenges and features that pertain to the issues of cardiac failure, fluid overload and possible diuretic use in this setting. The first relates to diagnosis. The clinical findings are clearly those of predominantly right-sided cardiac failure with elevated right atrial pressure, bilateral pleural effusions, and anasarca. Although the development of large pericardial effusion is likely to have contributed to the worsening clinical condition, it is likely that the pericardial effusion was both a consequence of and a contributor to anasarca.

There is growing evidence that high right atrial pressures are a more important predictor of renal dysfunction in patients with heart failure than measure of left-sided performance such as cardiac output or left-sided filling pressure [1–4]. Recently, Damman et al. [2] published a retrospective series of 2,557 patients who had right-sided cardiac catheterization because of variable causes of heart failure with documentation of central venous pressure (CVP). Multivariate analysis showed an independent and inversely proportional relationship between CVP and GFR. Higher CVP values correlated with greater renal deterioration ($p < 0.0001$). This relationship was maintained even after excluding patients with heart transplants and heart failure. In support of these observations, Mullens et al. [3] concomitantly published a retrospective study using a cohort of 145 acute heart failure (AHF) patients who required intensive medical care. Pulmonary artery catheter measurements were used to monitor progress towards therapeutic targets: cardiac indices higher than 2.4 l/min/m^2 , PCWP $\leq 18 \text{ mm Hg}$ and CVP $\leq 8 \text{ mm Hg}$. In total, 40% of patients developed acute kidney injury (AKI) despite optimization of heart function and reduction in indices of hypervolemia. Patients who developed AKI, compared to those with stable renal function, showed higher CVP values at the time of admission (18 ± 7 vs. $12 \pm 6 \text{ mm Hg}$, $p < 0.001$) and after medical therapy (11 ± 8 vs. $8 \pm 5 \text{ mm Hg}$, $p < 0.001$), despite having a better cardiac index both at baseline (2 vs. 1, $p < 0.008$) and after medical therapy (2.7 vs. 2.4, $p < 0.001$). The CVP value was as an independent predictor of renal dysfunction, with increasing progressive risk, particularly with CVP $> 24 \text{ mm Hg}$. No difference was found between groups when left side pressure (PCWP), pulmonary systolic pressure and arterial systolic pressure were evaluated. Deterioration of renal function in AHF patients is thus not totally dependent on pumping function. Hypervolemia, venous congestion and tissue edema might explain acute renal deterioration. In light of these observations, it can be logically argued that renal functional impairment in the setting of AHF should not be a reason to accept or undertreat hypervolemia. Indeed, its prevention or careful treatment may lead to better renal outcomes.

How can hypervolemia and edema cause kidney injury? Elevated right heart pressures are likely to induce decreased renal perfusion pressure through an increase in back pressure and the formation of renal edema. As renal perfusion

pressure is equal to mean arterial pressure minus intrarenal tissue pressure, an increase in such pressure due to higher right atrial pressures and organ edema will likely induce renal hypoperfusion and activate the renin-angiotensin-aldosterone system [5]. In addition, as the kidney is surrounded by a capsule, organ edema may generate further back pressure and a degree of intracapsular ‘tamponade’ with additionally decreased renal perfusion, decreased urine output, more fluid retention and further edema. This vicious cycle can easily contribute to diuretic resistance and anasarca. In such patients, even large doses of loop diuretics may fail to achieve a neutral or negative fluid balance. For example, the patient under discussion had been treated with 80 mg of frusemide twice a day for 10 days. This situation of deteriorating kidney function is further exacerbated by the effect of fluid accumulation and myocardial dilatation on cardiac output and systemic blood pressure, both of which decrease in this setting. Furthermore, in a patient with the features described above, stroke volume cannot be increased and remains ‘fixed’. The inability to adjust cardiac output by increasing stroke volume and thus improve oxygen delivery to tissues means that the only compensatory mechanism available is tachycardia (cardiac output = stroke volume $\times$ heart rate). If the patient, as in this case, has persistent bradycardia secondary to surgical injury to the conduction pathway, tissue edema, sick sinus syndrome or all of these, then the patient cannot increase cardiac output to meet the metabolic demands of his tissues and maintain renal perfusion. When all of the above cardiovascular and fluid retention states exist, then diuretic therapy is unlikely to succeed. In this particular case, it had dramatically failed.

Why did clinicians fail to address these issues? The most likely explanation lies in the stereotyped approach often taken in the care of cardiac failure patients, which involves the administration of drugs (diuretics included) on the basis of dosage rather than on the basis of physiological effect. This issue is particularly important for diuretics because these drugs have not been shown to change prognosis or outcome. Thus, diuretics are given to *relieve symptoms* and/or *modify physiology* to the advantage of the patient. If they fail to do so, the treating clinician needs to investigate the reasons for diuretic resistance and correct them or resort to other techniques (e.g. ultrafiltration) to relieve the symptoms of fluid overload and/or restore a desirable and safe physiological state [6–8].

Tackling Diuretic Resistance

Following arrival in the ICU and given the patient’s anasarca, an 80-mg bolus of frusemide was given and an intravenous frusemide infusion was started at 40 mg/h. After 2 h of infusion, his urinary output was still 25 ml/h, clearly demonstrating diuretic resistance. At this time, initiation of ultrafiltration may appear logical and desirable [6–8] and indeed would represent a reasonable and justifiable treatment in this patient. However, two causes of diuretic resistance still

remained untreated in this patient, which would, in the long term, continue to impede recovery: bradycardia with the possibility of an undiagnosed low cardiac output state (recent heart surgery, cool periphery, oliguria, increased blood lactate level) and low blood pressure. In this setting, it seems logical first to diagnose whether a low cardiac output state exists. To do this, a femoral PiCCO (pulse contour cardiac output) line was inserted to enable transpulmonary thermodilution measurements of cardiac output [9]. Such measurements showed a low cardiac index of $1.9 \text{ l/m}^2/\text{min}$. In response to this information, a dobutamine infusion was started at $5 \text{ }\mu\text{g/kg/min}$. After 30 min of treatment, the patient's heart rate had not changed appreciably and the cardiac output remained $2 \text{ l/m}^2/\text{min}$. The patient remained oliguric despite the continued administration of frusemide infusion. The blood pressure remained low at 90/50 mm Hg. A noradrenaline infusion was started to increase the mean arterial pressure to 75 mm Hg. At $0.1 \text{ }\mu\text{g/kg/min}$ infusion, the blood pressure increased to 115/60 mm Hg and the urinary output increased to 50 ml/h. Although the urinary output had doubled, it was hardly sufficient to achieve a resolution of the fluid overload state and was barely enough to compensate for the infusions being administered. It seemed likely that the low cardiac output state had to be corrected and that such correction required a restoration of a more physiological heart rate. A temporary pacing wire was inserted through the femoral vein and the heart rate was increased to 90 beats/min. The patient's cardiac index increased to $3.4 \text{ l/m}^2/\text{min}$ and noradrenaline was weaned because his blood pressure had now returned to 120/60 mm Hg. Within 1 h, his urinary output had increased to 400 ml/h.

Therapeutic Challenges

Having achieved a close to desired urine output, further issues related to diuretic use must be considered: what is a safe and yet sufficient urine output in this setting? What are the consequences of such urine output on electrolytes like sodium, chloride, potassium and magnesium? How much fluid should be removed? How can one know when an optimal fluid state has been achieved for a specific patient such as the one presented here?

Although only empirical observations can help address these issues in a specific patient, some general principles should be taken into account in all cases. First, a urine output of 3–4 ml/kg/h rarely causes intravascular volume depletion as capillary refill can meet such rates in almost all patients. Thus, in an 80-kg man, a urine output to 250 ml/h almost never causes hypotension or decreases in cardiac output. In this particular patient, a urinary output of 300 ml/h was aimed for and maintained by titrating diuretic infusion over 3 days without any changes in cardiac output as continuously measured by PiCCO technology. Second, diuretic infusion is clearly superior to boluses of diuretics in enduring both a steady, predictable and smooth urinary output. In addition, greater diuresis is typically achieved [10] and a lesser dose of loop diuretic is given. Finally, if large amounts of diuretics are necessary, the avoidance of rapidly given boluses lessens

the risk of temporary deafness. In the patient in question, frusemide infusion was titrated between 20 and 40 mg/h. Third, in a person who is not in pulmonary edema, tissue edema does not require correction over minutes or even hours. The fluid that has accumulated over days is more logically removed at a similar rate. This means that large volumes of hourly output are unnecessary and potentially dangerous. Fourth, a loop diuretic infusion will typically result in a marked kaliuresis. This requires that steps be taken to avoid hypokalemia. The administration of oral potassium preparation seems logical and easy. It is however, important to estimate the likely requirements. This can be done by measuring the urinary potassium concentration and calculating the daily losses of potassium which require replacement. For example, at 300 ml/h of diuresis and a potassium concentration of 50 mM, this patient required approximately 100 mmol of potassium every 6 h. This may not be achievable with oral therapy alone. A continuous potassium infusion may be necessary (and was used in this patient for 24 h at 8 mmol/h). An alternative may be to add potassium-sparing diuretics which are indicated to help improve outcome in patients with heart failure such as spironolactone [11]. Spironolactone therapy was started in this patient.

Another concern relates to magnesium losses [12]. Although the body has a large reservoir of magnesium in bones, magnesium replacement therapy in patients experiencing a large diuresis seems wise and can be achieved either intravenously or orally, typically with 20–30 mmol/day.

In some patients, chloride losses exceed sodium losses and hypochloremic metabolic alkalosis develops [12]. This is usually corrected with potassium chloride and magnesium chloride as described above, and is typically not a major source of concern. However, in some patients, clinicians may feel that intervention is warranted. In these patients, the addition of acetazolamide [13] and a decrease in loop diuretic use is sufficient to maintain diuresis and achieve normalization of chloride levels and metabolic acid-base status. This was done in this patient on day 2 and 3 of treatment successfully.

Finally, in some patients, diuresis is in excess of sodium losses leading to hyponatremia. In some patients, this can be an indication for ultrafiltration. In others cautious administration of water and the addition of a thiazide diuretic [14] can achieve improved natriuresis and maintain normal sodium levels by targeting yet another aspect of tubular function (table 1). Importantly, no matter what the chosen interventions are, assiduous monitoring of renal function and electrolytes is mandatory under these circumstances.

At this point, it must be noted that some authors have questioned the use of loop diuretics in heart failure, as described in this man. They comment that loop diuretics have not been shown to change the outcome of either heart failure or AKI, their impact on heart failure mortality is questionable and the use of large doses is associated with an increased mortality and risk of AKI [15]. However, loop diuretics are widely used in most types of cardiorenal syndromes [16] because they achieve specific relief of symptoms and resolution of the

Table 1. Diuretics used in this case, target and mechanism of action and amount of sodium reabsorbed in each target segment

Diuretic	Target	Mechanism	Percent of Na in target segment
Loop diuretics	loop of Henle	Na-K-2Cl cotransporter inhibitors	25
Acetazolamide	proximal tubule	carbonic anhydrase inhibitor	60 ¹
Thiazides	distal tubule	Na-Cl cotransporter inhibitor	10
Spironolactone	collecting duct	aldosterone antagonist	5

¹ Only a small fraction of this sodium load is targeted by acetazolamide.

congestive state in most patients. Moreover, their association with unfavorable outcome when given in large doses probably represents the fact that diuretic resistance is a powerful marker of disease severity.

Other newer approaches to diuresis in these patients have also recently been promoted. Nesiritide, a recombinant analog to brain natriuretic peptide (BNP), has been proposed for the management of AHF as it counteracts renin-angiotensin-aldosterone system hyperactivity and optimizes fluid management [17, 18]. However, results have not been optimal and on occasion, renal function deterioration has been observed. Thus, the role of nesiritide in the treatment of heart failure and fluid overload remains unclear [19, 20].

Ultrafiltration

Diuretic resistance has also resulted in the development of new technologies based on slow ultrafiltration beyond the traditional criteria for renal support. For example, slow ultrafiltration in patients with AHF refractory to diuretics can remove up to remove 5 l/day without hemodynamic instability. Edema is thus reduced, with an improvement in cardiac and respiratory function, increased diuretic responsiveness and hemodynamic stability.

For example, the RAPID [7] (Relief for Acute fluid overload Patients with Decompensated CHF) study randomly assigned patients to either receive diuretic management or ultrafiltration for 8 h. Fluid removal during the first 24 h was higher in the ultrafiltration group (4.6 vs. 2.8 l, $p = 0.001$) and occurred without renal functional deterioration or hemodynamic instability. In the larger UNLOAD trial [8], 200 patients were randomly assigned to receive either diuretic therapy or ultrafiltration. All patients with signs of fluid overload, independent of the ejection fraction, were included. The weight loss was greater in the ultrafiltration group (5.0 ± 3.1 vs. 3.1 ± 3.5 kg; $p = 0.001$; fig. 1). The requirement for

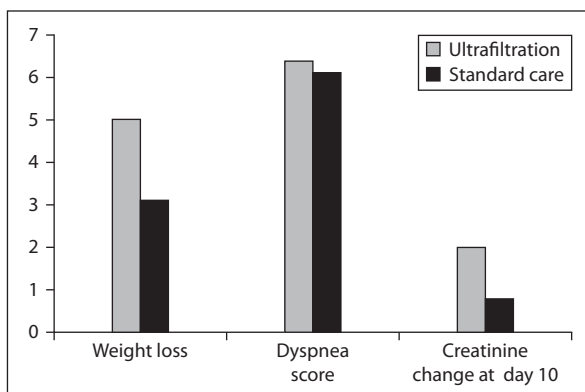


Fig. 1. Weight loss, changes in dyspnea score within 48 h and serum creatinine (in mg/dl) at day 10 during treatment with ultrafiltration compared to standard care. Modified from reference [8].

inotropic support was also decreased in the ultrafiltration group (3 vs. 12%, $p = 0.015$). The 90-day follow-up showed a lower rehospitalization rate for HF in the ultrafiltration group (18 vs. 32% $p = 0.022$), without renal functional deterioration in the final evaluation. However, of note, the mean dose of furosemide during the study period (48 h) was 180 mg. This is much less than the 1,560 mg given in the first 48 h to the patient described here. Finally, changes in serum creatinine during hospital admission showed no correlation with amount of fluid removed.

In some patients, deterioration of renal function can be substantial and dialytic therapy may become necessary. In these patients, continuous renal replacement therapy and peritoneal dialysis may be more appropriate than intermittent dialysis. Prompt referral of such patients to the intensive care and/or nephrology team is then a priority.

Given these choices based on ultrafiltration, why was diuretic therapy acceptable or chosen in the patient described above? The response relates to the fact that diuretic therapy remains simpler, less invasive and cheaper than ultrafiltration therapy. In this patient, with appropriate potassium supplementation, magnesium supplementation, careful reduction in dose of furosemide, the temporary addition of acetazolamide and hydrochlorothiazide, and adjunctive treatment with spironolactone, a negative fluid balance of >8 l was achieved over 4 days (fig. 2) and the patient could be stabilized on a combined regimen of furosemide and spironolactone, which he could take over the next few weeks to maintain a clinically desirable body weight. A permanent pacemaker was inserted and the patient was discharged home 8 days later with mild ankle edema.

During this process of diuresis, his creatinine rose to 205 μM and then stabilized around 190 μM . In these situations, the optimal fluid balance that achieves

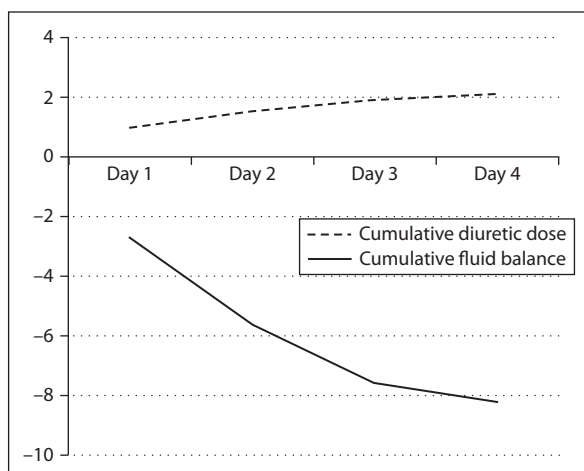


Fig. 2. Cumulative diuretic dose over 4 days (in grams) and cumulative fluid balance (in liters) during continuous diuretic infusion in case study patient.

symptomatic relief, safety, and a physiological state that achieves the best possible quality of life and the best possible long-term survival remains unknown and likely varies from patient to patient. While the worsening renal function is associated with increased risk of mortality [21–24], it is likely that such association mostly reflects illness severity [25]. Allowing patients to have severe edema in order to ‘protect’ the kidney is physiologically irrational and probably clinically undesirable. Similarly, the pursuit of a patient without any edema in the setting of right heart failure is likely to induce marked renal dysfunction with its attendant risks and consequences without appreciably improving the patient’s quality of life. More recently, biomarkers have been used to guide therapy and optimize fluid management [26]. In particular, BNP was used to guide therapy in randomized study and compared with symptom-guided treatment in 499 patients with systolic heart failure. In this study, BNP-guided therapy resulted in similar rates of survival free of all cause hospitalizations but improved the secondary endpoint of survival free of hospitalization for heart failure (hazard ratio of 0.68; 95% CI, 0.50–0.92). In addition, aldosterone-blocking diuretics were prescribed more frequently in the BNP-guided therapy group. This observation suggests that biomarkers like BNP may assist clinicians in titrating diuretic therapy.

Conclusions

Diuretics (especially loop diuretics) remain effect medications for the relief of symptoms and the improvement of pathophysiological states of fluid overload,

including heart failure. Their administration requires careful titration, occasional use of continuous infusion, attention to electrolyte and fluid balance, measured and slow removal of fluid, avoidance of excessive overall fluid removal, combination of different diuretic medications targeted to different aspects of tubular function and appropriate dosage. In cases of resistance, hemodynamic factors contributing to it must be addressed. In selected patients, ultrafiltration may be necessary to achieve the desired physiological and clinical goals. If clinicians adhere to the above principles, they will find that diuretics remain safe and useful tools in the treatment of congestive states.

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Pharmacological Therapy of Cardiorenal Syndromes and Heart Failure

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Abstract

Cardiorenal syndromes (CRS) are disorders of the heart and kidneys, whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other. The management of heart failure and CRS requires an understanding not only of the pathophysiology linking these two organ systems, but also an appreciation of the pharmacological effects of agents targeting one organ and their influence on the other. For instance, treatment of cardiovascular diseases and risk factors may influence, in a beneficial or harmful way, renal function and progression of renal injury. The same is true regarding management of renal disease and associated complications, where drug therapies may influence cardiac performance or modify risk of adverse cardiovascular outcome. In this chapter, pharmacological therapies in the management of patients with acute and chronic CRS are reviewed, novel regimens for prevention and treatment of worsening renal function in acute decompensated heart failure are discussed, and the need for high-quality future studies in this field is highlighted.

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Introduction

Renal insufficiency complicates a significant proportion of hospitalizations for heart failure. In acute decompensated heart failure (ADHF) patients, an increase in serum creatinine >0.3 mg/dl (>26 μM) is referred to as ‘worsening renal function’ or WRF, and this example of type 1 cardiorenal syndrome (CRS) is associated with poor outcomes. In chronic heart failure, coexisting renal insufficiency with glomerular filtration rate (GFR) <60 ml/min/1.73 m² (type 2 CRS) significantly increases the risk for mortality. In type 3 CRS, acute kidney injury, for example following contrast, has been associated with subsequent adverse cardiovascular events, while chronic kidney disease (CKD)

represents an independent risk factor for cardiovascular events and outcomes in type 4 CRS.

The purpose of this chapter is to review the pharmacological therapy of the various subtypes of CRS, and to highlight the need for high-quality future studies to better guide management. Furthermore, some novel regimens showing promise in the prevention and treatment of type 1 CRS are presented.

Management of Acute Cardiorenal Syndrome (Type 1)

The management and prevention of type 1 CRS in the setting of ADHF or cardiogenic shock, is largely empiric, as many of the traditional therapies to relieve congestive and/or ischemic symptoms (diuretics, vasodilators, morphine) [1] have not been rigorously studied. While strategies to improve cardiac output and renal perfusion pressure are important, recent evidence has implicated high venous pressures, raised intra-abdominal pressure and renal congestion as playing a more important contributory role than impaired cardiac output [2]. Hence, diuretics play an important role in early management, and are reviewed in greater detail in the previous chapter.

The goal of diuretic use should be to deplete the extracellular fluid volume at a rate that allows refilling from the interstitium to the intravascular compartment. Infusions of loop diuretics have been shown to be more effective than equal doses given intermittently [3], and the optimal dose and route is the subject of an ongoing randomized trial. During management of ADHF, one may see oliguria and/or WRF for a variety of potentially 'reversible' causes: decreased cardiac output or effective circulating volume; increased venous pressure causing renal venous congestion; increased intra-abdominal pressure; tubuloglomerular feedback; various vasoactive substances (adenosine, endothelin – ET) and diminished responsiveness to natriuretic peptides. Furthermore, autoregulation of GFR may be impaired by renin-angiotensin-aldosterone system (RAAS) blockade, and withholding or delaying the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers may be required to maintain the GFR [4].

When renal function is endangered by acute myocardial ischemia and/or cardiogenic shock, positive inotropes such as dobutamine or phosphodiesterase inhibitors may be required [1], though their use may in fact accelerate some pathophysiologic mechanisms such as ischemia or arrhythmia. In a randomized trial of milrinone in patients with ADHF, there was a higher incidence of hypotension, more arrhythmias, and no benefit on mortality or hospitalization [5]. Effects of this therapy on type 1 CRS were not reported. Levosimendan, a phosphodiesterase inhibitor with calcium-sensitizing activity improved hemodynamics and renal function in a small randomized trial when compared with dobutamine [6], but this result was not replicated in a larger study [7]; hence, its precise role in prevention of type 1 CRS is unclear.

Nesiritide, or recombinant B-type natriuretic peptide (BNP), decreases preload, afterload and pulmonary vascular resistance, increases cardiac output in

ADHF and causes effective diuresis, quickly relieving dyspnea in acute heart failure states [8]. However, a meta-analysis of randomized trials reported that its use actually increased the risk of WRF as well as mortality [9]. The conclusive answer to the safe use of nesiritide remains undetermined, and a large 7,000-patient multicenter study (ASCEND-HF) is underway to establish its role [10].

Certain patients may benefit from such nonpharmacological therapies as ultrafiltration to prevent or treat type 1 CRS, as reviewed in a subsequent chapter. When patients with ADHF or cardiogenic shock and type 1 CRS are resistant to therapy, more invasive therapies such as intra-aortic balloon pulsation, ventricular assist devices or artificial hearts may be required as a bridge to recovery of cardiac function or to transplantation, but these are beyond the scope of this chapter.

Management of Chronic Cardiorenal Syndrome (Type 2)

Interruption of the RAAS, where possible, represents a goal of paramount importance in the management of type 2 CRS. However, a particularly vexing problem in the clinical management of both acute and chronic CRS (types 1 and 2), is when RAAS blockade leads to significant changes in renal function or potassium. Heart failure studies have typically excluded patients with significant kidney dysfunction, but it is believed that these agents are renoprotective even with considerable renal insufficiency. For instance, in the CONSENSUS trial, creatinine increased by approximately 10–15% upon initiation of enalapril, and some experienced an increase of 30% or greater [11]. Creatinine tended to stabilize and in many instances improved over the course of the study. Typically, it is recommended that RAAS blockade may be carefully titrated provided the serum creatinine does not continue to rise beyond 30% and potassium is consistently below 5.6 mM.

In terms of aldosterone blockade, drugs such as spironolactone have important clinical benefits in patients with severe heart failure [12]. However, in combination with other RAAS blockade, the risk of hospitalizations and mortality related to hyperkalemia is significant [13]. Excluding patients with moderate CKD (creatinine level ≥ 2.5 mg/dl or $220 \mu\text{M}$) or hyperkalemia >5 mM has been suggested to minimize potential life-threatening complications [14].

Beta-blockers play an important role in patients with congestive heart failure, and/or ischemic heart disease, and their use is generally considered to be neutral to kidney function. Certain beta-blockers may be relatively contraindicated in subjects with impaired kidney function due to altered pharmacokinetics, such as atenolol, nadolol or sotalol [15], and it may be prudent to avoid such agents in patients with more advanced renal insufficiency. Carvedilol, a beta-blocker with α_1 blocking effects, has been demonstrated to have favorable renal effects in some subgroups with heart and kidney disease, hence may have a benefit over older formulations of beta-blockers [16].

Congestive heart failure is also associated with anemia, and preliminary clinical studies demonstrated that administration of erythropoiesis-stimulating

agents in patients with type 2 CRS and anemia led to improved cardiac function, reduction in left ventricular size and lowering of BNP [17]. However, a recent randomized trial failed to demonstrate any significant improvement in symptoms, quality of life, exercise duration or other clinical parameters [18]. Ongoing clinical trials are required to establish if erythropoiesis-stimulating agents have a role to play in the management of congestive heart failure and type 2 CRS.

Management of Acute Renocardiac Syndrome (Type 3)

In acute renocardiac syndrome, acute kidney injury is believed to be the primary inciting factor, and cardiac dysfunction is a common and often times fatal complication of acute renal failure [19]. As a typical scenario of type 3 CRS would include the development of acute kidney injury following contrast exposure, particularly in a susceptible population such as patients undergoing coronary angiography, prevention may provide an opportunity to improve outcomes. Many potential preventive strategies have been studied including choice of periprocedural fluids (hypotonic or isotonic saline or bicarbonate), diuretics, mannitol, natriuretic peptides, dopamine, fenoldopam, theophylline and N-acetylcysteine [20, 21]. To date, isotonic fluids have been the most successful intervention, with some controversy surrounding the effectiveness of N-acetylcysteine.

Treatment of acute renal parenchymal diseases such as acute glomerulonephritis or kidney allograft rejection may potentially lessen the risk of type 3 CRS, but this has not been systematically studied. Furthermore, many of the immunosuppressive drugs used for such treatment have adverse effects on the cardiovascular system through their effects on blood pressure, lipids and glucose metabolism [22, 23]. The role of immunosuppression in the prevention or, conversely, the development of type 3 CRS needs further study.

Management of Chronic Renocardiac Syndrome (Type 4)

The treatment of type 4 CRS (chronic renocardiac syndrome) focuses on the management of cardiovascular risk factors and complications common to CKD patients that include, but are not limited to, anemia, hypertension, altered bone and mineral metabolism, dyslipidemia, smoking, albuminuria and malnutrition [24, 25].

In observational studies, the treatment of anemia seems to lessen cardiovascular events; however, this has not been borne out in randomized trials where higher hemoglobin targets have been associated with increased risk [26–28]. Hence, the use of erythropoiesis-stimulating agents to prevent type 4 CRS remains an area of controversy and ongoing study.

Elevated homocysteine has been associated with worsening cardiovascular outcomes in a number of observational studies [29], and has been a target of study in CKD. However, vitamin therapy to lower homocysteine has not been shown to be of benefit [30, 31]. Likewise, elevated calcium-phosphate product, elevated phosphate, elevated parathyroid hormone and inadequate vitamin D

receptor activation have all been shown in observational studies to be risk factors for type 4 CRS [32–34]. Clinical trials to date have been generally disappointing, though a recent systematic review revealed that a drug used to lower parathyroid hormone, cinacalcet, results in decreased hospitalizations related to cardiovascular disease [35]. A large randomized trial of cinacalcet is examining hard cardiovascular endpoints and mortality [36], and trials of phosphate binders and vitamin D analogs are ongoing.

Finally, the use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors or ‘statins’ is an important adjunct to risk factor modification in all patients at risk for cardiac disease. However, two high-profile negative trials in dialysis patients [37, 38] have questioned the benefit of statins in CKD patients. In a recent meta-analysis, Strippoli et al. [39] found that statins did lead to significant reductions in cardiovascular end points in CKD patients, although all-cause mortality was not improved. Importantly, statins did not seem to have higher adverse event rates in subjects with kidney disease.

Novel Regimens in the Pharmacological Therapy of Type 1 CRS

Relaxin

Relaxin is responsible for modulating vasodilation and renal function during pregnancy, and it increases cardiac output, and decreases systemic vascular resistance and BNP. In the Pre-RELAX-AHF trial [40] in patients with ADHF and moderate kidney dysfunction, the intermediate dose (30 µg/kg/day) was associated with improved dyspnea, greater weight loss, less diuretic use, lower cardiovascular death or readmission. The clinical improvements in the intermediate group were not offset by any WRF.

Endothelin Receptor Antagonists

In type 1 and type 2 CRS, ET has been implicated as playing a role in both acute and chronic kidney dysfunction. Experimental blockade of the ET system has showed promise in various models of acute and chronic nephropathies, including heart failure/CRS models [41]. Unfortunately, the promise of ET receptor antagonists in human heart failure has to date been unfulfilled. As reviewed by Kirkby et al. [42], many trials have been neutral or suggested early worsening of heart failure. In terms of prevention of type 1 CRS, tezosentan was reported to have significant adverse events, including WRF in one study [43].

Adenosine Receptor Antagonists

Adenosine can affect renal function adversely through local effects on renal blood flow as well as modulation of tubuloglomerular feedback [44]. Adenosine blockade could hence be useful in type 1 CRS, and several small clinical trials have indicated a potential role [45, 46]. However, a recently completed study of rolofylline

in ADHF, which was presented at the European Society of Cardiology meeting (Barcelona, 2009) by Metra and colleagues, was negative. A combined outcome of 'success' or 'failure' based on dyspnea, death, worsening heart failure, rehospitalization, WRF or need for ultrafiltration was no different between groups. There were no differences in death, hospitalization or persistent renal impairment, but more rolofylline patients suffered seizures with a trend toward more strokes.

Vasopressin Receptor Antagonists (Vaptans)

Increased release of vasopressin has been suggested to be a contributor to type 1 CRS, and several agents have been shown in small studies to improve hemodynamics in congestive heart failure, increase urinary output in a dose-dependent fashion without increasing serum creatinine [47, 48]. Unfortunately, a large study of tolvaptan versus placebo in ADHF patients revealed more weight loss, improved dyspnea, better serum sodium, but no differences in mortality, and no significant differences in prespecified renal outcomes. In fact, there was a small but statistically significantly greater rise in serum creatinine in the tolvaptan group [49].

Other Natriuretic Peptides

CD-natriuretic peptide is a novel chimeric natriuretic peptide for type 1 CRS which was designed to have an effect on the kidneys like nesiritide, without causing significant hypotension [50]. In early studies in healthy volunteers, CD-natriuretic peptide increased urine output and natriuresis while decreasing aldosterone and preserving GFR with minimal impact on blood pressure. Preliminary studies in heart failure patients are ongoing.

Ularitide is the synthetic equivalent of urodilatin, a natriuretic peptide secreted within the kidney. In the SIRIUS-2 trial, ADHF patients received placebo or ularitide infusions, and the intermediate dose (15 ng/kg/min) improved heart failure symptoms and hemodynamics while preserving GFR [51]. Further studies will determine if ularitide can reliably prevent or treat type 1 CRS.

Conclusions

The subtypes of CRS discussed in this chapter each present their own particular therapeutic challenges. Many of the pivotal heart failure trials of the past decades have systematically excluded patients with significant kidney dysfunction, making it difficult to provide evidence-based guidelines for management of type 1 and 2 CRS; however, the recognition of WRF as an important clinical outcome has led to a tremendous burst of research activity in recent years. The importance of acute kidney injury as an inciting factor in type 3 has only recently been appreciated; hence, more study in this area is desperately required, and cardioprotective trials in type 4 CRS have largely been

disappointingly negative. Understanding the complex bidirectional pathways by which the heart and kidneys communicate will provide the rationale for future drug development and investigations into the prevention and management of CRS.

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Extracorporeal Fluid Removal in Heart Failure Patients

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Abstract

More than one million hospitalizations occur annually in the US because of heart failure (HF) decompensation caused by fluid overload. Congestion contributes to HF progression and mortality. Apart from intrinsic renal insufficiency, venous congestion, rather than a reduced cardiac output, may be the primary hemodynamic factor driving worsening renal function in patients with acutely decompensated HF. According to data from large national registries, approximately 40% of hospitalized HF patients are discharged with unresolved congestion, which may contribute to unacceptably high rehospitalization rates. Although diuretics reduce the symptoms and signs of fluid overload, their effectiveness is reduced by excess salt intake, underlying chronic kidney disease, renal adaptation to their action and neurohormonal activation. In addition, the production of hypotonic urine limits the effectiveness of loop diuretics in reducing total body sodium. Ultrafiltration is the mechanical removal of fluid from the vasculature. Hydrostatic pressure is applied to blood across a semipermeable membrane to separate isotonic plasma water from blood. Because solutes in blood freely cross the semipermeable membrane, large amounts of fluid can be removed at the discretion of the treating physician without affecting any change in the serum concentration of electrolytes and other solutes. Ultrafiltration has been used to relieve congestion in patients with HF for almost four decades. In contrast to the adverse physiological consequences of loop diuretics, numerous studies have demonstrated favorable responses to ultrafiltration. Such studies have shown that removal of large amounts of isotonic fluid relieves symptoms of congestion, improves exercise capacity, improves cardiac filling pressures, restores diuretic responsiveness in patients with diuretic resistance, and has a favorable effect on pulmonary function, ventilatory efficiency, and neurohormonal activation. Ultrafiltration is the only fluid removal strategy shown to improve outcomes in randomized controlled trials of patients hospitalized with decompensated HF.

Introduction

In the United States, 90% of more than one million annual hospitalizations for heart failure (HF) are due to symptoms of volume overload [1, 2]. Hypervolemia contributes to HF progression and mortality [3–5]. Treatment guidelines recommend that therapy of patients with HF be aimed at achieving euvolemia [6].

Intravenous loop diuretics induce a rapid diuresis that reduces lung congestion and dyspnea [7]. However, loop diuretics' effectiveness declines with repeated exposure [8]. Unresolved congestion may contribute to high rehospitalization rates [3]. Furthermore, loop diuretics may be associated with increased morbidity and mortality due to deleterious effects on neurohormonal activation, electrolyte balance, cardiac and renal function [7–10].

Ultrafiltration is an alternative method of sodium and water removal which safely improves hemodynamics in patients with HF [11–14].

The objective of this chapter is to review the epidemiology and pathophysiology of congestive HF, describe the rationale for fluid removal with ultrafiltration and review the results of clinical trials on the use of ultrafiltration in fluid-overloaded HF patients.

Epidemiology and Clinical Features of Acutely Decompensated Heart Failure

According to data from the American Heart Association, in the US 5 million individuals have HF, and this number is projected to double within the next 30 years. More than 500,000 new HF cases are diagnosed each year [1]. The growing HF epidemic is attributable to the aging of the population, to the improved survival of patients with acute cardiac illnesses, such as myocardial infarction, and to the rising incidence of conditions associated with an increased risk of HF, including hypertension, diabetes, and obesity [1].

According to the Framingham Heart Study, 1 in 5 HF patients will die within 1 year of diagnosis, 80% of males and 70% of females will die within 8 years of diagnosis and only 15% survive longer than 10 years [14]. Importantly, according to data from the National Discharge Survey, Center for Disease Control and Prevention and National Institute of Health, over the past 25 years, while deaths due to coronary artery disease (CAD) have decreased by half, those due to HF have tripled [15]. Because of its high morbidity, HF imposes an enormous financial burden on the US health care system, as demonstrated by the fact that in 2007 estimated direct and indirect cost for HF care were approximately 34 billion [1]. The mortality and costs associated with HF in the US are strikingly similar to those reported in Canadian and European analyses [16, 17]. In the US, HF decompensation is responsible for more than one million annual hospitalizations and is the most common cause of hospitalization in patients older

than 70 years [1]. From the 1970s to the present, hospitalizations due to HF have increased 6-fold and they continue to rise, with the rate of growth being higher in women than in men [18]. Of all HF hospitalizations, approximately 75% are due to decompensation of chronic HF, 15–20% to new-onset acute HF, and the remainder to cardiogenic shock. Data from large registries have been helpful in defining the characteristics of hospitalized HF patients. The mean age is 75 years and over one half are women. Dyspnea and signs of congestion are common [2]. At presentation, approximately 25% of patients have systolic blood pressure (BP) >160 mm Hg, <10% are hypotensive, most are taking diuretics, 50% angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, 50% beta-blockers, and 20–30% digoxin [2, 19]. A history of CAD is present in 60%, hypertension in 70%, diabetes in 40%, atrial fibrillation in 30%, and moderate to severe renal impairment in 20–30% [20].

Approximately 50% of patients hospitalized with acutely decompensated HF (ADHF) have a relatively preserved systolic function [21, 22]. These individuals are generally older and more likely to be female, to have a history of hypertension and atrial arrhythmias, and to present with severe hypertension [21–23].

Approximately 90% of HF hospitalizations are caused by symptoms and signs of fluid overload occurring in patients with a preserved cardiac output (CO) [7, 24]. Congestion, due to an increase in left ventricular filling pressure often results in jugular venous distention, pulmonary and/or peripheral edema, and/or an increase in body weight. Cardiac filling pressures often begin to rise days or even weeks before the onset of symptoms triggering hospitalization [25, 26]. Hospitalization for HF, in itself, is one of the most important predictors for rehospitalization [27, 28]. Both in the US and Europe, uncontrolled hypertension, ischemia, arrhythmias, exacerbation of chronic obstructive pulmonary disease with or without pneumonia, and medical noncompliance are the factors most frequently associated with ADHF [29]. In patients presenting with de novo HF, an acute coronary syndrome can often be the event precipitating HF decompensation [30]. Although volume overload is the main reason for hospitalization, many patients do not lose significant weight and are thus discharged with unresolved congestion [31, 32]. A comprehensive assessment of the underlying causes of ADHF is frequently omitted, and this may result in underutilization of therapies shown to decrease HF morbidity and mortality [31, 33, 34].

In the US, hospitalization length is, on average, 6 days (median: 4 days), and mortality ranges between 2 and 4% to >20% in patients with severe renal impairment and low BP [19]. Sixty- and 90-day mortality varies between 5 and 15% depending on BP at presentation (the higher the BP, the lower the mortality). Rehospitalization rates at 30 days approach 30%, independent of baseline BP [35]. Risk for these events is highest in the first few months following discharge [35]. Among patients admitted with chronic HF and low ejection fraction, approximately 40% will die from progressive HF and 30% will die suddenly and unexpectedly after discharge [34]. Notably, approximately 50% of readmissions

are unrelated to HF and caused by cardiac or noncardiac comorbidities, such as CAD, hypertension, atrial fibrillation, renal insufficiency, or stroke [34–37].

Consequences of Fluid Overload

The findings summarized above are especially intriguing in light of the growing evidence that hypervolemia per se is independently associated with mortality [5, 38]. A study prospectively comparing blood volume measured by a radio-labeled albumin technique with clinical and hemodynamic characteristics and outcomes in 43 nonedematous ambulatory HF patients demonstrated that 28 subjects (65%) were hypervolemic [5]. Importantly, blood volume was closely correlated with pulmonary capillary wedge pressure (PCWP) and independently predicted 1-year risk of death or urgent cardiac transplantation which was significantly higher in hypervolemic than in normovolemic patients (39 vs. 0%, $p < 0.01$) [5]. Furthermore, in an observational study of patients with ADHF, predischARGE reduction in PCWP below 16 mm Hg, but not increased cardiac index (CI), was associated with improved 2-year survival [39]. Interestingly, in a study evaluating the hemodynamic variables associated with worsening renal function (WRF) in 145 patients hospitalized with ADHF [40], elevated central venous pressure (CVP) on admission as well as insufficient reduction of CVP during hospitalization, were the strongest hemodynamic determinants for the development of WRF. In contrast, impaired CI on admission and improvement in CI following intensive medical therapy had little effect on WRF [40]. These findings raise three key questions: (1) what are the mechanisms by which venous congestion worsens renal function? (2) Why does hypervolemia per se decrease survival in a broad spectrum of cardiovascular diseases? (3) Why are the detrimental effects of hypervolemia on renal function and survival magnified in the setting of ADHF?

In a normal individual, of the total plasma volume, 3.9 l or 85% resides in the venous and only 0.7 l or 15% in the arterial circulation [41]. As it is explained below, the primary regulation of renal sodium (Na) and water excretion, and thus body fluid homeostasis, is modulated by the smallest body fluid compartment, thus enabling the system responsible for the perfusion of the body's vital organs to respond to small changes in body fluid volume [7]. A reduced CO due to systolic dysfunction, abnormal diastolic relaxation and/or decreased vascular compliance causing HF despite preserved systolic function or excessive vasodilatation in high CO HF all result in a decreased intra-arterial blood volume. Arterial hypovolemia results in inactivation of the high-pressure baroreceptors in the aortic arch and coronary sinus, attenuation of the tonic inhibition of afferent parasympathetic signals to the central nervous system and enhancement of sympathetic efferent tone with subsequent activation of the renin-angiotensin-aldosterone system (RAAS) and nonosmotic release of arginine-vasopressin

(AVP) [7]. In the kidney, increased angiotensin II (AII) causes renal efferent arteriolar vasoconstriction, resulting in decreased renal blood flow (RBF) and increased filtration fraction, the ratio between glomerular filtration rate (GFR) and renal plasma flow. Together with renal nerve stimulation, the increased peritubular capillary oncotic- and reduced peritubular capillary hydrostatic pressure augment Na reabsorption in the proximal tubule. In addition to its renal vascular effects, AII also directly stimulates Na reabsorption in the proximal tubule by activating basolateral Na-bicarbonate cotransporters and apical Na-hydrogen exchangers [42]. Finally, AII promotes aldosterone secretion which boosts Na reabsorption in the distal tubule and collecting duct [7]. Importantly, increased proximal Na reabsorption decreases distal Na and water delivery, the major stimulus for the cells of the macula densa to increase synthesis of renin which further amplifies neurohormonal activation [43]. Reduced distal Na and water delivery is also responsible for impaired escape from aldosterone-mediated Na retention and resistance to the actions of natriuretic peptides [7]. Nonosmotic release of AVP enhances vasoconstriction through vascular (V_1) receptors and distal free water reabsorption through the renal (V_2) receptor-mediated synthesis of aquaporins [44]. Enhanced renal Na and water reabsorption increases blood volume which predominantly fills the compliant venous circulation, resulting in increased central venous and atrial pressures. Under normal circumstances, an increase in left atrial pressure suppresses AVP release and thus enhances water diuresis (the Henry-Gauer reflex), decreases renal sympathetic tone and augments atrial natriuretic peptide secretion. In HF, these atrial-renal reflexes are overwhelmed by arterial baroreceptor-mediated neurohormonal activation, as evidenced by persistent renal Na and water retention *despite* elevated atrial pressures [7]. Transmission of venous congestion to the renal veins further impairs glomerular filtration. Because the capsule encasing the kidney is rigid, edema further raises renal interstitial and venous pressures and stimulates the RAAS [7]. A 1931 isolated mammalian kidney study showed that increased renal venous pressure was associated with reduced RBF, urine flow, and urinary Na excretion. Importantly, these abnormalities were reversed by lowering renal venous pressure [45]. Fifty-seven years later, hypervolemia experimentally induced in dogs directly led to a decreased GFR, independent of CO and RBF [46]. A contemporary study in ADHF patients showed that an elevated intra-abdominal pressure caused by ascites and visceral edema was closely correlated with the severity of renal dysfunction and that reduction of intra-abdominal pressure improved renal function [40]. Furthermore, in a recent analysis from the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE), right atrial pressure emerged as *the only* hemodynamic variable significantly correlated with baseline renal function, an independent predictor of mortality and HF hospitalization [47].

In light of these findings, a key question is which measure of renal function best reflects the severity of congestion and the effects of hypervolemia

on kidney function. Most published studies use a creatinine-based formula to estimate GFR [48]. However, the modification of diet in renal disease equation may underestimate the severity of renal dysfunction because creatinine, which is freely filtered and not reabsorbed, undergoes tubular secretion [48]. Blood urea nitrogen (BUN) has been considered an unreliable measure of renal function because it is influenced by protein intake, catabolism and tubular reabsorption. However, BUN reabsorption is flow dependent, increasing as urine flow rates decrease. Of even greater importance is the fact that reabsorption of urea in the distal nephron is regulated by the effect of AVP on the urea transporter in the collecting duct. Because nonosmotic AVP release increases with escalating neurohormonal activation, a rise in BUN may serve as an index of neurohormonal activation over and above any fall in GFR [49]. This hypothesis is strongly supported by the finding in a retrospective analysis of the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbation of Chronic Heart Failure that admission BUN and change in BUN during hospitalization, independent of admission values, were a statistically better predictor of the 60-day death rate and days of rehospitalization than was estimated GFR [50].

Importantly, the relationship between CVP and GFR is bound to be bidirectional, because CVP-mediated renal dysfunction will initiate Na and water retention which will aggravate congestion. In addition, it is possible that not only the reduction in CVP, but also the specific method used to achieve such goal may critically impact renal function and outcomes. Loop diuretics act in the thick ascending limb of the loop of Henle where the macula densa is located. Therefore, independent of any effect on Na and water balance, loop diuretics block Na chloride uptake in the macula densa, thereby stimulating the RAAS [51].

The observation that a single ADHF episode worsens not only short-term but also long-term outcomes suggests that ADHF is complicated by events which accelerate disease progression. A seldom considered fact is that hypervolemia may be associated with edema in the myocardium *itself*. In an isolated heart model, experimentally induced myocardial edema was associated with a reduction of contractility, increase in chamber stiffness and compromise of baseline and maximal coronary flow rate [52]. Myocardial edema, RAAS activation with the associated abnormalities in calcium handling, inflammatory cytokines, nitric oxide dysregulation, oxidative and mechanical stress, as well as the use of drugs, such as inotropes, which increase myocardial oxygen consumption create the 'perfect storm' leading to myocyte injury or death. Indeed, measurement of troponin in 67,924 hospitalized ADHF patients revealed that patients who were positive for troponin had higher in-hospital mortality than those who were not (8.0 vs. 2.7%, $p < 0.001$) [53]. While exacerbating myocardial damage, the pathologic events complicating ADHF also cause acute renal injury by further reducing renal perfusion (from reduced CO and/or increased CVP), oxygen delivery, GFR and responsiveness to natriuretic peptides. Renal injury results in greater Na and water retention and neurohormonal activation which

accelerate HF progression. Albeit at a slower pace, these events are also operative in the setting of chronic HF. Thus, it is not surprising that renal dysfunction is the strongest predictor of poor outcomes in HF patients, regardless of whether systolic function is decreased or preserved. Conversely, primary acute and chronic renal disease can cause, respectively, acute HF and worsening of cardiac abnormalities, including myocardial ischemia, left ventricular hypertrophy, diastolic dysfunction and cardiac dilatation-induced mitral regurgitation [54, 55]. Indeed patients with chronic kidney disease have between a 10- and 20-fold increased risk for cardiac death compared to age-/gender-matched control subjects with intact renal function [54]. These bidirectional cardiorenal interactions are magnified by systemic diseases, such as diabetes and hypertension, which simultaneously affect both heart and kidney and impair critically important renal mechanisms of autoregulation [54]. Indeed several studies show that, for similar CVP, renal dysfunction is greater in patients with a history of diabetes and hypertension [37, 55].

Rationale for the Use of Ultrafiltration in Heart Failure

As described above, the majority of ADHF hospitalizations are caused by fluid overload which independently worsens HF outcomes [56]. Thus, the primary therapeutic goals for acute HF exacerbation include removal of fluid overload, reduction in ventricular filling pressures and increase in CO, myocardial protection, neurohormonal modulation, and renal function preservation. Although intensive IV treatment with loop diuretics may initially facilitate fluid loss and improve symptoms, their use is associated with enhancement of neurohormonal activation, intravascular volume depletion, hemodynamic impairment, and renal function decline. Moreover, diuretic use has been shown to be associated with poorer outcomes and a dose-dependent inverse relation between loop diuretics use and survival has been recently demonstrated in advanced HF [57, 58]. However, because fluid overload heavily influences both quality and length of life in these patients, alternative therapeutic strategies are needed to overcome the development of resistance to diuretics, particularly in patients in whom progressively higher diuretic doses are required.

Ultrafiltration was first utilized for the treatment of fluid overload in HF more than 50 years ago [59], and in the last 25 years several studies have confirmed its clinical efficacy, as well as its safety profile [12, 13, 60]. When applied to HF patients, ultrafiltration, in the short term, reverses the vicious circle responsible for the progression of the disease – in which a fall in CO, neurohormonal activation, and renal dysfunction exert mutually negative effects [61] (table 1). The unique feature of ultrafiltration is its ability to remove excessive fluid from the extravascular space, without significantly reducing intravascular blood volume. Most of ultrafiltration's observed clinical, hemodynamic and respiratory effects

Table 1. Rationale for the use of ultrafiltration in HF

Rationale	Therapeutic goal
Fluid regulation	Reduce ascites and/or peripheral edema Hemodynamic stabilization Improve oxygenation Facilitate blood product replacement without excessive volume Enable parenteral nutritional support without excessive volume
Solute regulation	Correct acid-base balance Correct serum sodium content Eliminate 'myocardial depressant factor' or known toxins Correct uremia Correct hyperkalemia and other electrolyte disturbances
Establish homeostasis	Reset water hemostat Restore diuretic responsiveness Reduce neurohormonal activation

result from this mechanism [12, 13, 60, 61]. Reduction in extravascular lung water with ultrafiltration allows the rapid improvement of respiratory symptoms (dyspnea and orthopnea), pulmonary gas exchange, lung mechanics and radiological signs of pulmonary vascular congestion and alveolar and interstitial edema. Removal of systemic extravascular water allows resolution of peripheral edema and, when present, ascites and pleural and pericardial effusions [13]. The subtraction of extravascular pulmonary water by reducing the intrathoracic pressure and, thus, the diastolic burden on the heart exerts a positive influence on cardiac dynamics [62]. The hemodynamic improvement following ultrafiltration is the result of both the reduction in the extracardiac constraint and the optimization of circulating blood volume. Withdrawal of several liters of fluid over a period of a few hours can be safely performed without hemodynamic deterioration, and clinical improvement is usually sustained even after a single ultrafiltration session [12, 13]. During ultrafiltration, circulating blood volume – the true cardiac pre-load – is preserved, or even optimized by refilling of the intravascular space with fluid from the interstitium. The decrease in ventricular filling pressures purely reflects the reduction in intrathoracic pressure and in pulmonary stiffness due to reabsorption of the excessive extravascular lung water that burdens the heart. Recovery in pulmonary mechanics improves cardiac function as indicated by a reduction in heart size and improvement in Doppler-derived variables indicative of hemodynamic restriction [62–64].

In addition to edema removal, ultrafiltration effects are especially beneficial in patients with coexisting advanced HF and renal insufficiency. These

include correction of hyponatremia, restoration of urine output and diuretic responsiveness, reduction in circulating levels of neurohormones, and, possibly, removal of other cardiac-depressant mediators [13, 61, 65, 66]. The mechanism by which ultrafiltration may improve renal function is still unclear, but it can be explained by the interaction of multiple factors, such as reduction in venous congestion and improvement in CO and intravascular volume. These favorable hemodynamic changes reestablish an effective transrenal arterial-venous pressure gradient and increase GFR [40]. Furthermore, the clearance of several neurohumoral factors with vasoconstrictive and water- and salt-retaining properties may also contribute to renal function improvement in HF patients treated with ultrafiltration. Recovery of diuretic responsiveness is an important clinical effect of ultrafiltration, because it contributes to the amplification over time of the clinical benefits achieved with a single session of ultrafiltration. Moreover, it permits the use of lower diuretic doses, which reduces the exposure to the adverse effects of these drugs.

Importantly, the favorable effects of ultrafiltration are not reproduced by the removal of an equivalent fluid volume by high-dose IV diuretic infusion [67]. When the two strategies – mechanical and pharmacological – for fluid withdrawal are compared, divergent effects on Na removal capacity, on intravascular volume, and on RAAS activity are usually achieved. Indeed, the fluid removed with the two treatments has a different tonicity (isotonic, with ultrafiltration and hypotonic with loop diuretics), and whereas intravascular volume is preserved with ultrafiltration, it is reduced by loop diuretics. These disparate effects on intravascular volume and on the amount of Na eliminated despite removal of a similar fluid volume may explain the differential consequences of ultrafiltration and diuretics on neurohormonal activation, resulting in a more favorable water and salt balance after ultrafiltration. Indeed, while after ultrafiltration reduced water reabsorption and weight loss are sustained, a rapid return to baseline conditions occurs after administration of IV loop diuretics [67] (fig. 1). This observation underscores the clinical relevance of a ‘physiologic’ dehydration in HF.

Hyponatremia, hypokalemia, and RAAS activation, all of which occur with chronic diuretic treatment, are known to portend a poor prognosis in HF patients. Presumably, long-term treatment with serial ultrafiltration sessions which do not lower Na and potassium serum concentrations and do not activate the RAAS, could have a favorable effect on disease progression, edema formation, and, ultimately, on mortality. To date, the ability of ultrafiltration to prolong survival in patients with HF has not been confirmed in controlled clinical trials.

Although ultrafiltration is usually recommended for treatment of patients with refractory HF, namely those in whom diuretics have failed to achieve a negative fluid balance, it may also be a valuable first-line therapy in fluid-overloaded HF patients with preserved responsiveness to diuretics [66]. This is

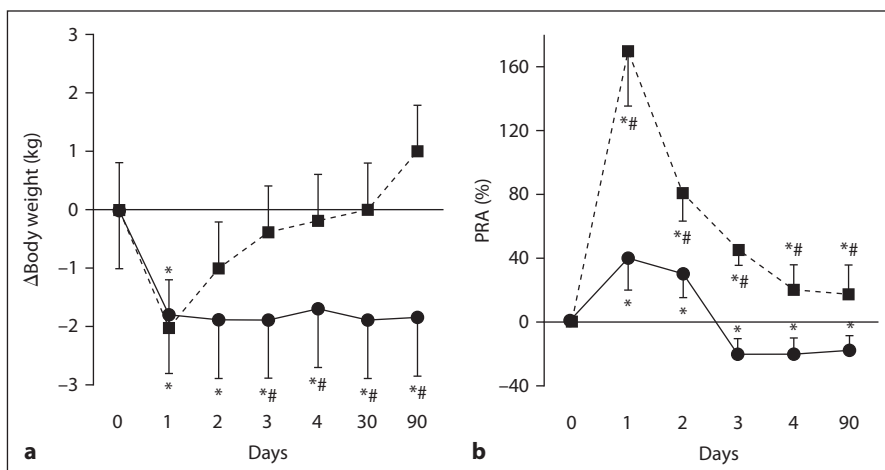


Fig. 1. Changes in body weight (**a**) and average percent changes from baseline of circulating plasma renin activity (PRA; **b**) at various periods after isolated venovenous ultrafiltration (d) or intravenous furosemide (+). Data are presented as means $\pm$ SEM. Differences from baseline (asterisks) are significant at $p < 0.01$; differences from the corresponding value in the other group (diamonds) are significant at $p < 0.01$. Reproduced from Agostoni et al. [67], with permission. b = Baseline; d = day; m = month.

particularly true in patients with severe congestion and concomitant renal insufficiency and hyponatremia. Indeed, the early use of ultrafiltration may offer two relevant clinical advantages. First, because euolemia is usually achieved within 24 h when ultrafiltration is efficiently carried out, hospital length of stay can be shortened. Second, the ‘more physiologic’ dehydration obtained with ultrafiltration than with diuretic therapy attenuates neurohormonal compensatory mechanisms, resulting in sustained clinical benefits and, consequently, in fewer rehospitalizations [67]. Earlier use of ultrafiltration decreases the clinical relevance of establishing whether or not diuretic resistance is present. Although a single session of ultrafiltration is usually sufficient to meaningfully reduce fluid overload, repeated treatment may be needed when continuous nursing surveillance is unavailable, when it is difficult to predict the total fluid volume which must be removed or the time needed to restore clinical stability and an adequate urine output or when the sheer amount of fluid to be removed requires prolongation of treatment beyond patients’ tolerance.

In the course of an ultrafiltration session, patients are exposed to rapid variations of body fluid composition. Since fluid is withdrawn from the intravascular compartment, the transient reduction of blood volume elicits the process of intravascular refill from the overhydrated interstitium. Plasma refilling rate depends on fluid movement through the capillary walls, a result of hydrostatic and oncotic pressure gradient changes between the intravascular and the

interstitial compartments, generated by ultrafiltration itself [12]. Refilling with fluid from the extravascular space is usually adequate to replace the intravascular fluid removed by ultrafiltration, thus preventing hypovolemia and hemodynamic instability. Adequate refilling, as well as plasma volume changes, can be easily monitored through serial evaluation of changes in hematocrit values which can be measured either using serial blood samples or continuously using hematocrit sensors placed in the withdrawal line. When the hematocrit does not significantly change during ultrafiltration, regardless of the amount of fluid removed, this indicates a proportional shift of water from the extravascular to the intravascular phase. If the hematocrit increases, it may indicate either an insufficient refilling rate or the complete removal of the extravascular edema. In both cases, any prolongation of ultrafiltration or failure to decrease the fluid withdrawal rate may cause severe hypovolemia-related hypotension, CO reduction and acute WRF. Acute kidney injury, requiring rapid fluid infusion and, in some cases, temporary or permanent renal replacement therapy, represents the most serious complication of ultrafiltration which may negate its clinical benefit. A practical approach to avoid this grave complication in clinical practice is to estimate the patient's total weight gain from excess fluid and limit fluid removal to 50–60% of that value. Even if hypervolemia is not completely resolved, the benefits of ultrafiltration, in terms of increased urine output and diuretic responsiveness facilitate the achievement of a negative fluid balance over the next several days without the detrimental renal effects resulting from excessively rapid fluid removal.

Clinical Studies of Ultrafiltration in Heart Failure

Ultrafiltration in Advanced Heart Failure

Ultrafiltration has been consistently shown to improve signs and symptoms of congestion, increase diuresis, lower diuretic requirements, and correct hyponatremia in patients with advanced HF [65]. Among 32 NYHA class II–IV HF patients with varying degrees of hypervolemia, the baseline 24-hour diuresis and natriuresis were inversely correlated with neurohormone levels and renal perfusion pressure (mean aortic pressure – mean arterial pressure). The response to ultrafiltration ranged from neurohormonal activation and reduction in diuresis in patients with the mildest hypovolemia and urine output >1,000 ml per 24 h to neurohormonal inhibition and potentiation of diuresis and natriuresis in those with the most severe volume overload and urine output <1,000 ml per 24 h [65]. In the majority of cases, the decrease in norepinephrine level was proportional to the potentiation of diuresis. These results support the proposed mechanisms of ultrafiltration's benefit described in the preceding section of this chapter.

In 36 patients with ADHF, ultrafiltration was associated with an increased CI and oxygenation status, decreased pulmonary artery pressure and vascular

resistance, as well as reduced requirement for inotropic support [68]. Slow continuous ultrafiltration or daily ultrafiltration has also been shown to effectively control volume in patients with severe congestive HF regardless of concomitant renal function [69]. It is not known if the clinical benefits of ultrafiltration translate into improved survival. Acute HF, which is most commonly due to decompensation of chronic HF, can also occur in the setting of circulatory collapse complicating myocardial infarction, hypertension, pericardial disease, cardiomyopathy, myocarditis, pulmonary embolus, or arrhythmias or after cardiac surgery [70–72]. In these clinical settings, ultrafiltration has been used predominantly after diuretics have failed or in the presence of acute renal failure. However, the results of some studies suggest that earlier utilization of ultrafiltration can expedite and maintain compensation of acute HF by simultaneously reducing volume overload without causing intravascular volume depletion and reestablishing acid–base and electrolyte balance [73].

The use of ultrafiltration in patients with advanced HF has also highlighted the risks associated with mechanical fluid removal. Overly aggressive ultrafiltration in patients with decompensated HF can convert nonoliguric renal dysfunction into oliguric failure by increasing neurohormonal activation and decreasing renal perfusion pressure, with minimal opportunity of recovery of renal function. Patients with this outcome become permanently dependent on dialysis. In addition, permanent renal loss can eliminate the option of heart transplantation in patients with end-stage HF. Prior to initiating a treatment course with extracorporeal therapies, the clinician must clearly explain the risk and potential pitfalls of this technique. It is generally disastrous to add a chronic need for dialysis to an already decompensated cardiac status. In some cases, a trial of ultrafiltration can be offered for a limited time to evaluate potential benefits. However, there must be a clearly delineated plan to withdraw support if predefined parameters of improvement are not achieved [74–81]. Severity of renal dysfunction influences the type and intensity of ultrafiltration approach. HF patients without overt renal impairment may benefit from isolated ultrafiltration. In patients with moderate to severe renal dysfunction, stabilization of cardiac and metabolic functions can only be achieved with hemofiltration [81].

Role of Ultrafiltration in Heart Failure Patients Undergoing Cardiac Surgery

Open heart surgery is usually associated with hypervolemia because of the 3–4 l of crystalloids and colloids typically infused during cardiopulmonary bypass (CPB), including CBP pump prime, cardioplegia, and fluid administered to reverse intraoperative hypotension. In addition, patients may undergo heart surgery in conditions that may induce or worsen preexisting HF. Regardless of the circumstances, fluid overload aggravates postoperative hypoxemia and organ edema, which, in turn, delays recovery and worsens outcomes [82]. Furthermore, perioperative hypervolemia is augmented by the inflammatory

response induced by CPB [83]. In this setting, removal of 3–4 l of fluid by hemofiltration produces enough hemoconcentration to reduce postoperative anemia, thrombocytopenia, and hypoalbuminemia [83]. Preservation of colloid osmotic pressure by hemofiltration has also been shown to reduce the incidence of postoperative pleural effusions requiring invasive chest drainage [82]. Experimental and clinical evidence has also shown that hemofiltration can remove by convective clearance myocardial depressant factors such as tumor necrosis factor- α and interleukin-1 β [85]. In one study in which patients with postoperative inflammation underwent high-volume (6 l per hour) hemofiltration, hemodynamic improvement was associated with significant reduction in C3a and C5a anaphylatoxins [82]. In inotrope-dependent heart surgery patients, vasoactive drugs were removed by hemofiltration at rates only slightly higher than by endogenous clearance [86]. This finding suggests that hemofiltration does not reduce the therapeutic actions of these medications. In early studies in which hemofiltration was applied late (>8 days) and at rates ≤ 1 l per hour to treat postoperative hypervolemia, mortality rates after treatment have ranged between 52 and 87.5% [87–89]. In contrast, early and intensive application of hemofiltration in heart surgery patients with volume overload and renal dysfunction was associated with lower posttreatment mortality rates ranging from 40 to 60% [82, 90].

Studies of Intermittent Isolated Ultrafiltration with Central Venovenous Access

Intermittent isolated ultrafiltration has been described in more than 100 NYHA class IV HF patients who have failed aggressive vasodilator, diuretic, and inotropic therapy [91, 92]. Of 52 such patients treated with slow isolated ultrafiltration, 13 died at less than 1 month during treatment (nonresponders), 24 had both cardiac and renal improvement (responders) for either <3 months ($n = 6$) or for >3 months ($n = 18$), and 15 (partial responders) had hemodynamic improvement but WRF requiring either long-term weekly ultrafiltration ($n = 8$), continuous ambulatory peritoneal dialysis ($n = 1$), or intermittent high-flux hemofiltration or hemodiafiltration ($n = 6$). Adequate diuresis was restored within 1 month in 24 of the 39 responders and partial responders. Four of the 15 partial responders had sufficient recovery of renal function to undergo heart transplantation 3–9 months after isolated ultrafiltration. Thus, intermittent ultrafiltration can be used as a nonpharmacologic approach for the treatment of congestive HF refractory to maximally tolerated medical therapy.

Restoration of diuresis and natriuresis after intermittent ultrafiltration identified patients with recoverable cardiac functional reserve. Intermittent isolated ultrafiltration is valuable in partial responders because it improves quality of life and may be used as a bridge to heart transplantation.

The high short-term mortality in this and in another study (in which 23 of 86 patients (27%) died within 2 months after ultrafiltration) is consistent with the poor prognosis associated with very advanced HF.

Simplified Intermittent Isolated Ultrafiltration with Peripheral Venovenous Access

A device that permits both withdrawal of fluid and blood return through peripheral veins has been available for more than 5 years (Aquadex System 100, CHF-Solutions, Minneapolis, Minn., USA). However, central venous access remains an option with this device. Fluid removal can range from 10 to 500 ml per hour, blood flow can be set at 10–40 ml per minute, and total extracorporeal blood volume is only 33 ml. The device consists of a console, an extracorporeal blood pump, and venous catheters. The device has recently been improved with the insertion of an on-line hematocrit sensor.

To date, four clinical trials of intermittent peripheral venovenous ultrafiltration have been completed. In the first study (21 fluid-overloaded patients), removal of an average of $2,611 \pm 1,002$ ml (range 325–3,725 ml) over 6.43 ± 1.47 h reduced weight from 91.9 ± 17.5 to 89.3 ± 17.3 kg ($p < 0.0001$), and also reduced signs and symptoms of pulmonary and peripheral congestion without associated changes in heart rate, BP, electrolytes, or hematocrit [14]. The aim of the second study was to determine if ultrafiltration with this same Aquadex System 100 before intravenous diuretics in patients with decompensated HF and diuretic resistance results in euvolemia and hospital discharge in 3 days, without hypotension or WRF. Ultrafiltration was initiated within 4.7 ± 3.5 h of hospitalization and before intravenous diuretics in 20 HF patients with volume overload and diuretic resistance (age 74.5 ± 8.2 years; 75% ischemic disease; ejection fraction $15 \pm 3\%$), and continued until euvolemia. Patients were evaluated at each hospital day, at 30 days, and at 90 days. An average of $8,654 \pm 4,205$ ml was removed with 2.6 ± 1.2 8-hour ultrafiltration courses. Twelve patients (60%) were discharged in ≤ 3 days. One patient was readmitted in 30 and 2 patients in 90 days. Weight ($p = 0.006$), Minnesota Living with Heart Failure scores ($p = 0.003$), and Global Assessment ($p = 0.00003$) were improved after ultrafiltration at 30 and 90 days. B-type natriuretic peptide levels were decreased after ultrafiltration (from $1,236 \pm 747$ to 988 ± 847 pg/ml) and at 30 days (816 ± 494 pg/ml; $p = 0.03$). BP, renal function, and medications were unchanged. The results of this study suggest that in HF patients with volume overload and diuretic resistance, early ultrafiltration before intravenous diuretics effectively and safely decreases length of stay and readmissions. Clinical benefits persisted at 3 months after treatment [66].

The aim of the third study was to compare the safety and efficacy of ultrafiltration with the Aquadex System 100 device versus those of intravenous diuretics in patients with decompensated HF. Compared to the 20 patients randomly assigned to intravenous diuretics, the 20 patients randomized to a single, 8-hour ultrafiltration session had greater median fluid removal (2,838 vs. 4,650 ml; $p = 0.001$) and median weight loss (1.86 vs. 2.5 kg; $p = 0.24$). Ultrafiltration was well tolerated and not associated with adverse hemodynamic renal effects. The results of this study show that an initial treatment decision to administer ultrafiltration in patients with decompensated congestive HF results in greater fluid

removal and improvement of signs and symptoms of congestion than those achieved with traditional diuretic therapies [93].

The findings of these studies stimulated the design and implementation of the ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated HF (UNLOAD) trial [94]. This study was designed to compare the safety and efficacy of venovenous ultrafiltration and standard intravenous diuretic therapy for hospitalized HF patients with ≥ 2 signs of hypervolemia. Two hundred patients (63 ± 15 years; 69% men; 71% ejection fraction, $\leq 40\%$) were randomized to ultrafiltration or intravenous diuretics. At 48 h, weight (5.0 ± 3.1 vs. 3.1 ± 3.5 kg; $p = 0.001$) and net fluid loss (4.6 vs. 3.3 l; $p = 0.001$) were greater in the ultrafiltration group. Dyspnea scores were similar (fig. 2). At 90 days, the ultrafiltration group had fewer patients rehospitalized for HF [16 of 89 (18%) vs. 28 of 87 (32%); $p = 0.037$], HF rehospitalizations (0.22 ± 0.54 vs. 0.46 ± 0.76 ; $p = 0.022$), rehospitalization days (1.4 ± 4.2 vs. 3.8 ± 8.5 ; $p = 0.022$) per patient, and unscheduled visits [14 of 65 (21%) vs. 29 of 66 (44%); $p = 0.009$; fig. 3]. Changes in serum creatinine were similar in the two groups throughout the study. The percentage of patients with rises in serum creatinine levels >0.3 mg/dl was similar in the ultrafiltration and the standard care group at 24 h [13 of 90 (14.4%) vs. 7 of 91 (7.7%); $p = 0.528$], at 48 h [18 of 68 (26.5%) vs. 15 of 74 (20.3%); $p = 0.430$], and at discharge [19 of 84 (22.6%) vs. 17 of 86 (19.8%); $p = 0.709$].

There was no correlation between net fluid removed and changes in serum creatinine in the ultrafiltration ($r = -0.050$; $p = 0.695$) or in the intravenous diuretics group ($r = 0.028$; $p = 0.820$). No clinically significant changes in serum BUN, Na, chloride, and bicarbonate occurred in either group. Serum potassium <3.5 mEq/l occurred in 1 of 77 (1%) patients in the ultrafiltration and in 9 of 75 (12%) patients in the diuretics group ($p = 0.018$). Episodes of hypotension during 48 h after randomization were similar [4 of 100 (4%) vs. 3 of 100 (3%)].

Thus, the UNLOAD trial demonstrated that in decompensated HF, ultrafiltration safely produces greater weight and fluid loss than intravenous diuretics, reduces 90-day resource utilization for HF, and is an effective alternative therapy. It is also important to recognize the limitations of the UNLOAD trial. The treatment targets for both diuretics and ultrafiltration were not prespecified. Although treatment was not blinded, it is unlikely that a placebo effect influenced either weight loss or the improved 90-day outcomes associated with ultrafiltration.

The possibility that standard care patients were inadequately treated is diminished by the observation that improvements in symptoms of HF, biomarkers, and quality of life were similar in the two treatment groups throughout the study. Furthermore, 43% of patients in the standard care group lost at least 4.5 kg during hospitalization, a weight loss greater than that observed in 75% of patients enrolled in the Acute Decompensated Heart Failure National Registry [2]. Although the study did not include measurements of blood volume, plasma refill rate, interstitial salt and water, cardiac performance, or hemodynamics, ultrafiltration was not associated with excessive hypotension or renal or electrolyte abnormalities.

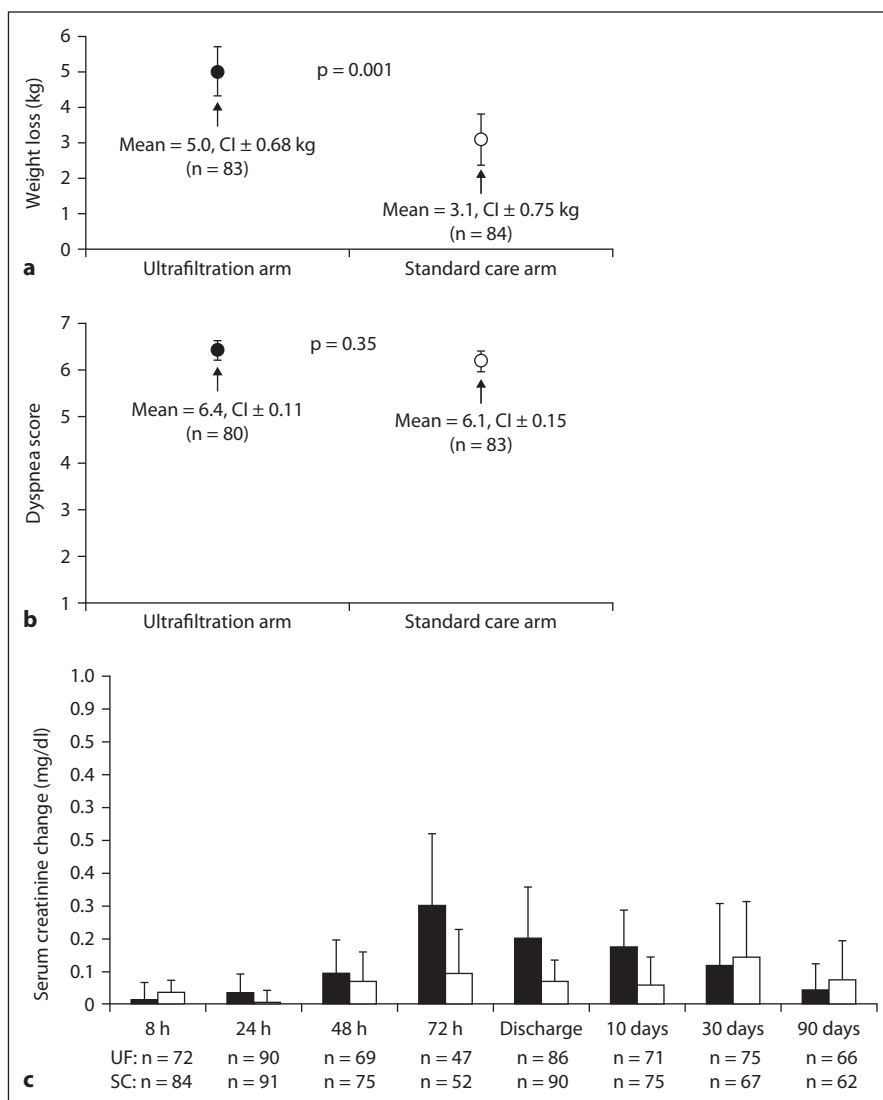


Fig. 2. Primary efficacy and safety endpoints in the UNLOAD clinical trial. Mean weight loss (**a**) and mean dyspnea score (from 1 – markedly worse, to 7 – markedly better; **b**) at 48 h after randomization in the ultrafiltration (F) and standard care (D) groups; p values are for the comparison between ultrafiltration and standard care. Error bars indicate 95% confidence intervals (CIs). **c** Mean changes from baseline serum creatinine levels at 8, 24, 48, and 72 h after randomization, at discharge and 10, 30, and 90 days in the ultrafiltration (i) and standard care (g) groups. Error bars indicate 95% CIs. Differences between groups at each time point were evaluated with the Wilcoxon rank-sum test; $p > 0.05$ at all time points for the comparison of mean change in serum creatinine levels between groups. Reproduced from Costanzo et al. [94], with permission.

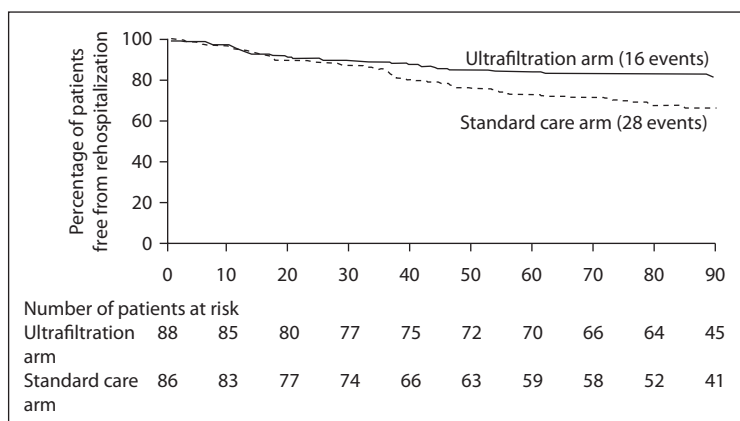


Fig. 3. Freedom from HF rehospitalization at 90 days in the UNLOAD clinical trial. Kaplan-Meier estimate of freedom from rehospitalization for HF within 90 days after discharge in the ultrafiltration and standard care groups ($p = 0.037$). Reproduced from Costanzo et al. [94], with permission.

In a subsequent analysis from the UNLOAD trial, the outcomes of 100 patients randomized to ultrafiltration were compared with those of patients randomized to standard IV diuretic therapy with continuous infusion ($n = 32$) or bolus injections ($n = 68$). Choice of diuretic therapy was by the treating physician [95].

At 48 h, weight loss (kg) was 5.0 ± 3.1 in the ultrafiltration group, 3.6 ± 3.5 in patients treated with continuous IV diuretic infusion, and 2.9 ± 3.5 in those given bolus diuretics ($p = 0.001$ ultrafiltration vs. bolus diuretic; $p > 0.05$ for the other comparisons). Net fluid loss (l) was 4.6 ± 2.6 in the ultrafiltration group, 3.9 ± 2.7 in patients treated with continuous IV diuretic infusion, and 3.1 ± 2.6 in those given bolus diuretics ($p < 0.001$ ultrafiltration versus bolus diuretic; $p > 0.05$ for the other comparisons). At 90 days, rehospitalizations plus unscheduled visits for HF/patient (rehospitalization equivalents) were fewer in the ultrafiltration group (0.65 ± 1.36) than in the continuous infusion (2.29 ± 3.23 ; $p = 0.016$ vs. ultrafiltration) and bolus diuretics (1.31 ± 1.87 ; $p = 0.050$ vs. ultrafiltration) groups. No serum creatinine differences occurred between groups up to 90 days. The results of this analysis from the UNLOAD clinical trial show that despite the lack of statistical difference in weight and fluid loss by ultrafiltration and IV diuretics administered by continuous infusion, more patients treated with ultrafiltration had a sustained clinical benefit, as indicated by fewer rehospitalizations and unscheduled HF office or ED visits. These findings support the hypothesis that removal of isotonic fluid by ultrafiltration, rather than hypotonic urine by IV diuretics, may contribute to the sustained clinical benefit associated with this treatment strategy. Among 15 ADHF

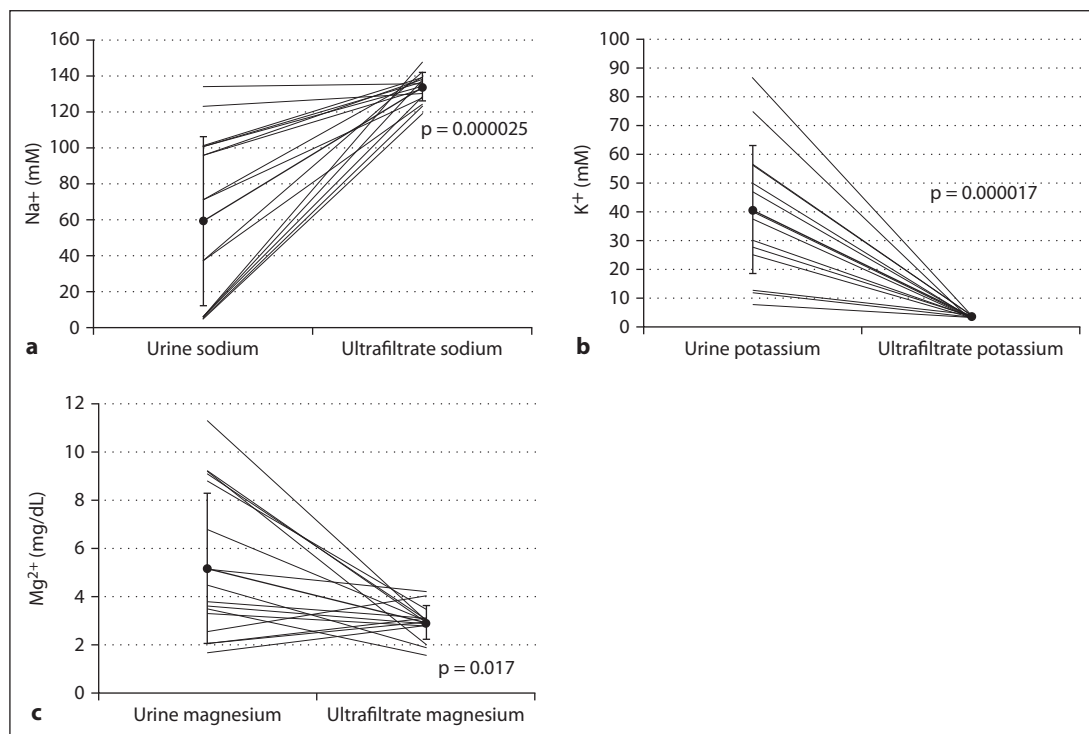


Fig. 4. Differential effects of ultrafiltration and furosemide on electrolytes. Na (a), potassium (b) and magnesium (c) concentration in urine prior to ultrafiltration and in the ultrafiltrate 8 h after initiation of ultrafiltration. Reproduced from Ali et al. [96], with permission.

patients treated first with a furosemide IV bolus and then with ultrafiltration because congestion persisted despite therapy with the IV loop diuretics, Na concentration in the ultrafiltrate sampled after 8 h of therapy was significantly higher than the urinary Na concentration after the IV furosemide bolus (134 ± 8.0 mM vs. 60 ± 47 ; $p = 0.000025$) [96]. Importantly, while the Na concentration of the ultrafiltrate was similar in all 15 patients, urinary Na concentration was highly variable, ranging from <20 to 100 mM in 13 (87%) of the subjects. Only 2 patients had urinary Na concentrations comparable to those of the ultrafiltrate [96]. Volume overload in HF patients is inevitably related to an increase and abnormal distribution of total body Na [7]. Thus, a treatment strategy which is simultaneously more effective in reducing total body Na and excess fluid may improve outcomes better than therapies which remove either hypotonic fluid or free water (fig. 4). Indeed, the results of the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan

showed that, compared to placebo, removal of excess free water with the vasopressin V_2 receptor blocker tolvaptan had no effect on long-term mortality or HF-related morbidity of patients hospitalized for worsening HF [97]. It is also possible that prehospitalization loop diuretic use itself may reduce the natriuresis achievable with IV loop diuretics [98].

Another key finding of this analysis is that hypokalemia, defined as serum potassium <3.5 mEq/l, occurred less frequently in the ultrafiltration-treated patients than in those treated with IV continuous diuretic infusion (1 vs. 22%; $p = 0.003$). Notably, in the study by Ali et al. [96], urine potassium concentration in response to IV furosemide administration was significantly higher than the concentration of this electrolyte in the ultrafiltrate after 8 h of therapy (41 ± 23 vs. 3.7 ± 0.6 mM; $p = 0.000017$). The observation that potentially deleterious excessive potassium losses associated with diuretic therapy may not occur with ultrafiltration raises the possibility that avoidance of electrolyte abnormalities may also account for the improved outcomes associated with ultrafiltration. Analyses from two large controlled clinical trials have shown that use of non-potassium-sparing diuretics in HF patients is an independent predictor of all-cause mortality and death due to either progression of HF or sudden cardiac death [10, 99].

In all three treatment groups, there was no correlation between net fluid loss during hospitalization and number of times patients were rehospitalized for HF. The absence of a relationship between volume of fluid removed and outcomes supports the hypothesis that the *composition* of the fluid removed may have a greater effect than its *quantity* on improving outcomes of congested HF patients. In 16 HF patients treated with either ultrafiltration or diuretics to achieve equivalent fluid removal, sustained improvement in functional capacity occurred only in the ultrafiltration-treated group [67]. Furthermore, compared to the diuretic group, the ultrafiltration group had lower plasma renin activity and norepinephrine and aldosterone levels up to 90 days after treatment [67]. The improved neurohormonal profile in the ultrafiltration group may be due to the fact that, unlike diuretics, ultrafiltration does not decrease Na presentation to the macula densa, an event which stimulates renin secretion and thus promotes Na and water reabsorption mediated by the RAAS [7, 100, 101]. Edema in fluid-overloaded HF patients is isotonic, and therefore eunatremic patients with edema have appreciable total body Na excess. Thus, loop diuretic-induced diuresis of hypotonic fluid will reduce excess total body water while failing to eliminate excess total body Na [7, 41, 102]. Incomplete resolution of total body Na excess may explain the return of congestion seen after hospitalization in patients treated with IV loop diuretics [2, 7, 67, 100, 101, 103, 104].

The UNLOAD trial has important limitations. In the UNLOAD study, treatment was not blinded and therefore the introduction of investigator bias cannot be excluded with absolute certainty. However, it is unlikely that a placebo effect influenced either weight loss or the improved 90-day outcomes associated

with ultrafiltration. The comparison of outcomes in the three groups, ultrafiltration, IV bolus and continuous loop diuretic infusion, was not prespecified. Additionally, for the UNLOAD patients randomized to the standard care group, the treating physician determined the diuretic treatment of the patient, including the choice of bolus injection versus continuous IV infusion of diuretics [94]. In the UNLOAD study, total Na removed by ultrafiltration versus that eliminated with the two IV diuretic treatment regimens was not measured. Serum and urine osmolality before and after treatment was not measured. In the UNLOAD trial, plasma renin activity, norepinephrine and aldosterone levels were not determined, and therefore it cannot be proven that the outcomes after ultrafiltration are better than those after treatment with either IV bolus or continuous diuretic infusion due to decreased neurohormonal activation with ultrafiltration.

The economic impact of ultrafiltration as an initial strategy for decompensated HF was not addressed in the UNLOAD trial. Although the costs associated with ultrafiltration during the index hospitalization may exceed those of IV diuretics, total cost over time may be lower because of decreased resource utilization for HF. An exhaustive pharmacoeconomic analysis of ultrafiltration therapy should evaluate many variables, including the amortized cost of the ultrafiltration device itself, the decreased cost of ultrafiltration filters associated with their use for longer periods of time, the savings resulting from decreased 90-day rehospitalization rates and reduced length of HF rehospitalization. On the other hand, assessment of health care expenses associated with IV diuretic therapy should consider the bed cost and the cost for adjunctive care, including the possible use of vasoactive drugs. In addition, costs to an individual hospital are highly dependent on numerous variables including nursing staffing models, bed allocation schemes, negotiated product acquisition costs, hospital geographic location and type (teaching vs. community hospital) and increased 90-day HF rehospitalization rates and duration.

Additional prospective, randomized studies are needed to confirm or refute the hypothesis that removal of isotonic rather than hypotonic fluid is a key factor in producing sustained clinical benefit in congested HF patients and to determine if clinical features predictive of natriuretic failure in response to diuretics can be identified and if diuretic strategies can be developed to effectively reduce total body sodium excess.

Conclusions

Of the ultrafiltration approaches described, the most practical are venovenous ultrafiltration techniques in which isotonic plasma is propelled through the filter by an extracorporeal pump. These approaches avoid an arterial puncture, remove a predictable amount of fluid and are not associated with significant

hemodynamic instability. Ultrafiltration has been used in patients with decompensated HF and volume overload refractory to diuretics. These patients generally have preexisting renal insufficiency and, despite daily oral diuretic doses, develop signs of pulmonary and peripheral congestion. Ultrafiltration and diuretic holiday may restore diuresis and natriuresis. Some patients with volume overload refractory to all available intravenous vasoactive therapies have had significant improvements in symptoms, hemodynamics, and renal function following ultrafiltration. A strategy of *early* ultrafiltration and diuretic holiday can result in more effective weight reduction and can shorten hospitalization.

Patients should not be considered for ultrafiltration if the following conditions exist: venous access cannot be obtained; there is a hypercoagulable state; systolic BP is <85 mm Hg or there are signs or symptoms of cardiogenic shock; patients require intravenous pressors to maintain an adequate BP, or there is end-stage renal disease, as documented by a requirement for dialysis approaches.

Ultrafiltration can be carried out in patients with hematocrit levels >40% only if it can be proven that hypovolemia is absent.

Many questions regarding the use of ultrafiltration in HF patients remain unanswered and must be addressed in future studies. These include optimal fluid removal rates in individual patients, effects of ultrafiltration on cardiac remodeling, influence of a low oncotic pressure occurring in patients with cardiac cachexia on plasma refill rates, and the economic impact of ultrafiltration to determine whether the expense of disposable filters is offset by the cost savings caused by reduced rehospitalization rates.

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Technical Aspects of Extracorporeal Ultrafiltration: Mechanisms, Monitoring and Dedicated Technology

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Abstract

Fluid overload may occur in patients with heart failure. Further complications may arise when cardiorenal syndromes develop and the kidneys are unable to eliminate the accumulated fluid. Diuretics represent the first line of treatment, although in some cases they may be ineffective or even dangerous for the patient. In these conditions, extracorporeal ultrafiltration may be required. Extracorporeal ultrafiltration can be performed continuously or intermittently, using dedicated machines. The goal is to remove the right amount of fluid without causing hemodynamic instability or further ischemia to the kidneys. For this purpose, special technologies are available and they can be utilized in combination to prevent iatrogenic complications. First of all, a complete analysis of heart and kidney function should be carried out. Then, an evaluation of biomarkers of heart failure and a careful analysis of body fluid composition by bioimpedance vector analysis should be carried out to establish the level of hydration and to guide fluid removal strategies. Last but not least, an adequate extracorporeal technique should be employed to remove excess fluid. Preference should be given to continuous forms of ultrafiltration (slow continuous ultrafiltration, continuous venovenous hemofiltration); these techniques guided by a continuous monitoring of circulating blood volume allow for an adequate restoration of body fluid composition minimizing hemodynamic complications and worsening of renal function especially during episodes of acute decompensated heart failure.

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Fluid overload refractory to medical therapy represents one of the most frequent indications for the application of extracorporeal therapies in critically ill patients. In the intensive care unit, patients may become fluid overloaded because of decreased urine output or fluid retention in heart failure and

cardiorenal syndromes [1, 2]. The critically ill patient often presents hemodynamic instability or multiple organ dysfunction, especially when sepsis or septic shock are present. In such circumstances, an accurate management of the fluid balance becomes mandatory to improve pulmonary gas exchanges and organ perfusion while maintaining stable hemodynamic parameters.

Continuous renal replacement therapies (CRRTs) represent a well-established form of renal support in intensive care. Fluid removal is operated by the CRRT machines through a process of extracorporeal ultrafiltration. Slow continuous ultrafiltration (SCUF) is a type of CRRT used to achieve safe and effective management of severe fluid overload when medical therapy proves inadequate. SCUF has been used as an adjunctive therapy for heart failure patients, achieving improvement in cardiac filling pressures, without dangerous reductions in circulating blood volume [3]. When a more complex manipulation of body fluid composition is required, continuous venovenous hemofiltration (CVVH) is utilized.

Extracorporeal Ultrafiltration Techniques

SCUF is a venovenous pump-driven technique utilizing an ultrafiltration control system to maintain the ultrafiltration rate at the desired levels [4]. Temporary venous catheters represent an efficient access to the circulation. Generally, SCUF can be performed with low blood flow rates (between 50 and 100 ml/min), and ultrafiltration rates between 100 and 300 ml/h according to fluid balance requirements. Because of the low ultrafiltration and blood flow rates required, relatively small surface area filters can be employed with reduced heparin doses to maintain circuit patency. The main purpose of treatment is to achieve volume control; therefore, no fluids are administered either as dialysate or replacement fluids [3]. Synthetic high-flux membranes are generally employed because of their excellent permeability and biocompatibility characteristics [3]. If additional blood purification or electrolyte equilibration is required, hemofiltration can be used. In this case, the ultrafiltration rate exceeds the target fluid balance and final balance is achieved by reinfusion of replacement solutions. Sessions of SCUF or CVVH generally last several days, while isolated ultrafiltration or hemofiltration sessions may be scheduled for 4–6 h intermittently on different days of the week. In intermittent sessions, the rate of fluid removal is generally higher with possible hemodynamic complications. The process of ultrafiltration consists of the production of plasma water from whole blood across a semipermeable membrane in response to a transmembrane pressure gradient. Because of the sieving capacity of ultrafiltration membranes, ultrafiltrate contains crystalloids but not cells or colloids. Therefore, the ultrafiltrate produced in extracorporeal treatments is iso-osmotic compared to plasma water. There are slight differences between ultrafiltrate and plasma water due to Donnan's equilibrium, but they can be considered practically negligible. The pressure gradient is generated by the classic Starling

forces including hydrostatic pressures in the blood and ultrafiltrate compartments and the oncotic forces generated by plasma proteins. The correlation between ultrafiltration rate and transmembrane pressure gradient describes membrane hydraulic permeability. The correlation is linear within a certain range of pressure. Beyond this limit, it tends to plateau due to the interference of plasma proteins and boundary layer formation at the blood-membrane interface.

One specific comment must be made concerning the difference between CVVH and all other techniques including dialysis and the use of diuretics. In all pharmacological and dialytic techniques, the removal of sodium and water cannot be dissociated and the mechanisms are strictly correlated. In particular, the diuretic effect is based on remarkable natriuresis, while ultrafiltration during dialysis may become hypo- or hypertonic depending on the interference with diffusion of other molecules such as urea. In such circumstances, water removal is linked to other solutes and dependent on the technique used. In SCUF, the mechanism of ultrafiltration produces a fluid which is substantially similar to plasma water except for a minimal interference due to Donnan effects. In such technique, ultrafiltration is basically iso-osmotic and iso-natric, and water and sodium removal cannot be dissociated with sodium elimination linked to sodium plasma water concentration. In CVVH and in hemofiltration in general, ultrafiltrate composition is definitely similar to plasma water, but sodium balance can be significantly affected by the sodium concentration in the replacement solution. Thus, sodium removal can be dissociated from water removal in CVVH obtaining a real manipulation of the sodium pool in the body, and this cannot be achieved with any other technique. The advantage is that not only plasma concentrations can be normalized but also the electrolyte content in the extracellular and possibly intracellular volume.

Ultrafiltration Equipment

Different machines have been proposed and utilized for CRRT [5], while intermittent isolated ultrafiltration has been mostly carried out with standard dialysis machines utilized in ultrafiltration mode. In contrast, only a few machines have been designed specifically for SCUF. In the US, the Aquadex system (CHF solutions, USA) has been used in some cases [6], whereas in Europe a significant use of the DEDYCA machine and its previous prototypes (Bellco, Mirandola, Italy) has been observed [7–9].

DEDYCA is a simple yet accurate piece of equipment. It is transportable and adequate to perform ultrafiltration therapies in different settings (fig. 1). The circuit is simple and consists of a venovenous circulation driven by a peristaltic pump, a highly permeable low surface area hemofilter and a precise ultrafiltration control system (fig. 2). The machine runs by a dedicated software and allows for an automatic fluid balance management. A heparin pump provides accurate continuous anticoagulation. Blood flow ranges between 0 and 100 ml/min, while



Fig. 1. The DEDYCA machine for SCUF in fluid-overloaded patients. The machine presents the following features: (a) dedicated software; (b) automatic management; (c) hematocrit sensor; (d) blood flow between 0 and 100 ml/min; (e) ultrafiltration speed between 0 ml/h and 1,000 ml/h; (f) heparin pump.

ultrafiltration rates can be scheduled between 0 and 1,000 ml/h. The disposable kit is self-loading, and it can be primed easily and rapidly (fig. 3). The priming volume of the circuit is less than 100 ml, allowing a significant hemodynamic stability during priming procedures. The system, once in place, can run for up to 24–48 h without interruption. After that time frame, replacement of the filter is recommended to prevent infectious complications and decreased efficiency.

Ultrafiltration Prescription and Monitoring

Extracorporeal ultrafiltration may require additional technology for a safe and smooth administration of the treatment. We might, for example, consider

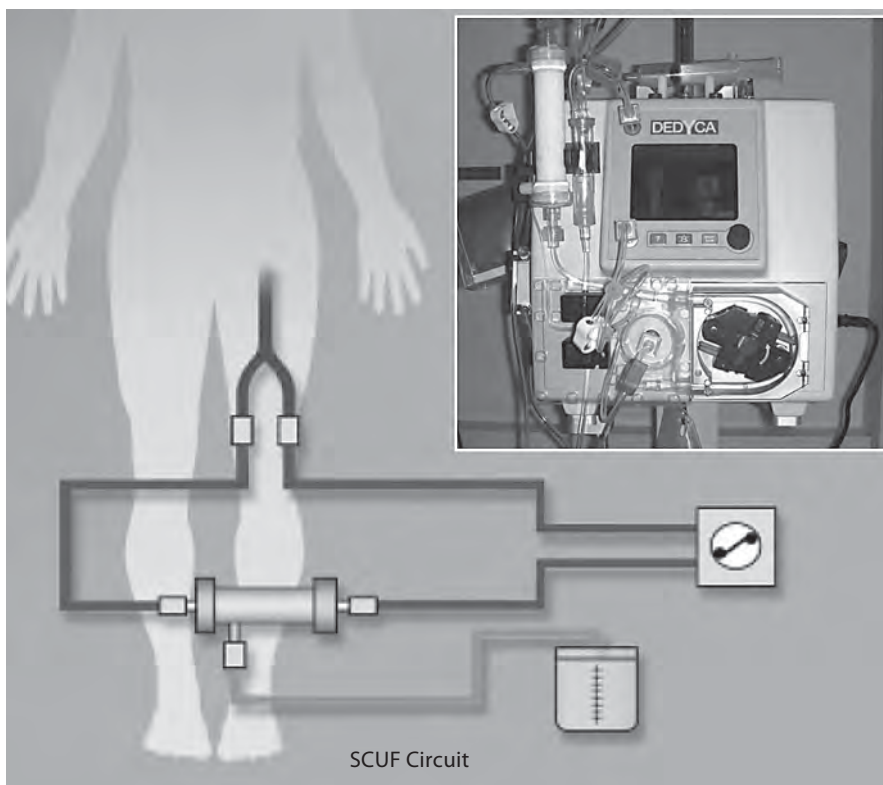


Fig. 2. Extracorporeal circuit of the DEDYCA machine with a view of its application in a patient.

monitoring of blood volume during treatment and analysis of body fluid status by bioimpedance.

The DEDYCA machine includes a hematocrit sensor to monitor blood volume during treatment. The system, based on a specific wavelength light sensor provides information on variations in blood volume in response to ultrafiltration. The system allows a continuous analysis of the intravascular refilling describing potential conditions in which hemodynamic instability may occur. The second aspect is represented by the overall body fluid status. This can be assessed by a bioelectrical impedance monitor, which can be utilized at several moments of the treatment. This system, through a bioimpedance vector analysis (BIVA), allows to establish with significant accuracy the level of overhydration and the target dry weight in an overhydrated patient. At the same time, the system allows to detect possible excess in fluid removal leading to iatrogenic hemodynamic instability due to excessive overall ultrafiltration volume. Using these two technologies, treatment can be monitored and thus guided towards an

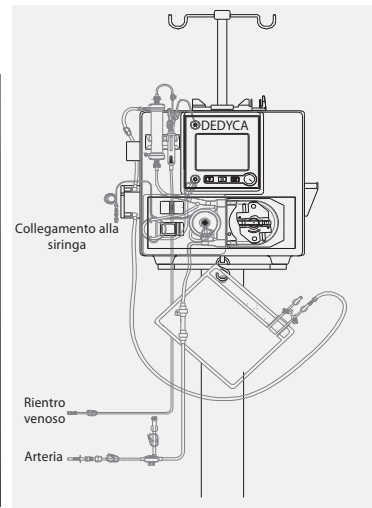
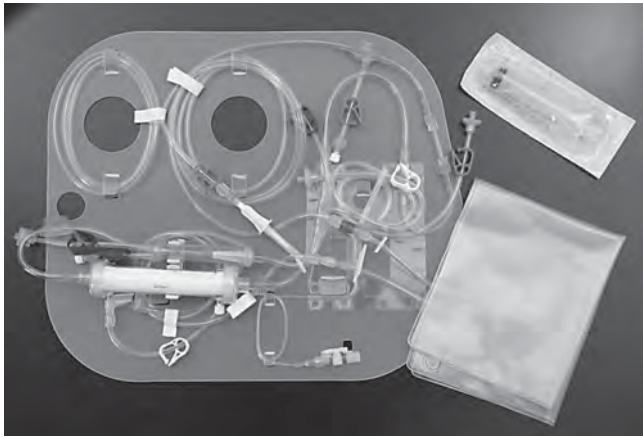


Fig. 3. DedyKit is the complete set of tubings that is loaded into the DEDYCA machine for extracorporeal ultrafiltration therapy.

ideal final level of patient's hydration. An adequate ultrafiltration therapy then requires a parallel determination of biomarkers (such as B-type natriuretic peptide and neutrophil gelatinase-associated lipocalin) that may help determine the level of overhydration and at the same time the potential damage to the kidney induced by excessive ultrafiltration rates.

Of course, other technologies can be used in critically ill patients to determine fluid status including noninvasive cardiac output monitoring, echocardiographic and Doppler analysis, stroke volume variation analysis, and finally invasive techniques such as Swan-Ganz catheters and associated direct pressure measurements. However, in clinical routine a combination of biomarker, BIVA and blood volume measurement may represent the optimal compromise for an adequate monitoring of ultrafiltration techniques (fig. 4).

As in the case of early fluid trials advocated by Rivers in patients with septic shock, we must advocate a rapid and effective fluid removal in patients that are admitted to the intensive care unit after an intensive fluid resuscitation therapy in the emergency department. But, how much and how fast can we or should we remove the excess of fluid? The requirements of an adequate ultrafiltration therapy when oliguria or anuria impede the normalization of fluid balance by diuretics are: (1) not to harm, (2) prescribe a fluid removal rate that is clinically tolerated, and (3) prescribe a correct amount of total negative fluid balance [10, 11].

It is our opinion that the first requirement can be met with SCUF and dedicated equipment. The second requirement can be met using technological support such as blood volume measurement that clearly describes the process

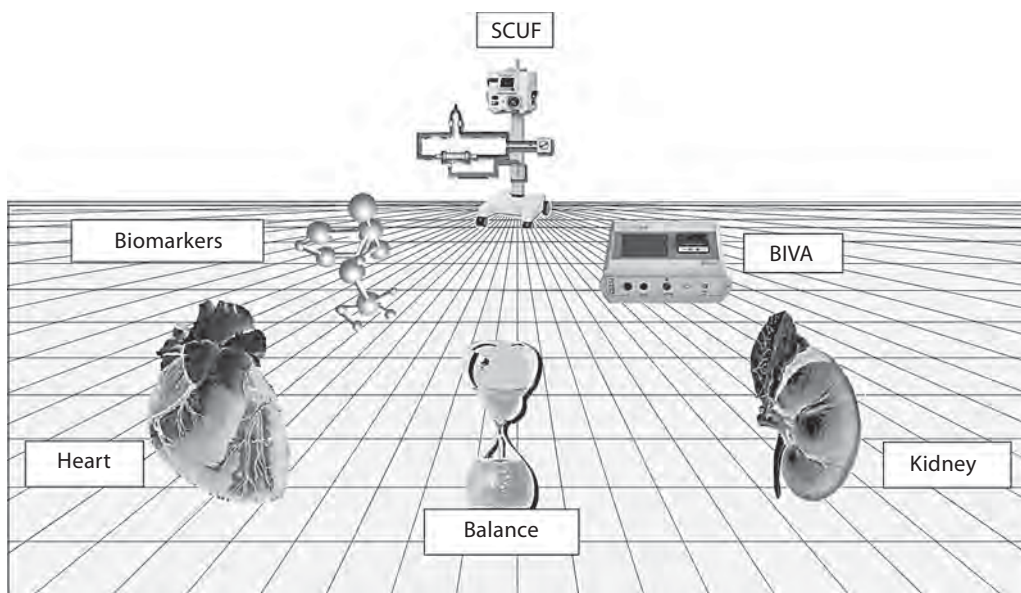


Fig. 4. The pathway for a correct management of fluid overload is staged as follows: (1) careful evaluation of heart and kidney function; (2) evaluation of heart and kidney biomarkers of organ damage together with BIVA-derived evaluation of fluid status, and (3) use of extracorporeal ultrafiltration where treatment can be indicated by previous steps, but it can also be guided by a continuous loop measurement of biomarkers, blood volume and BIVA.

of intravascular refilling rate and allows for the maintenance of a hemodynamically adequate circulating blood volume. The third requirement can be met by establishing a correct fluid status. While different approaches have been tried for this task, including hemodynamic parameters, filling pressures, stroke volume variation and other, we feel that the solid experience with BIVA acquired in the nephrology area should be extended to the intensive care patient. BIVA is based on the epidemiology of the specific resistivity and permittivity of whole-body bioelectrical measurements. Humans can be measured in vivo with the injection of alternating microcurrents at relatively high frequency (most commonly at 50 kHz) with a standard and well-established tetrapolar system method. The opposition to the AC stream is referred to as impedance, which on its turn from live soft tissue conductors is formed by a complex network of parallel and series resistive and capacitive conductors that are reflecting in a direct way the presence of fluids and cells. A wide dataset (collected so far from over 18,000 male and female Caucasians) of resistance (R), reactance (X_c), gender, stature height and age has been analyzed with a bivariate statistical analysis method on sex-separated specific impedance

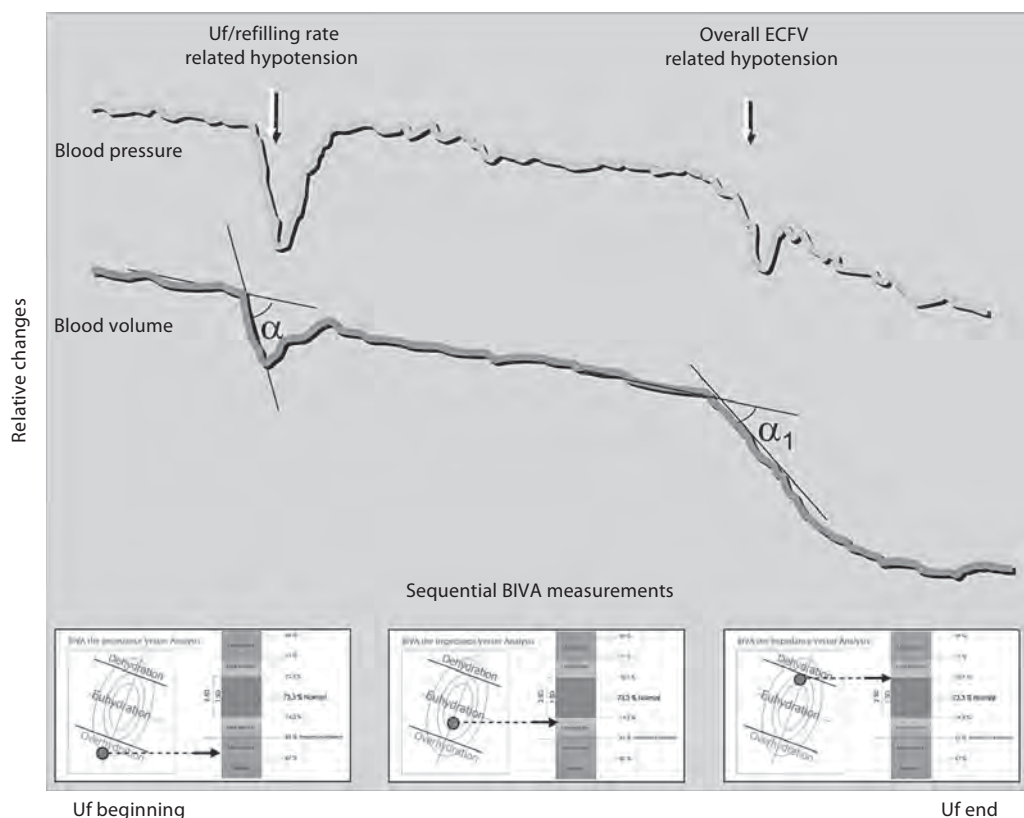


Fig. 5. Blood pressure and blood volume behavior in an overhydrated patient, where blood volume measurement and BIVA can guide both the rate and the amount of fluid removal by extracorporeal ultrafiltration (Uf). ECFV = Extracellular fluid volume.

values (R/height and Xc/height), and relevant confidence and tolerance limits norms have been published [12]. The nomograms have later been used to classify and manage hydration on miscellaneous states and diseases forms [13, 14]. The necessity of a simple ‘number’ or scoring system that could easily be associated with other ‘standard’ values such as B-type natriuretic peptide, blood pressure, etc. led to development of a numerical based hydration scale (EFG Z-analyzer), providing a rapid bedside tool that within a few minutes allows the physician to perform a highly sensitive and specific determination of hydration state. Multicentric trials in Europe and the USA are now in progress to validate the utilization of this method for the evaluation of hydration target values. Figure 5 describes a typical blood volume and blood pressure behavior in an overhydrated patient where blood volume measurement and BIVA can guide both the rate and the amount of fluid removal by extracorporeal ultrafiltration.

Towards Wearable Ultrafiltration Devices

The number of patients with symptomatic congestive heart failure (CHF) continues to increase in North America and Europe. As cardiac output falls, the natural compensatory response to arterial underfilling is increased neurohormonal activation, which paradoxically can lead to further reduction in cardiac output, compromising renal and gut blood flow [10]. This may result in deteriorating renal function and diuretic resistance. In these patients, the level of rehospitalization for acutely decompensated heart failure is generally high and the resulting costs for the society are becoming enormous. One future approach could be to create a truly wearable device that would allow patients to ambulate whilst being treated. To allow mobility, patients will require a dual lumen central venous access catheter coupled to a miniaturized blood pump with accurate battery-powered mini-pumps to regulate the ultrafiltration flow, and heparin infusion for anticoagulation [15]. We have performed the first human trial on such a prototype and published encouraging results [16]. Six volume-overloaded patients were treated for 6 h with a wearable ultrafiltration system. Blood flow through the device was around 116 ml/min with an ultrafiltration rate ranging from 120 to 288 ml/h, leading to an average of 151 mmol of sodium removed during the treatment. More importantly, during the study all patients maintained cardiovascular stability. This device designed to operate continuously can remove fluid at a slower hourly rate compared to standard intermittent hemodialysis. In this way, refilling of the plasma volume from the extravascular spaces can be maintained, thus avoiding episodes of cardiovascular instability. Further developments are underway to create new devices designed to allow fluid-overloaded patients with symptomatic CHF to be managed as outpatients, or day ward patients.

Conclusions

CHF or other clinical conditions characterized by refractory severe fluid overload should be managed by a multidisciplinary taskforce considering the complex pathophysiologic and biochemical mechanisms involved in the pathogenesis of the disorder. At present, theoretical knowledge and technological developments have made SCUF one of the safest and effective approaches for fluid overload in patients refractory to pharmacological treatment. Indications for these treatments have widely increased aiming at improvement of patient's quality of life, although a curative effect cannot be expected.

The reduction in hospitalization, or at least the need for intensive care hospitalization, may represent a remarkable result and should definitely be explored on a large prospective scale. The potential for a home-based application utilizing transportable or even wearable devices represents a further stimulating concept to be investigated. Such an approach should be explored testing new

technologies in the coming years in the attempt to find simple and cost-effective answers to the enormous clinical demand.

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Use of Brain Natriuretic Peptide and Bioimpedance to Guide Therapy in Heart Failure Patients

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Abstract

The key management goals for the stabilization of patients admitted for acutely decompensated heart failure (ADHF) include relief of congestion and restoration of hemodynamic stability. Nevertheless, in spite of clinical improvement, many patients are discharged with hemodynamic congestion. In response to volume expansion, the heart secretes the brain natriuretic peptide (BNP) with a biological action that counter-regulates the activation of the renin-angiotensin-aldosterone system. Since BNP is released by increased volume load and wall stretch, and declines after treatment with drugs of proven efficacy, on the basis of an improvement in filling pressures the level of BNP has been proposed as a 'measure' of congestion. The BNP level of a patient who is admitted with ADHF comprises two components: a baseline, euvolemic 'dry' BNP level and a level induced by volume or pressure overload ('wet' BNP level). So, the prognostic value of BNP during hospitalization depends on the time of measurement: from the lowest on admission when congestion is present (wet BNP) to the highest on clinical and instrumental stability (dry BNP), following the achievement of normohydration, as determined by fluid volume measurement. Euvolemia can be set as the primary goal of treatment for ADHF with dry BNP concentration as a target for discharge other than improvement of symptoms, because high BNP levels predict rehospitalization and death. Discharge criteria utilizing both BNP and hydration status measurement which account for the heterogeneity of the patient population and incorporate different strategies of care should be developed. This could in the next future offer an aid in monitoring heart failure patients or actively guiding optimal titration of therapy.

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Despite advances in pharmacological therapy and intensive application of guidelines [1], acute decompensated heart failure (ADHF) is the leading cause of hospitalization [2] and readmission [3] in many hospitals worldwide. As a

consequence, all intervention strategies for acute heart failure in the field of health economics mainly focus on the early identification of clinical and instrumental indicators, which allow in-hospital treatment and stratification of high-risk patients at discharge [4].

ADHF is a largely hemodynamic disorder, with 90% of hospitalized patients presenting with volume overload (evaluated on a clinical basis) [5]. The key management goals for the initial stabilization of patients include relief of congestion and restoration of hemodynamic stability to prevent renal dysfunction.

Under conditions of blood pressure overload and in response to blood volume expansion, the heart secretes natriuretic peptides with a biological action that counter-regulates the activation of the renin-angiotensin-aldosterone system [6]. Plasma levels of brain natriuretic peptide (BNP) reflect left ventricular dysfunction, with high filling pressures secondary to volume overload, and decrease in concert with a reduction in either filling pressures or body hydration during acute diuretic and vasoactive therapy [7, 8].

In spite of clinical improvement, many patients are discharged with signs and symptoms of ‘hemodynamic’ congestion. It has been demonstrated that most patients hospitalized for acute heart failure show evidence of volume overload at discharge [9]. Furthermore, subclinical volume expansion may cause diuretic undertreatment, leading to symptom worsening and disease progression with an unfavorable outcome [10]. Episodes of decompensation requiring hospitalization are characterized by hemodynamic deterioration and water and sodium retention. A recent review by Gheorghiade and Pang [11] states that strategies for discharge after complete resolution of signs and symptoms compared with earlier discharge with residual symptoms and close follow-up for further optimization should be investigated.

The treatment strategy of patients with ADHF in the hospital setting relies on the understanding of the hemodynamic determinant(s) of elevated BNP levels.

Rationale for Lowering Natriuretic Peptides in Acute Decompensated Heart Failure

Since BNP release is triggered by increased volume load and wall stretch [6], the level of BNP/NT-proBNP has been proposed as a ‘measure’ of congestion [12]. The plasma concentrations of BNP increase in unstable patients with ADHF and decline after treatment with drugs of proven efficacy (diuretics, vasodilators, ACE inhibitors, angiotensin receptor blockers, beta-blockers and aldosterone antagonists), on the basis of an improvement in filling pressures [7, 8]. It has been hypothesized that the BNP level of a patient who is admitted with ADHF comprises two components: a baseline, euvolemic ‘dry’ BNP level and a level induced by acute pressure or volume overload (‘wet’ BNP level) [13]. Valle et al. [14] demonstrated that reduction in BNP levels

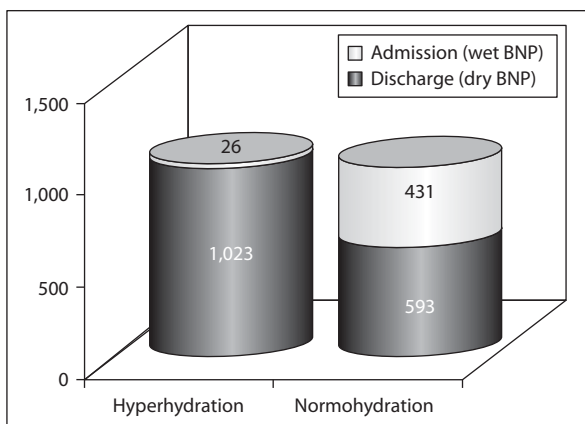


Fig. 1. BNP changes according to hydration status at discharge as determined by BIVA.

correlates with reduction in fluid overload and improvement of body hydration status (fig. 1).

The prognostic value of BNP during hospitalization depends on the time to measurement: it is the lowest on admission when congestion is present (wet BNP), intermediate during episodes of clinical stability (dry BNP), and the highest after clinical and instrumental stability following the achievement of normohydration as determined by fluid volume measurement (optivolemic BNP) [14].

Bettencourt et al. [9] found that variations of natriuretic peptides during hospitalization (a reduction of >30% from baseline) as well as predischarge levels are predictors of hospital readmission and death within 6 months. Logeart et al. [15] examined the prognostic value of serial admission and discharge BNP measurements among 105 patients surviving hospital stay for decompensated heart failure. Patients with a predischarge BNP level of 350–700 pg/ml had a five times higher risk of death or rehospitalization for heart failure than patients with a predischarge BNP <350 pg/ml. A predischarge BNP level >700 pg/ml was associated with an increased risk of death and rehospitalization for heart failure by a factor of 15 and reached a rate of 90%. Cournot et al. [16] reported data from a prospective cohort study of 61 consecutive patients hospitalized for decompensated heart failure. Cardiac death or readmission were predicted by changes in BNP, with the poorest prognosis in patients who did not achieve a decrease of at least 40%.

Current evidence suggests that whatever the risk profile of the patient studied, a correct interpretation of ‘BNP variations’ in the acute phase has implications for risk stratification as a result of a dynamic process. BNP changes during hospitalization are strongly dependent on resolution of congestion, and elevated BNP levels at discharge usually reflect persistent congestion.

BNP concentrations when euvolemia is achieved are closely related to both functional class and prognosis in heart failure, and either 'predischarge BNP values' or 'changes in BNP from admission to discharge' predict medium-term prognosis [14, 17].

It is well-known that plasma BNP levels are affected by the presence of congestion and volume overload. However, it is worth noting that dry BNP levels at discharge for prognostic purposes are often subjective and loosely based on clinical criteria.

Use of Bioimpedance Vector Analysis and Brain Natriuretic Peptide to Guide Therapy in Patients with Acute Decompensated Heart Failure

The prognostic role of neurohumoral markers in ADHF during hospitalization is of great interest and clinical relevance. In patients admitted for ADHF, BNP levels rapidly decrease after short-term therapeutic interventions [7, 8], and the reduction in BNP levels correlates with a reduction in fluid overload and an improvement in body hydration status [14, 18]. However, growing evidence shows that hypervolemia by itself is independently associated with mortality [19–22]. Several indices have been employed to assess hydration status, including changes in body weight and hematologic, urinary, and cardiovascular indices. Nevertheless, targeting a specific reduction of body weight is often challenging because of the difficulty in defining adequate hydration status. Recent studies have suggested minimal weight changes before, during and after an episode of acute heart failure. The ADHERE registry reported that body weight was not decreased but rather increased during hospitalization in about half of the patients admitted for heart failure.

Evidence from the last decade supports the use of bioimpedance vector analysis (BIVA) to monitor hydration status [23–26]. Notwithstanding certain limitations (e.g. dependence on factors such as skin temperature, food or drink consumption, and body posture during measurement), BIVA is a noninvasive and practical method for assessing total body water. As a consequence, BIVA can be used to guide fluid-related therapies. It allows a rapid, accurate and noninvasive determination of body hydration status, correlates with NYHA class and seems to have a high diagnostic accuracy in the differential diagnosis of heart failure-induced dyspnea [27]. The relationship between body hydration status and BNP levels in patients receiving diuretic therapy remains to be clearly elucidated in the setting of ADHF. The adverse effects of diuretic use on ADHF may also cause acute renal injury by further reducing renal perfusion, glomerular filtration rate, and responsiveness to natriuretic peptides regardless of whether systolic function is decreased or preserved [28]. BIVA adds useful information to standard clinical parameters in monitoring patients with congestion during diuretic treatment. Most importantly, BNP/BIVA-guided management allows

to detect dry BNP values avoiding unnecessary overtreatment of patients with unrecognized body normohydration or dehydration resulting in renal impairment. BNP levels measured during clinical stability should reflect euvolemia or optovolemia defined as the attainment of adequate hydration to maintain renal function. Moreover, BNP levels may be persistently elevated even after adequate hydration has been achieved due to myocardial stretching (dry BNP). BNP concentrations are also found to vary considerably from one measurement to another, with values during clinical stability tightly correlated with the disease state and the underlying cardiac dysfunction. Therefore, it can be reasonably hypothesized that in a sizeable proportion of patients BNP levels at discharge, i.e. during clinical stability, do not truly reflect dry weight BNP, especially in those overtreated with diuretics. As a consequence, decompensated patients show wide fluctuations in BNP concentration that may also exhibit significant increases with respect to values measured during clinical stability.

This concept has been stressed in a recent consensus paper on natriuretic peptides in clinical practice [12]. It suggests predischARGE BNP/NT-proBNP as a tool to establish the patient's 'dry weight', although patients often need additional diuresis after discharge. Our aim is to extend this concept to include the use of BIVA as an adjunct to support clinical decision making. In a previous study from our research group, the extent and rapidity of BNP changes during hospitalization (an average of 5.5 days) were shown to be a reliable outcome predictor in ADHF [14]. This study demonstrates that, during hormone-guided treatment, variations in BNP levels and changes in bioelectrical impedance as a surrogate marker for body hydration status allow appropriate timing of patient discharge and predict the occurrence of cardiovascular events at 6 months. We retrospectively evaluated 186 patients admitted with ADHF. Therapy was titrated according to BNP levels, and bioelectrical impedance was measured serially. A target value of <250 pg/ml was reached in 54% of patients. A BNP value of <250 pg/ml at discharge predicted a 16% event rate at 6 months, whereas a BNP value of >250 pg/ml was associated with a far higher rate of adverse events (78%). No significant differences in event rates were found in relation to the time necessary to obtain a reduction in BNP levels below 250 pg/ml (fig. 2). This study is consistent with findings from other authors [7, 8, 18]. In particular, Johnson et al. [8] reported that neurohormonal activation rapidly decreases after short-term therapy tailored to decrease severely elevated filling pressures in patients admitted for class III–IV heart failure. Furthermore, bioelectrical impedance analysis seems to be able to monitor diuretic therapy in acute heart failure as well as to assess serial changes in body fluids [18, 26] and increases the usefulness of BNP as a 'guide' to treatment, as previously reported [14, 29]. This study extends these observations to hospitalized patients, showing that BNP can be used to guide treatment during acute heart failure. For strictly clinical purposes, the patients admitted for acute heart failure who respond quickly to intravenous diuretics and experience a decline in BNP values below 250 pg/ml (reaching

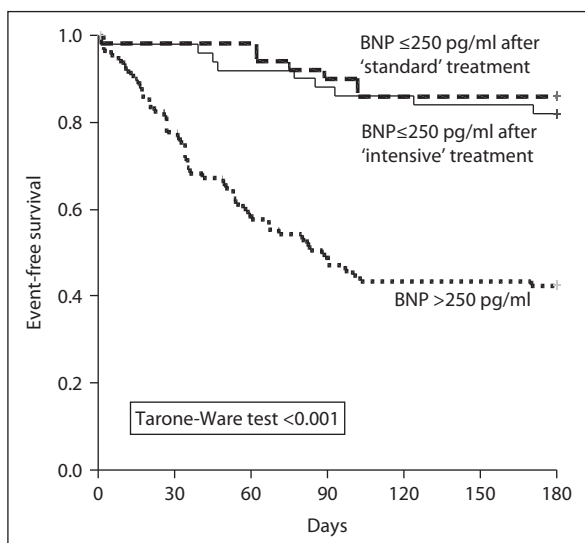


Fig. 2. Kaplan-Meier curves showing the cumulative incidence of death and readmission according to predischARGE BNP levels.

euvolemia and clinical stability) may be safely discharged avoiding unnecessary prolonged hospitalizations. Conversely, clinically stable patients with BNP levels still elevated above 250 pg/ml probably deserve further evaluation to ascertain subclinical volume overload amenable to more aggressive treatment, preventing inappropriate discharge.

Conclusion

Patients hospitalized for heart failure represent a heterogeneous population, and the identification of those who may benefit from more aggressive intervention is a critical issue that remains challenging.

In patients with congestion, a strong relationship does exist between clinical signs of fluid retention and increased BNP levels. Euvolemia can be set as the primary goal of treatment for ADHF with dry BNP concentration as a target for discharge other than improvement of symptoms, because high BNP levels not only predict rehospitalization within 30 days but also indicate high mortality rates. The addition of BIVA (a simple, noninvasive tool to objectively measure body water) to serial BNP measurement may provide more accurate risk stratification, especially in patients receiving diuretic therapy.

Discharge criteria utilizing both BNP and BIVA which account for the heterogeneity of the patient population and incorporate different strategies of care

should be developed. This could in the future offer an aid in monitoring heart failure patients or actively guiding optimal titration of therapy.

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Fluid Management in Pediatric Intensive Care

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Abstract

Fluid balance management in pediatric critically ill patients is a challenging task, since fluid overload (FO) in the pediatric ICU is considered a trigger of multiple organ dysfunction. In particular, the smallest patients with acute kidney injury are at highest risk to develop severe interstitial edema, capillary leak syndrome and FO. Several studies previously showed a statistical difference in the percentage of FO among children with severe renal dysfunction requiring renal replacement therapy. For this reason, in children priority indication is currently given to the correction of water overload. If this concept is so important in the critically ill small children, where capillary leak syndrome is a dramatic manifestation, it has probably been underestimated in critically ill adults and only recently re-evaluated. The present review will shortly describe nutrition strategies in critically ill children, it will discuss dosages, benefits and drawbacks of diuretic therapy, and alternative diuretic/nephroprotective drugs currently proposed in the pediatric setting. Finally, specific modalities of pediatric extracorporeal fluid removal will be presented. Fluid management, furthermore, is not only the discipline of removing water: it should also address the way to optimize fluid infusions and, above all, one of the most important fluids infused to all ICU patients with renal dysfunction: parenteral nutrition.

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Pediatric Fluid Overload

The reported mortality rates for critically ill children requiring dialysis range from 35 to 73% [1]. However, more recent pediatric acute kidney injury (AKI) demographic data have stratified diagnoses and clarified outcome numbers, suggesting that refinement of variables, use of severity of illness scores, and subsequent earlier intervention may lead to improved outcomes [1]. Nevertheless, current clinical approach to the child with renal dysfunction and/or fluid

overload (FO) secondary to sepsis would lead the operators to administer aggressive diuretic use, since the patient is still making urine, rather than early initiation of renal replacement therapy (RRT). In truth, diuretics may be not beneficial: it is well established in the adult population that diuretics do not prevent the occurrence of AKI and diuretic support has been associated with increased mortality rates [2]. Perhaps the most important development in the approach to AKI in pediatrics comes from the Prospective Pediatric Continuous Renal Replacement Therapy (ppCRRT) registry [3, 4]. This group and others have published several pediatric-specific observational studies showing that the degree of FO is an independent predictor of mortality in the pediatric group [5–7]. FO at CRRT initiation is calculated in children as follows:

$$\frac{\text{Fluid in} - \text{fluid out}}{\text{ICU admission weight}} \times 100$$

where ‘fluid in’ and ‘out’ are the fluidic intake and outtake on a given day.

The ppCRRT showed that survival rates in patients with multiorgan dysfunction syndrome were significantly better for patients with less than 20% FO (58% survival rate) versus greater than 20% FO (40% survival rate) at CRRT initiation, even though the pediatric risk of mortality scores were similar in the two groups at pediatric ICU admission or CRRT initiation [5]. The majority of the 116 patients analyzed in this study had sepsis (39%) as the primary disease entity requiring RRT.

However, pediatric risk mortality calculation is rather imperfect, and it is still possible that more severely ill patients are those who receive the relatively higher amount of fluids, and this could explain the more positive fluid balance of non-surviving patients. A prospective trial should now definitely clarify if this group would really benefit from a goal-directed aggressive ultrafiltration therapy.

Diuretics

Loop diuretics are the most used in the critically ill children, and furosemide is by far the most popular one [8]. Dosage and administration modality vary from boluses (1 mg/kg every 12 or 8 h) to continuous infusion (up to 10–20 mg/kg/day). The administration strategy in these patients has been recently reevaluated in the light of the results obtained in post-heart surgery infants treated with continuous vs. intermittent furosemide. Furosemide continuous infusion has been demonstrated to be generally more advantageous if compared to bolus administration in that it yields an almost comparable urinary output with a much lower dose, less hourly fluctuations [9] and less urinary wasting in sodium and chloride [10]. Doses of furosemide continuous infusion range from 0.1 to 0.2 mg/

kg/h. The increase in the initial dose until the desired urinary output is reached is the most commonly used strategy. However, in a 3-day trial on 13 post-heart surgery infants and children, van der Vorst et al. [11] noted that a mean starting dose of 0.093 required a significant increase to 1.75 mg/kg/h in 10/13 patients without reaching furosemide ototoxic levels. These authors suggested a starting dose of 0.2 mg/kg/h and eventual tapering. The major side effects of diuretic use are electrolyte disturbance (hypokalemia and hyponatremia), metabolic alkalosis with hypochloremia and diuretic resistance. This last effect consists in an absolute or relative inefficiency of diuretic standard dosing and may depend on heart failure per se (inability to reach the optimal peak intraluminal levels of drug; hypoalbuminemia that causes less intravascular binding of the diuretics and less delivery to the proximal tubular cells), hyponatremia (hyperaldosteronism, vasopressin production and less free water excretion), and the so called 'bracking effect' (decreased clinical responsiveness to diuretics with time due to possible sodium retention secondary to volume changes and activation of the RAAS and adrenergic mechanisms). Strategies to overcome diuretic resistance include use of continuous infusions and increased dosages of loop diuretics, use of combined therapy to block sodium resorption at multiple sites of action, correction of electrolyte imbalance, metabolic derangements and excessive intravascular depletion [8].

Recently, there has been a great interest in the use of fenoldopam, a dopamine-receptor agonist. Fenoldopam selectively binds to dopamine DA 1 receptors on smooth muscle cells of renal and splanchnic vascular beds. Activation of these receptors increases intracellular cyclic adenosine monophosphate (cAMP)-dependent protein kinase A activity, enhancing relaxation of vascular smooth muscle [12]. In the kidneys, increased concentration of cAMP in the proximal tubules and medullary portion of the ascending loop of Henle inhibits of the the sodium-potassium adenosine triphosphatase pump and the sodium-hydrogen exchanger. Fenoldopam infusion blunts aldosterone production and results in increased renal blood flow, urinary sodium excretion, and urine output. Fenoldopam is rapidly titratable, with an elimination half-life of about 10 min [13]. In a retrospective series of 25 postcardiopulmonary bypass (CPB) neonates, Costello et al. [14] reported a significant improvement in diuresis with the use of fenoldopam as compared with chlorothiazide and furosemide. Despite overt limitations of the study (retrospective, cardiac output and oxygen delivery not measured, diuresis improvement possibly due to renal injury natural course), fenoldopam might represent an important tool in these patients, often resistant to conventional diuretics. In a recent prospective controlled trial in post-CPB neonates, low-dose fenoldopam infusion did not show beneficial effects in urine output compared with a control population [15]. Fenoldopam did not significantly affect any of secondary outcomes (AKI incidence, fluid balance control, time to sternal closure, time to extubation and time to ICU discharge). A slight trend to a higher urine output and a more negative fluid

balance early after surgery could be observed. Fenoldopam did not cause any side effect and drug-related tachycardia or hypotension. The rationale for using this agent in such a trial came from experimental and adult clinical studies. Low-dose fenoldopam (0.1 µg/kg/min) was selected for this pilot experience because this was the first prospective study in children. However, many previous studies in adults administered similar dosages with positive results [16, 17]. In this light, it is possible that neonatal kidneys were relatively resistant to stimulation of DA1 receptors related to ontogenic differences in receptor density, affinity, coupling to intracellular second messengers or more distal mechanisms [18]: these receptors might require higher fenoldopam doses to achieve significant clinical effects. Further studies are required to determine if larger doses are beneficial in neonates undergoing cardiac surgery.

Renal Replacement Therapy in Critical Care Infants

The indication for RRT in pediatric patients has changed through the years and the present tendency is that of a wider application of this kind of treatment [19]. In our opinion, this is due to two main causes. (1) Although no clear recommendation is made for the application of RRT in patients without acute renal failure, it is now widely accepted that RRT is able to positively affect the clinical course of the multiple organ disease syndrome. (2) The prevention of fluid accumulation has been recently associated with improved survival [19]. In post-CPB children with AKI, the application of preventive dialysis has been proposed years ago [20] and it has recently been associated with very low mortality in these patients [21, 22]. The two dialysis modalities most frequently used in infants are peritoneal dialysis (PD) and CRRT.

Peritoneal Dialysis

PD is relatively easy to perform, it does not require heparinization or vascular access (often complicated in infants), and it is generally well tolerated also in hemodynamically unstable patients [23]. Nonetheless, one of the main disadvantages of PD in these patients is a relative lack of efficiency especially in water removal with direct consequences on fluid balance and frequent limitation of parenteral nutrition in particular when treatment of a highly catabolic patient is required. Given these limitations, the early application of PD in order to achieve the prevention and treatment of FO is presently accepted [24]. In particular, infants and children with specific risk factors for AKI should be considered for the preventive use of PD. In our center, the intraoperative placement of a PD catheter in post-cardiosurgical children is a routine procedure [25, 26]. Sorof et al. [20] described an extraordinary high survival rate (80%) in a group of infants with post-heart surgery AKI in which PD was started much earlier than in other studies (time to PD application after surgery: 5–40 h). Although a very

limited experience, this study confirms that prevention of renal failure and/or fluid accumulation directly affects survival in these patients. PD is known to offer a limited depurative performance if compared with extracorporeal techniques [26]. Moreover, in hemodynamically unstable infants, the application of high dialysate volumes to increase PD clearance is difficult. Unfavorably, modifications of atrial, mean pulmonary artery and systemic pressure have been observed in chronic PD and in children [27]. For this reason, a PD prescription of 10 ml/kg, previously defined as 'low volume PD', is commonly prescribed during neonatal RRT [23]. In recent years, a long debate has been ongoing about the beneficial effect of removing other solutes such as inflammation mediators through RRT [19]. As with CRRT (see below), PD is able to remove these mediators. Bokesch et al. [28] have measured significant levels of proinflammatory molecules and cytokines on peritoneal fluid after CPB in neonates. In one study, Dittrich et al. [29] showed a renoprotective influence of PD related to proinflammatory cytokine removal in post-heart surgery newborns. These authors hypothesized that the removal of glomerular-filtrated proinflammatory interleukins could protect renal tubular cells from postischemic damage. In the same study, interleukin clearance by ultrafiltration, by PD and by native kidney was compared. Ultrafiltration clearance was more than 1,000 times and by PD more than 100 times more effective as interleukin clearance by the kidney [29].

Continuous Renal Replacement Therapies

Both ultrafiltration and solute clearance occur rather slowly in patients undergoing PD. Consequently, PD may not be the optimal modality for patients with severe volume overload who require rapid ultrafiltration, or for patients with severe life-threatening hyperkalemia who require rapid reduction in serum potassium. Moreover, the amount of ultrafiltration is often unpredictable due to the impaired peritoneal perfusion in hemodynamically unstable patients like post-heart surgery infants. In such conditions, the ultrafiltration capacity of PD may not cope with the desired amount of fluid removal and, if scarce, it is obligatorily dedicated to patient's weight loss rather than to the balance of nutrition intake with subsequent risk of malnutrition in hypercatabolic patients. These limitations of PD explain the increasing utilization of extracorporeal dialysis in critical pediatric patients [30] and in post-heart surgery infants [31]. Extracorporeal dialysis can be managed with a variety of modalities, including intermittent hemodialysis, and continuous hemofiltration or hemodiafiltration. The choice of dialysis modality to be used is influenced by several factors, including the goals of dialysis, the unique advantages and disadvantages of each modality, and institutional resources. Intermittent dialysis may not be well tolerated in infants because of its rapid rate of solute clearance [32] and in particular in hemodynamically unstable pediatric cardiac surgery patients [33]. These children are generally treated by CRRT that provides both fluid and solute re-equilibration and proinflammatory mediator removal. Commercially available

circuits with reduced priming volume together with monitors providing an extremely accurate fluid balance have rendered CRRT feasible in infants [34, 35]. Concerning the removal of proinflammatory mediators, post-heart surgery infants are the most exposed to the risk of water accumulation, AKI and inflammation due to the massive exposure of blood to the artificial surface of CPB. However, when the exact moment of the renal-inflammatory injury (i.e. CPB) is predictable, post-heart surgery patients receive ultrafiltration already during CPB in a preventive way with the filter placed in parallel with the CPB circuit in order to remove inflammatory mediators from the beginning of their generation. There is some evidence that this approach is able to exert positive effects on hemodynamics, metabolism and inflammation in the postoperative period [36, 37]. Furthermore, the analysis of this period has revealed a significant correlation between intraoperative fluid balance and cardiac function [38].

With regard to the recommended CRRT modality during pediatric AKI, Parakininkas and Greenbaum [39] compared in vitro the solute clearance in three modes of CRRT at the low blood flow rates typically used in pediatric patients and concluded that postdilution continuous venovenous hemofiltration (CVVH) and continuous venovenous hemodialysis (CVVHD) gave nearly equivalent clearances. At the low blood flow rates used in pediatric patients, which raise concerns about high ultrafiltration during postdilution CVVH causing excessive hemoconcentration and filter clotting, CVVHD appeared to be the optimal modality for maximizing clearance of small solutes during CRRT. Nevertheless, if we consider the advantages of hemofiltration with respect to hemodialysis on the clearance of medium and higher molecular weight solutes together with the increased risk of filter clotting, predilution hemofiltration might be the preferred modality in small patients. There are no randomized trials guiding the prescription of CRRT in children; a small solute clearance of $2 \text{ l/h} \times 1.73 \text{ m}^2$ has been recommended in children [40].

Catheter size ranges from 6.5 f (7.5 cm long) for <10 kg patients to 8 f (15–20 cm long) for 11- to 15-kg patients. Blood priming may be indicated if more than 8 ml/kg of patient's blood is necessary to fill CRRT circuit. Full anticoagulation must be always maintained in order to avoid excessive blood loss in the case of circuit clotting [41].

Pediatric Nutrition

Children with AKI and sepsis are often at risk for undernutrition. Undernutrition can be exacerbated further by fluid restriction even after RRT has been initiated [42]. Inadequate nutrition provision might be associated with decreased patient survival rates in AKI patients: no pediatric-specific studies have been conducted to date. CRRT has been used as a technique to deliver at least 100% recommended daily allowance of nutrition either by enteral or total parental

nutrition (TPN). An important consideration of nutrition in AKI includes the concept of nutritional loss when using CRRT/PD for patient care. RRT can contribute to the development of a negative nitrogen balance through loss of free amino acids and peptides. In a prospective pediatric study, children receiving standard administration of 1.5 g/kg/day of protein were randomized to either CVVH or CVVHD for the first 24 h, and then crossed over to the opposite therapy [43]. Both prescriptions resulted in a net negative nitrogen balance with an average loss of amino acids of approximately 10 g/1.73 m² (about 10% of protein intake). Similarly, the delivery of 2.5 g/kg/day in adult patients on CVVHDF resulted in a net negative nitrogen balance [44]. Although the patients' nitrogen balance was improved compared with standard lower protein supplementation, the overall nitrogen balance still was negative, characterized by a preferential glutamine clearance. Ongoing work in glutamine supplementation in hypermetabolic patients (i.e. sepsis, acute renal failure, bone marrow transplants) continues to evaluate and elucidate the role of this nonessential but obvious key nutrient for cellular recovery [45]. Vitamins and trace elements are components added to standard TPN solutions. Recently, it was shown that some of these are lost at a significant rate into the ultrafiltrate. One recent study showed clinically significant losses of amino acids, folate, and some trace metals during the provision of CVVHD in pediatric patients measured over a 5-day period. Of particular note was the significant loss of folate (from CVVHD initiation to day 5), evident by a clearance rate of 16 ml/min/1.73 m² with a concomitant reduction in serum folate levels [46]. Other trace elements and vitamins, particularly manganese, thiamine, selenium, and copper, may require increased replacement doses greater than standard amounts found in TPN or formulas [46]. Current pediatric recommendations for CRRT suggest 2.5–3.0 g/kg/day of protein (with a target BUN of around 60 mg/dl), with a daily caloric intake 20–30% above normal resting energy expenditure in the form of TPN or, better yet, enteral feeds [1].

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Fluid Assessment and Management in the Emergency Department

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Abstract

Evaluation of hydration state or water homeostasis is an important component in the assessment and treatment of critically ill patients in the emergency department (ED). The main purpose of ED physicians is to immediately distinguish between normal hydrated, dehydrated and hyperhydrated states. Fluid depletion may result from renal losses and extrarenal losses (from the GI tract, respiratory system, skin, fever, sepsis, third space accumulations). Total body fluid increase can result from heart failure, kidney disease, liver disease, malignant lymphoedema or thyroid disease.

In patients with fluid overload due to acute heart failure, diuretics should be given when there is evidence of systemic volume overload, in a dose up-titrated according to renal function, systolic blood pressure, and history of chronic diuretic use. The bioelectrical impedance vector analysis (BIVA) is a noninvasive technique to estimate body mass and water composition by bioelectrical impedance measurements, resistance and reactance. In patients with hyperhydration state due to heart failure, some authors showed that reactance is strongly related to BNP values and the NYHA functional classes. Other authors found a correlation between impedance and central venous pressure in critically ill patients.

We have been analyzing the hydration state at admission to the ED, 24, 72 h after admission and at discharge, and found a significant and indirectly proportional correlation between BIVA hydration and the Caval index at the time of presentation to the ED and 24 and 72 h after hospital admission. Moreover, at admission we found an inverse relationship between BIVA hydration and reduced urine output that became directly proportional at 72 h. This confirms the good response to diuretic therapy with the shift of fluids from interstitial spaces.

Evaluation of hydration state or water homeostasis is an important component in the assessment and treatment of critically ill patients in the emergency department (ED). Water constitutes approximately 60% of body weight, varying somewhat with age, sex and amount of body fat. Total body water content is distributed between the intracellular fluid (ICF) and the extracellular fluid (ECF) compartments. The ECF is further divided into intravascular and interstitial spaces in a ratio of 1:4. Most studies suggest that 55–65% of total body water resides in the ICF and 35–45% is in the ECF [1, 2].

Water homeostasis results from the balance between total water intake and the combined water loss from renal excretion, respiratory system, skin and gastrointestinal sources.

Disorders of body water content are among the most commonly encountered problems in the practices of clinical medicine and in particular of all acute settings. This is in large part due to the fact that many different diseases can potentially disrupt the finely balanced mechanisms that control intake and output of water and solute [1].

Water and Sodium Metabolism

The body water can be estimated using the following formula:

$$P_{\text{osm}} (\text{mosm/kg H}_2\text{O}) = 2 \times \text{serum } [\text{Na}^+] (\text{mM}) + \text{glucose} (\text{mM}) + \text{blood urea nitrogen} (\text{mM})$$

The two major mechanisms responsible for regulating water metabolism are thirst through the activation of low and high pressure baroreceptors and pituitary secretion of the hormone vasopressin from the hypothalamus supraoptic and paraventricular nuclei in response to osmotic and volumic fluctuations. Although specific mechanisms exist for regulated renal excretion of all major electrolytes, none is as numerous or as complex as those controlling Na^+ excretion, which is not surprising in view of the fact that maintenance of ECF volume is crucial to normal health and function. One of these mechanisms that regulate renal sodium is the tubuloglomerular feedback in which an increase of filtered Na^+ load determines an increase in its absorption in the proximal tubule. Modifications of the glomerular filtration rate can significantly modulate renal Na^+ excretion. The second major mechanism consists in aldosterone secretion, which increases sodium reabsorption in the distal nephron by inducing the synthesis and activity of ion channels that affect sodium reabsorption and $\text{Na}^+ - \text{K}^+$ exchange in tubular epithelial cells, particularly the epithelial sodium channel [3, 4].

Fluid Assessment in the Emergency Department

Although clinical assessment remains the mainstay of estimating hydration state in patients, it could be challenging in all acute diseases to evaluate subtle hyperhydration or dehydration, which may result in increased short and long-term morbidity. Consequently, the main purpose of ED physicians is to immediately distinguish between (1) normal hydrated, (2) dehydrated and (3) hyperhydrated patient.

Normal Hydrated Patient

A 70-kg man, for instance, would consist of 42 l of water, with 28 l of ICF and 14 l of ECF. The intravascular compartment would contain 3.5 l (about 1/4) of water and the interstitial compartment 10.5 l (about 3/4).

Minimum water requirements for daily fluid balance can be approximated from the sum of the minimum urine output necessary to excrete the daily solute load (500–675 ml/day), the water lost in stool (200 ml/day) and the insensible water losses from the skin and the respiratory tract. The volume of water produced from endogenous metabolism (250–350 ml/day) should be subtracted from this total. This comes to a minimum of about 1,400 ml/day of water needed for maintenance. The electrolyte requirement depends on minimum obligatory and ongoing losses. Normally, the kidneys are able to compensate for wide fluctuations in dietary Na^+ and K^+ intake [5].

Dehydrated Patient

Fluid depletion may result from:

- renal losses due to use of diuretics, salt-losing nephritis, mineralcorticoid deficiency or osmotic diuresis in acute tubular necrosis that lead to deficit of Na^+ and water.
- extrarenal losses including those from the GI tract, respiratory system, skin, fever, sepsis and third space accumulations [6] (fig. 1).

Clinical Presentation

History and physical examination may be enough to assess a volume depletion state. Symptoms are usually nonspecific and include thirst, fatigue, weakness, muscle cramps and postural dizziness. Signs include low jugular venous pressure, postural hypotension and tachycardia. Diminished skin turgor and dry mucous membranes are poor markers of decreased interstitial fluid. Larger fluid losses often present as hypovolemic shock characterized by evidence of insufficient tissue perfusion (obtundation, oliguria, peripheral cyanosis) due to

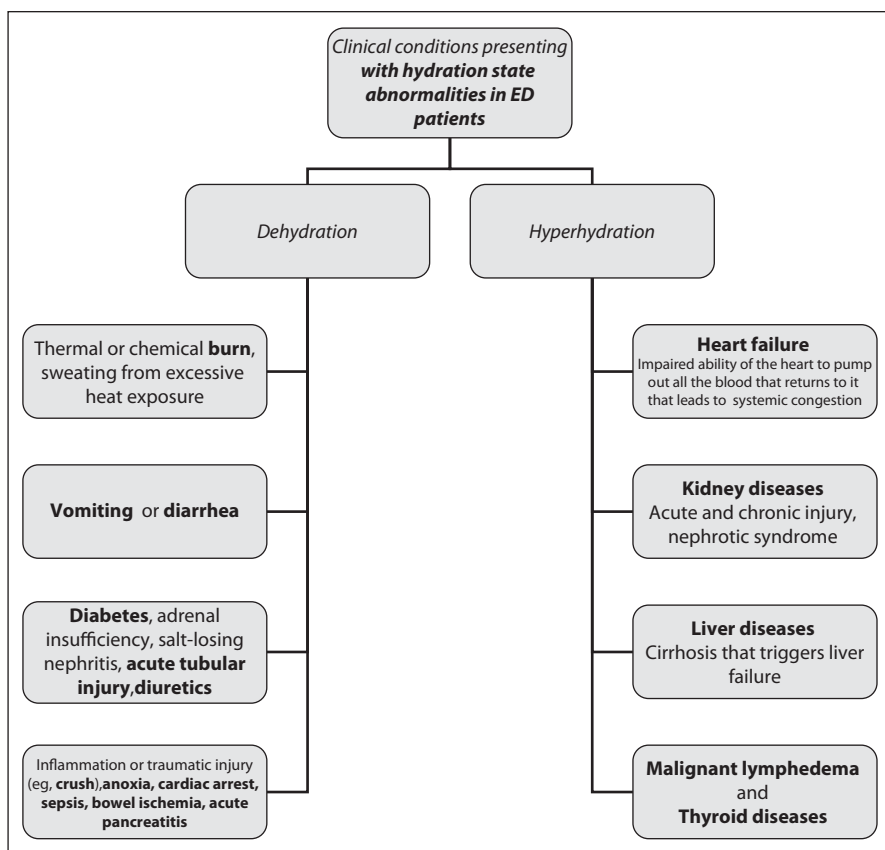


Fig. 1. Clinical conditions presenting with hydration state abnormalities in ED.

a critical decrease in intravascular volume and signs of compensatory mechanisms (tachycardia, tachypnea, diaphoresis, piloerection).

Laboratory

High urine osmolality, low urinary Na^+ and contraction alkalosis may be present but would be affected by the acid-base characteristics of the lost fluid and by the renal disease that may cause the volume depletion. Even if serum $[\text{Na}^+]$ does not reflect total body Na^+ content, a high serum $[\text{Na}^+]$ suggests the presence of a water deficit. There can be a relative increase in the hematocrit and serum [albumin] from hemoconcentration.

Treatment

It is often difficult to estimate the volume deficit, so therapy is largely empiric. The therapeutic goal is to replace intravascular volume with isotonic fluid and then

Table 1. ED predictors of HF presence

Variable	Sensitivity	Specificity	Accuracy
History of HF	62	94	80
Dyspnea	56	53	54
Orthopnea	47	88	72
Rales	56	80	70
S3 heart sound	20	99	66
Jugular venous dilatation	39	94	72
Edema	67	68	68

Percent values; from Peacock et al. [12].

restore the total body fluid distribution. Normal saline (0.9% NaCl) is the initial fluid of choice, especially in patients with hypotension or shock. Only approximately one third to one fourth of the administered volume will remain in the intravascular space, while the rest will leak into the interstitium. Frequent reassessments of hydration state, both clinical and instrumental, should be done during the treatment.

A safe way to replace the intravascular volume consists in administering a bolus of isotonic fluid (normal saline or Ringer's solution) in a volume of 1–2 l, depending on the fluid deficit. If the patient still appears to be intravascularly volume depleted, another cycle of fluid therapy followed by reassessment should be undertaken, and so on. Smaller volumes (e.g. 250–500 ml) are used for patients with signs of high right-sided pressure (e.g. distention of neck veins) or acute myocardial infarction [7].

Hyperhydrated Patient

Total body fluid increase can result from: heart failure (HF), kidney disease, liver disease, malignant lymphedema or thyroid disease.

Fluid overload in patients with acute HF can be caused primarily by acute fluid redistribution, presenting with pulmonary edema and normal or increased systolic pressure, or by fluid accumulation, due to a progressive increase in body fluid amount with predominant systemic congestion. This distinction is important to achieve a tailored therapy [8].

Heart Failure Clinical Presentation

At ED presentation in patients with shortness of breath due to congestive HF, the most powerful diagnostic data can be immediately obtained through an accurate anamnestic and clinical evaluation (table 1):

- Orthopnea is the most sensitive and specific symptom of elevated capillary wedge pressure, with a sensitivity approaching 90% [9];
- Peripheral edema is present in 50% of the patients with decompensated HF [9];
- Pulsus alternans indicating depressed left ventricle may be observed;
- Rales indicating new-onset acute HF or rapid elevation of filling pressures in congestive HF;
- Increased intensity of second sound pulmonary component as a result of elevated pulmonary artery pressure and appearance of S3 ventricular gallop [10];
- Jugular venous distention and abdomino-jugular reflux.

Although the classical hemodynamic profiling (cold and wet, cold and dry, warm and wet and warm and dry) has a prognostic value and may be used to lead the therapy, there is poor interobserver agreement between different physicians in evaluating and clinically stratifying the patients [11].

Laboratory

Laboratory assessment includes complete blood count, Na⁺, K⁺, glucose, blood urea nitrogen, serum creatinine, troponin I and arterial blood gas count. Natriuretic peptides are useful biomarkers that provide information about the gravity of fluid overload state and decreases markedly the rate of misdiagnosis, especially when their levels fall outside the range of 100–400 pg/ml [12]. Moreover, change in natriuretic peptides tends to correlate with change in filling pressures [13].

Chest Radiography

Chest radiography is a quick and almost ubiquitously available tool, but approximately 1 of every 5 patients admitted from the ED with acute decompensated HF has no signs of congestion on X-ray, so clinicians should not rule out HF in patients with no radiographic signs of congestion [14]. Peribronchial cuffing and the reader's overall impression show the highest accuracy for the ED diagnosis of HF [15].

Bedside Ultrasound in the Emergency Department

Thoracic Ultrasonography

Ultrasonography shows better accuracy than radiography, especially in the detection of very small (<100 ml) and small (<400 ml) amounts of pleural effusion [16]. Specific echographic patterns of acute pulmonary edema are still not well identified.

Respiratory Variation of Inferior Vena Cava Diameter

Exploiting the less dynamic diameter of the inferior vena cava dilated by the venous congestion, it is possible to assess a volume overload state. A cutoff of ≤15% respiratory variation of inferior vena cava diameter has been found to

achieve a 92% sensitivity and 84% specificity for the diagnosis of HF. If a 10-mm cutoff for absolute diameter was added to the diagnostic criteria for HF, the specificity of the test increased to 91% [17].

Echocardiography

The evaluation of echocardiogram in ED is very useful in detecting morphological alterations of heart valves and chambers and the presence of pericardial effusion. Systolic and diastolic impairment in HF can be also measured using the transmitralic pulsate Doppler to identify the diastolic function. The systolic function can be evaluated by ejection fraction. This procedure may be an alternative to traditional invasive hemodynamic monitoring [18].

Invasive Hemodynamic Monitoring

The insertion of a pulmonary artery catheter in order to monitor cardiac output and filling pressure is suggested in hemodynamically unstable patients not responding to traditional treatments or who are refractory to initial therapy, who have a combination of congestion and hypoperfusion, whose volume status and cardiac filling pressures are unclear, or who have clinically significant hypotension and worsening renal function during therapy [19].

Fluid Management

Diuretics should be given when there is evidence of systemic volume overload. The recommended initial dose is furosemide 20–40 mg IV at admission [19]. The dose should be up-titrated according to renal function, systolic blood pressure, and history of chronic diuretic use. However, high doses are not recommended because they may be detrimental to renal function. Usually, patients presenting with pulmonary edema and systolic blood pressure >140 mm Hg can be treated only with vasodilators, such as nitrates, avoiding diuretics, because they are often euvoletic or hypovolemic, and their misdistribution of the systemic fluid is due to diastolic dysfunction and not real overhydration.

It is very important to correctly use diuretics in these patients in the ED to avoid kidney involvement. Diuretics should always be administered according to kidney function.

New Perspectives: Bioimpedance Vector Analysis

The bioimpedance vector analysis (BIVA) is a noninvasive technique to estimate body mass and water composition by bioelectrical impedance measurements, resistance and reactance [20, 21]. BIVA quickly evaluates body mass in normal, extremely obese, and undernourished patients [22, 23] and assesses the hydration state in normal (72.7–74.3%), hyperhydrated and dehydrated (Hydragram®) patients.

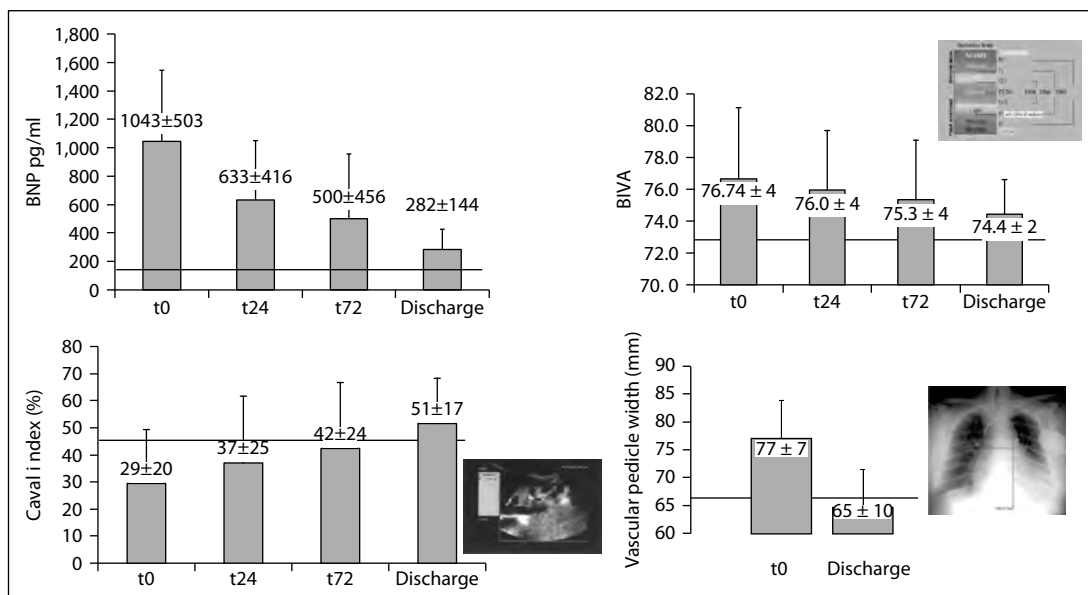


Fig. 2. Effects of diuretic treatment in ADHF patients: monitoring BNP and fluid content. The hydration state was analyzed at admission to the ED, 24 and 72 h after admission and at discharge together with BNP, ultrasonographic measurement of the Caval index and vascular pedicle width obtained through chest radiography. All the methods confirmed a good response to diuretic therapy with the shift of fluids from interstitial spaces.

In recent past, this technique was performed in limited medical areas. Today, it is performed in many critical areas such as EDs, intensive care, dialysis [24], and cardiology [25]. In EDs, achieving normal hydration in critical patients should be an important clinical target. Although in first studies BIVA did not show relevant results [26], in most recent studies the method proved its utility in fluid balance management [27].

In patients with hyperhydration due to HF, some authors showed that reactance is strongly related with BNP values and the NYHA functional classes [28]. Other authors found a correlation between impedance and central venous pressure in critically ill patients [29].

Our clinical experience with BIVA showed positive results when performed in acute HF patients admitted to the ED. Together with BIVA, we evaluated BNP, ultrasonographic measurement of the Caval index and vascular pedicle width obtained through chest radiography. Hydration status was analyzed at admission to ED and 24, 72 h after admission and at discharge. From our data, it is possible to conclude that BIVA measurements are strictly related to the other three methods. In our preliminary results, BIVA hydration and Caval index showed a significant and indirectly proportional correlation at the time of presentation

and 24 and 72 h after hospital admission. Moreover, at admission we found an inverse relationship between BIVA hydration and reduced urine output.

These data confirm the strong correlation between hyperhydration and central venous congestion and between hyperhydration and oliguria. The correlation between BIVA hydration and diuresis at 72 h was directly proportional. This confirms the good response to diuretic therapy with the shift of fluids from interstitial spaces: the more the patients were hyperhydrated, the more the diuresis was conspicuous. BIVA confirmed the utility to evaluate the return to a normal hydration state at 24 and 72 h with a specificity of 100% (AUC 0.7, $p = 0.04$, 24 h; AUC 0.9, $p = 0.0001$, 72 h). The efficacy of diuretic therapy and the validity of BIVA measurements were also confirmed by normalization of BNP levels, vascular pedicle width and Caval index values at discharge (fig. 2). These results suggest that BIVA, more than clinical empirical signs, can be useful in the management of diuretic therapy in critical HF patients in the ED.

Finally, particularly interesting is the evaluation of the hydration state and body mass in cardiac cachexia patients. If the reduction in body size is an important target in HF patients, weight loss due to body wasting, cachexia, is particularly dangerous. In fact, cardiac cachexia is a terminal multifactorial stage of HF resulting in catabolic imbalance of the body leading to the loss of lean and fat mass. This combination of fat and lean tissues loss, when present, can confound the clinical evaluation. In this condition, BIVA would be useful in assessing correct hydration as well as body mass loss. In the future, the reliability of BIVA in cardiac cachexia patients should be validated.

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Author Index

- Agostoni, P. 173
Aspromonte, N. 209
- Bagshaw, S.M. 24, 54
Bellomo, R. VII, 153
Bouchard, J. 69
- Chaney, E. 46
Costanzo, M.R. VII, 173
Cruz, D.N. 24, 54
- Daniels, L.B. 88
De Cal, M. 118
Di Somma, S. 227
- Echeverri, J.E. 153
- Favia, I. 217
- Garisto, C. 217
Garzotto, F. 199
Gori, C.S. 227
Grammaticopoulos, S. 118
Grandi, T. 227
- House, A.A. 164
- Jankowska, E.A. 11
- Kellum, J.A. 39
- Lentini, P. 118
- Macedo, E. 79
Maisel, A.S. VII, 88
Marenzi, G. 173
Mehta, R.L. 69, 79
- Nalesso, F. 199
Nuti, R. 1
- Palazzuoli, A. 1
Peacock, W.F. 128
Picardo, S. 217
Piccinni, P. 118
Piccoli, A. 143
Ponikowski, P. 11
Prowle, J.R. 153
- Ricci, Z. 24, 217
Rimmelé, T. 39
Risicato, M.G. 227
Ronco, C. VII, 24, 33, 118, 199
Rosner, M. 118
Rossi, E. 217
- Salvatori, E. 227
Shaw, A. 46
Slavin, L. 88
Soni, S. 118
Soto, K.M. 128
- Valle, R. 209

Subject Index

- Abdominal compartment syndrome (ACS), acute renal failure 119
 - Acoustic cardiography, fluid status assessment 134
 - Acute decompensated heart failure (ADHF)
 - B-type natriuretic peptide
 - lowering rationale 210–212
 - monitoring of fluid status 212–214
 - clinical features 174–176
 - early treatment and prognosis 128, 129
 - epidemiology 174, 210
 - fluid overload consequences 176–179
 - progression 178
 - Acute Dialysis Quality Initiative, *see* Cardiorenal syndromes
 - Acute kidney injury (AKI)
 - biomarkers
 - creatinine 120–122
 - cystatin C 123
 - ideal properties 122
 - interleukin-18 124
 - kidney injury molecule-1 123, 124
 - N-acetyl- β -(D)
 - glucosaminidase 124
 - neutrophil gelatinase-associated lipocalin 109, 122, 123
 - oliguria 119, 120
 - urea 121
 - cardiorenal syndromes 29, 30
 - classifications
 - Acute Kidney Injury Network 25–28
 - Risk-Injury-Failure-Loss-End-stage renal disease 25–28
 - definitions 25
 - epidemiology 24, 25, 60
 - fluid accumulation 61–64
 - fluid balance 29
 - fluid overload and oliguria 42–44
 - pathophysiology 60, 61
 - renal replacement therapy
 - timing 61–63
- Adenosine receptor antagonists
 - cardiorenal syndrome type 1
 - management 168
 - prerenal azotemia management in congestive heart failure 85
- Adrenomedullin
 - biology 97
 - mid-regional proadrenomedullin as heart failure marker 97, 98
- Anthropometry, fluid status assessment 144
- Arginine vasopressin (AVP)
 - fluid retention pathophysiology in heart failure 49, 50
 - receptors 177
- Arterial underfilling hypothesis, fluid retention pathophysiology in heart failure 47, 48
- Atrial natriuretic peptide (ANP)
 - critically ill patient fluid retention role 70

- fluid retention pathophysiology in
 - heart failure 51
 - heart failure marker 58
- Auscultation, fluid status assessment 133, 134
- Beta-blockers, cardiorenal syndrome management 166
- Bioimpedance, *see* Bioimpedance vector analysis; Impedance cardiography
- Bioimpedance vector analysis (BIVA)
 - acute decompensated heart failure monitoring of fluid status 212–214
 - basic patterns 145, 146
 - fluid status assessment 137
 - heart failure findings in emergency department patients 233–235
 - observations
 - critically ill patients 149, 150
 - heart failure patients 148, 149
 - hemodialysis patients 146–148
 - localized edema 150
 - peritoneal dialysis patients 148
 - principles 145
 - ultrafiltration monitoring 203–206
- B-lines, fluid status assessment 137–139
- Body water, estimation formula 228
- Brain natriuretic peptide, *see* B-type natriuretic peptide
- B-type natriuretic peptide (BNP)
 - acute decompensated heart failure monitoring of fluid status 212–214
 - peptide lowering rationale 210–212
 - biology 90, 91
 - fluid status assessment 135, 136
 - heart failure marker
 - acute heart failure 91–93
 - caveats 93–95
 - overview 58
 - prognostic value 95
 - specificity of elevation 93
 - therapy monitoring 95, 96
- Cardiopulmonary bypass (CBP), ultrafiltration therapy 184, 185
- Cardiorenal syndromes (CRS)
 - Acute Dialysis Quality Initiative consensus conference classification
 - acute cardiorenal syndrome 35
 - acute renocardiac syndrome 36
 - chronic cardiorenal syndrome 35, 36
 - chronic renocardiac syndrome 36
 - secondary cardiorenal syndromes 36
 - definition 35
 - overview 24, 34
 - classification 29, 30, 34–37
 - definitions 34
 - management
 - type 1 disease
 - adenosine receptor antagonists 168
 - CD-natriuretic peptide 169
 - diuretics 165
 - endothelin receptor antagonists 168
 - nesitiride 165, 166
 - relaxin 168
 - vaptans 169
 - type 2 disease 166, 167
 - type 3 disease 167
 - type 4 disease 167, 168
 - prerenal azotemia management in congestive heart failure 83, 84
- CD-natriuretic peptide, cardiorenal syndrome type 1 management 169
- Central venous pressure (CVP), glomerular filtration rate relationship 178
- Chest radiography, fluid status assessment 134, 135, 232
- Cinacalcet, cardiorenal syndrome management 168
- Coronary artery disease (CAD), heart failure 2–4
- C-reactive protein (CRP)
 - biology 100
 - heart failure marker
 - high-sensitivity C-reactive protein and susceptibility 100–103

- prognostic value 100, 103–106
- Creatinine, acute kidney injury
 - biomarker 120–122
- Critically ill patients, *see also* Pediatric intensive care
 - bioimpedance vector analysis
 - findings 149, 150
 - fluid accumulation and organ dysfunction 75, 76
 - fluid management
 - initial versus cumulative fluid administration 74, 75
 - overview 70
 - prospective observational trials 73
 - randomized trials and outcomes 71, 72
 - recommendations 76
 - retrospective trials 74
 - terminology 71
 - pathophysiology of fluid shifts 70
- C-type natriuretic peptide (CNP)
 - fluid retention pathophysiology in heart failure 51
 - heart failure marker
 - acute heart failure 91–93
 - caveats 93–95
 - prognostic value 95
 - specificity of elevation 93
 - therapy monitoring 95, 96
- Cystatin C, acute kidney injury
 - biomarker 123
- DEDYCA, ultrafiltration equipment 201–203
- Dilutometry, fluid status assessment 144
- Diuretics
 - cardiorenal syndrome type 1
 - management 165
 - emergency department use 233
 - heart failure management in
 - fluid-overloaded patients
 - case example 153, 154
 - diagnostic challenges 155, 156
 - resistance to diuretics 156–159
 - ultrafiltration therapy in resistant patients 159–161
 - pediatric intensive care use 218–220
- prerenal azotemia management in congestive heart failure 84, 85
- Echocardiography (ECG), fluid status assessment 134, 232
- Emergency department (ED)
 - normal hydrated patient findings 228, 229
 - dehydrated patients
 - clinical presentation 229
 - laboratory findings 229
 - management 229, 230
 - hyperhydrated patients
 - bioimpedance vector analysis 233–235
 - fluid management 233
 - heart failure
 - chest radiography 232
 - clinical presentation 231
 - laboratory findings 232
 - invasive hemodynamic monitoring 232, 233
 - ultrasonography 232
- Endothelin-1 (ET-1)
 - fluid retention pathophysiology in heart failure 50, 51
 - receptor antagonists in cardiorenal syndrome type 1 management 168
- ESCAPE study 177
- Extracellular fluid (ECF) 227, 228
- Fenoldopam, pediatric intensive care use 219, 220
- Furosemide, *see* Diuretics
- Glomerular filtration rate (GFR)
 - central venous pressure
 - relationship 178
 - reduction in oliguria 41, 42
- Heart failure (HF), *see also* Acute decompensated heart failure
 - associated conditions 9, 21
 - bioimpedance vector analysis
 - findings 148, 149
 - biomarkers

- adrenomedullin
 - biology 97
 - mid-regional
 - proadrenomedullin 97, 98
- C-reactive protein
 - biology 100
 - high-sensitivity C-reactive
 - protein and
 - susceptibility 100–103
 - prognostic value 100, 103–106
- ideal properties 89
- natriuretic peptides
 - acute heart failure 91–93
 - biology 90, 91
 - caveats 93–95
 - prognostic value 95
 - specificity of elevation 93
 - therapy monitoring 95, 96
- neutrophil gelatinase-associated
 - lipocalin
 - acute kidney injury 109
 - biology 109
 - heart failure 109
- ST2
 - biology 98
 - marker utility 98–100
- troponin
 - acute heart failure 107
 - biology 106, 107
 - chronic heart failure 107, 108
- classification
 - ACC/AHA guidelines 14, 16, 20
 - acute heart failure 18–20
 - decompensated heart failure 18–20
 - etiology and comorbidities 21
 - heart failure with preserved and
 - reduced ejection fraction 18
 - New York Heart Association
 - functional classification 13–15
 - severity of symptoms and structural
 - changes in heart 12–16
 - signs of heart failure 16–18
- clinical features 7, 8
- diagnostic criteria 11, 12
- diuretic therapy in fluid-overloaded
 - patients
 - case example 153, 154
 - diagnostic challenges 155, 156
 - resistance to diuretics 156–159
 - ultrafiltration therapy in resistant
 - patients 159–161
- emergency department patients
 - bioimpedance vector analysis
 - 233–235
 - chest radiography 232
 - clinical presentation 231
 - fluid management 233
 - invasive hemodynamic
 - monitoring 232, 233
 - laboratory findings 232
 - ultrasonography 232
- epidemiology 1, 2, 55
- fluid accumulation as marker 57–59
- fluid overload consequences 176–179
- fluid retention pathophysiology
 - arginine vasopressin 49, 50
 - arterial underfilling hypothesis 47, 48
 - endothelin-1 50, 51
 - natriuretic peptides 51
 - overview 46, 47
 - renin-angiotensin-aldosterone
 - system 49
 - sympathetic nervous system 48
 - tumor necrosis factor- α 50
- neurohormonal activation 4, 5
- pathophysiology 2, 21, 56
- prerenal azotemia, *see* Prerenal
 - azotemia
- pump dysfunction and cardiac
 - remodeling 2–4
- salt and water retention 5–7
- time course of clinical presentation 12
- ultrafiltration therapy
 - advanced heart failure 183, 184
 - intermittent isolated ultrafiltration
 - with central venous access 185–192
 - intraoperative cardiac surgery 184, 185
 - rationale 179–183
 - UNLOAD trial 187–192
- Hepatojugular reflex (HJR), fluid status
 - assessment 131, 132

- History, *see* Medical history
- Impedance cardiography (ICG), fluid
 - status monitoring in heart failure 59, 64, 136, 137
- Intensive care, *see* Critically ill patients; Pediatric intensive care unit
- Interleukin-18 (IL-18), acute kidney injury biomarker 124
- Intracellular fluid (ICF) 227
- Jugular venous distention (JVD), fluid status assessment 131, 132
- Kidney injury molecule-1 (KIM-1)
 - acute kidney injury biomarker 123, 124
- Left ventricle, heart failure
 - function 7, 8
 - remodeling 3
- Medical history, fluid status
 - assessment 130, 131
- N-acetyl- β -(D)glucosaminidase (NAG), acute kidney injury biomarker 124
- Nesiritide, cardiorenal syndrome type 1
 - management 165, 166
- Neutrophil gelatinase-associated lipocalin (NGAL)
 - acute kidney injury marker 109, 122, 123
 - biology 109
 - heart failure marker 109
 - prerenal azotemia diagnosis 83
- Nutrition, pediatric intensive care 222, 223
- Oliguria
 - acute kidney injury biomarker 119, 120
 - definitions 119
 - epidemiology 39, 40
 - etiology 119
 - fluid overload 42–44
 - glomerular filtration rate
 - reduction 41, 42
 - treatment 120
 - urine output and renal function 40, 41
- Orthostatic vital signs, fluid status
 - assessment 132, 133
- Pediatric intensive care unit (PICU)
 - continuous renal replacement therapies 221, 222
 - diuretics for fluid management 218–220
 - nutrition 222, 223
 - outcomes of fluid overload 217, 218
 - peritoneal dialysis 220, 221
- Peritoneal dialysis (PD)
 - bioimpedance vector analysis
 - findings 148
 - pediatric intensive care unit 220, 221
- Physical examination, fluid status
 - assessment
 - auscultation 133, 134
 - hepatojugular reflex 131, 132
 - jugular venous distention 131, 132
 - orthostatic vital signs 132, 133
- PICARD study 73
- Prerenal azotemia
 - diagnosis 82, 83
 - kidney reserve concept and preprerenal state 80
 - management in congestive heart failure 83–85
 - pathophysiology of prerenal failure in congestive heart failure 80, 81
 - progression to acute tubular necrosis 79, 80
 - prospects for study 85, 86
- Pulmonary capillary wedge pressure (PCWP), blood volume
 - correlation 176
- Radioimmunoassay, fluid status
 - assessment 134
- Relaxin, cardiorenal syndrome type 1
 - management 168

- Renin-angiotensin-aldosterone system (RAAS)
 - activation in heart failure 4, 5
 - fluid retention pathophysiology in heart failure 49
- Risk-Injury-Failure-Loss-End-stage renal disease (RIFLE), acute kidney injury classification 25–28
- Rolofylline, prerenal azotemia
 - management in congestive heart failure 85
- Slow continuous ultrafiltration, *see* Ultrafiltration
- ST2
 - biology 98
 - heart failure marker utility 98–100
- Statins, chronic kidney disease patient findings 168
- Sympathetic nervous system (SNS)
 - activation in heart failure 4, 5
 - fluid retention pathophysiology in heart failure 48
- Thoracic ultrasound, fluid status
 - assessment 137–139, 232
- Troponin
 - biology 106, 107
 - heart failure marker
 - acute heart failure 107
 - chronic heart failure 107, 108
- Tumor necrosis factor- α (TNF- α)
 - critically ill patient fluid retention role 70
 - fluid retention pathophysiology in heart failure 50
- Ultrafiltration
 - continuous venovenous
 - hemofiltration 200, 201
 - equipment 201, 202
 - heart failure management in
 - fluid-overloaded patients
 - advanced heart failure 183, 184
 - diuretic-resistant patients 159–161
 - intermittent isolated ultrafiltration with central venous access 185–192
 - intraoperative cardiac surgery 184, 185
 - rationale 179–183
 - UNLOAD trial 187–192
 - prescription and monitoring 202–206
 - slow continuous ultrafiltration 200–202
 - wearable devices 207
- Ultrasonography, *see* Echocardiography; Thoracic ultrasound; Vena cava diameter ultrasound
- UNLOAD trial 187–192
- Urea
 - acute kidney injury biomarker 121
 - blood urea nitrogen and renal function 178
- Vaptans, cardiorenal syndrome type 1
 - management 169
- Vasopressin, *see* Arginine vasopressin
- Vena cava diameter ultrasound, fluid status assessment 139, 232
- Worsening renal function (WRF) 30, 183