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SPECIAL ARTICLE

New insights in cardiovascular anesthesia: a dual focus on clinical practice and research

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Abstract
Accumulation of the results of basic and clinical research has advanced the safety and quality of management in cardiovascular anesthesia. To address recent developments in this field, a symposium was held during the 71th Japanese Society of Anesthesiologists annual meetings in 2024, focusing on new advancements in both clinical and basic research in cardiovascular anesthesia. During this symposium, four experts reviewed recent findings in their respective areas of study, covering the following topics: clinical reliability and concerns regarding volatile anesthetics during cardiopulmonary bypass; novel basic and clinical findings regarding the cardioprotective effects of dexmedetomidine; advancements in optimizing blood and hemostasis management during cardiovascular surgery; and innovative strategies for managing postoperative cognitive disorders following cardiovascular and thoracic surgery. Each expert summarized recent novel findings, clinical reliability and concerns, as well as future directions in their respective topics. We believe that this special article provides valuable insights into both clinical practice and basic research in cardiovascular anesthesia while also inspiring anesthesiologists to pursue further research in this field.

Keywords Pharmacological cardioprotective effects · Blood coagulation and hemostatic management · Postoperative delirium · Cardiovascular and thoracic surgery

Introduction

Numerous basic and clinical studies have contributed to the recent advancements in cardiovascular anesthesia. Given the broad scope of this field, staying fully updated on all new developments can be challenging. To address these challenges, a symposium entitled "Cardiovascular Anesthesia: A dual focus on clinical practice and research" organized by the Journal of Anesthesia (JA) was held at the 71th Japanese Society of Anesthesiology (JSA) annual meeting (Kobe, Japan). The symposium featured reviews and discussions led by four experts on key topics: clinical reliability and potential concerns regarding the use of volatile anesthetics during cardiopulmonary bypass; cardioprotective effects of dexmedetomidine; optimization of blood and hemostasis management; and innovative strategies for preventing postoperative cognitive disorders in cardiovascular anesthesia. The symposium speakers were Dr. Takahiro Tamura (Nagoya), Associate Professor of Nagoya University School of Medicine; Dr. Yusuke Yoshikawa (Sapporo), Assistant Professor of Sapporo Medical University School of Medicine; Dr. Satoru Ogawa (Kyoto), Assistant Professor of Kyoto Prefectural University of Medicine; and Dr. Mitsuru Ida (Nara), Assistant Professor of Nara Prefectural University of Medicine. Each speaker in the symposium provided valuable guidance on how anesthesiologists can effectively contribute to both clinical practice and research endeavors.

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Fundamental efforts to utilize the cardioprotective effects of volatile anesthetics in cardiac surgery (Takahiro Tamura)

Some reports have suggested that volatile anesthetics (VAs) have myocardial protective effects against cardiac ischemia–reperfusion injury [1–3]. Therefore, their application during cardiopulmonary bypass (CPB) may improve prognosis compared with the use of total intravenous anesthesia (TIVA). The use of VAs during CPB is widespread since some guidelines recommend their use in cardiovascular surgery [4, 5] based on their potential myocardial protective effects. In the Mortality in Cardiac Surgery Randomized Controlled Trial of Volatile Anesthetic (MYRIAD) study, no statistically significant difference was found in 1-year mortality rates between patients undergoing coronary artery bypass graft with VAs and those receiving total intravenous anesthesia [6]. However, because the VA administration protocol was not rigid [7], there is room for further consideration to determine the utility of VAs during CPB.

TIVA is considered to be the preferred anesthesia for CPB in Japan. Therefore, it is necessary to educate anesthesiologists who can administer VAs during CPB, so that clinical studies can be conducted in Japan. To ensure safe sedation during CPB, being knowledgeable about VA risks and adverse events is crucial. I have covered and suggested seemingly problematic issues such as intraoperative awareness during surgery, air pollution in the operating room, staff exposure to gas, and artificial lung damage from VA use [8].

Intraoperative awareness

Although it has been reported that the use of a poly-methylpentene membrane oxygenator resulted in intraoperative awareness during CPB [9], our investigation with a polypropylene membrane oxygenator showed comparable blood levels of VA to those without an oxygenator [10]. In addition, the use of two vaporizers minimizes the decrease in VA concentration associated with CPB switching, but it should be noted that if there is no dedicated vaporizer for VA delivery, there is a significant decrease in blood VA concentration between the time immediately after the start of CPB and the start of VA to the oxygenator [11].

Occupational exposure to volatile anesthetics

Air pollution in the operating room from VA leakage through gas outlet ports of oxygenators can pose a risk of occupational exposure for operating room staff. Although there are no current international standard occupational exposure values, VA exhaust in the operating room should be avoided if possible. Therefore, we developed an improved VA suction system to prevent VA leakage for a Japanese clinical situation [12, 13]. Since no damage to the membranes of oxygenators or other anticipated complications occurred [10], VA anesthesia management can be practiced during CPB in clinical settings if sufficient knowledge is acquired to apply VAs to the oxygenators, and this would lead to clinical studies.

Cardioprotective effects of dexmedetomidine (Yusuke Yoshikawa)

Recently, a growing body of evidence has suggested a direct protective effect of dexmedetomidine (DEX) against ischemia/reperfusion injury (IRI) in various organs including the hearts. Here, we provide an overview of evidence for a cardioprotective effect of DEX in preclinical studies.

Okada et al. first reported a direct cardioprotective effect of DEX against IRI using isolated rat hearts on a Langendorff apparatus. The results showed that 1–10 nM of DEX reduced infarct size and that yohimbine, an alpha2 adrenaline receptor antagonist, attenuated the cardioprotective effect of DEX, indicating that DEX directly protected the heart via cardiac alpha2 adrenaline receptors [14]. A following study confirmed DEX-induced cardioprotection in ex vivo and in vivo IRI experiments in rats [15]. Among the proposed molecular mechanisms underlying the cardioprotective effect of DEX, the most extensively studied mechanism is activation of endothelial nitric oxide synthase (eNOS) [15].

Although we and others have clearly revealed that each subtype of alpha2 adrenaline receptors exists on various cell types including endothelial cells and cardiomyocytes in rodent and human hearts [16–18], it is still unclear which cell type is the direct effect site of DEX for its cardioprotective effect [19, 20].

It is noteworthy that DEX exerts a cardioprotective effect when administered after an ischemic event as a postconditioning therapy. In an ex vivo study, the postconditioning effects of DEX at various concentrations were investigated, and it was revealed that DEX at a concentration greater than 1 nM successfully decreased infarct size [21]. The postconditioning effect is considered to be of greater importance from the viewpoint of broader application of the use of DEX as a cardioprotective agent. For instance, patients with acute myocardial infarction can receive drug treatment only after onset of the disease in most clinical settings, which increases the value of postconditioning.

Considering application of the cardioprotective effect of DEX in a broader area of clinical practice, the other issue that needs to be addressed is the effects of comorbidities such as hypertensive hypertrophy and diabetes. Since several intracellular signaling pathways can be altered in these diseased hearts, some pharmacological and non-pharmacological interventions lose their cardioprotective effects in these unhealthy hearts [22, 23]. Regarding DEX, we previously reported that DEX administered before ischemia maintains its direct cardioprotective effect even in hypertensive hypertrophied hearts in an eNOS independent manner, which involves a different mechanism from that in healthy hearts [16]. In diabetes hearts, a previous study in which the preconditioning effect of DEX was investigated in an in vivo IRI model in rats with diabetes showed that DEX successfully reduced infarct size [24]. Those studies highlight the possibility that DEX exerts its cardioprotective effect even in hearts with comorbidities; however, the postconditioning effect of DEX in those diseased hearts, which is the most important clinically relevant situation, has been rarely studied.

For the application of DEX in various patients including patients with acute coronary syndrome, future studies are needed to determine the cardioprotective effects, particularly the postconditioning effect, of DEX in hearts with comorbidities.

Blood coagulation and hemostatic managements (Satoru Ogawa)

To implement coagulation factor replacement therapies in cardiac surgery, the clinical usefulness of coagulation management using point-of-care (POC) testing has recently been reported. Viscoelastic measurement tests are commonly used as POC testing in cardiac surgery [25]. Although various novel viscoelastic devices were developed besides thromboelastometry (ROTEM) and thromboelastography (TEG), the interchangeability between assays among those devices is controversial [26]. Yoshii et al. prospectively compared a wide range of assays in ROTEM and modified thromboelastometry, ClotPro, in cardiopulmonary bypass (CPB) surgical patients [27]. In their study, a strong correlation for clot firmness between two devices was confirmed, but lower interchangeabilities in clotting times were clearly found. The extrapolation of new viscoelastic testing results for an established transfusion algorithm using ROTEM or TEG should be considered with caution.

Although POC laboratory tests for tranexamic acid (TXA) concentrations are not clinically available, a tissue-factor triggered thromboelastometric test, TPA-test, that enables measurement of TXA-induced inhibition of fibrinolysis has recently been developed [28]. In a prospective observational study in which the performance of the TPA-test in CPB surgical patients was evaluated, the test parameters could detect changes in the antifibrinolytic effect of TXA during and after surgery [29]. The anti-fibrinolytic effect in an intensive care unit was attenuated in a time-dependent manner in most patients, whereas complete inhibition of fibrinolysis by TXA continued in a few patients who had severe renal impairment until postoperative day 1. The TPA-test is a practical monitoring tool for postoperative fibrinolytic activity in cardiac patients for reducing the total amount of TXA and minimizing seizures or thrombotic complications.

Dilutional coagulopathy is the major cause of hemostatic disorders after CPB [30], and the effectiveness of acute normovolemic hemodilution (ANH) for reducing the amount of allogeneic blood products has recently been re-evaluated. The blood reduction effect has been reported to be dependent on the blood collection volume [31], but ANH is performed less frequently in Asian patients with a lower body weight who have a smaller blood volume [32, 33]. The prevention of hypotension during blood collection is very important to maximize the effect of ANH. In a recent retrospective study in CPB patients, Takahashi, et al. found that hemodynamic changes during blood collection were minimal under remimazolam anesthesia and that high-volume ANH was feasible in patients with a mean body mass index of 23.2 kg/m^2 (blood volume: 740 ± 222 mL) [34]. Remimazolam have less cardiovascular depressant responses [35] and thus may enhance the effect of ANH by mitigating the hemodilution with reduction in the total volume of infusions.

Further clinical studies are needed to verify the impact of optimizing blood coagulation management on clinical outcomes in cardiac surgical patients.

New prevention and treatment strategies for postoperative delirium in cardiothoracic surgery (Mitsuru Ida)

Postoperative delirium (POD) is one of the most common postoperative complications. However, effective treatments for POD have not been established and prevention is therefore the most effective strategy in POD management [36]. Although various possible mechanisms for POD have been investigated, its pathophysiology remains unclear. Currently available evidence suggests the involvement of the following four factors: neurodegenerative disease, neuroinflammation resulting from the spread of peripheral inflammation induced by surgical invasion into the brain, axonal damage caused by surgical invasion, and conditions of advanced age, such as frailty [37].

The overwhelming factor regarding death and other outcomes after cardiac surgery is the preoperative patient profile. This would be a plausible reason to enhance patients' reserve preoperatively, leading to improvement in postoperative outcomes. Evidence for the usefulness of preoperative optimization of physical and cognitive functions of patients, which is known as prehabilitation, is insufficient; however, its implementation has been identified as one of the priority research issues for adult cardiac surgery [38].

With regard to intraoperative management, although animal studies have shown an association between inhaled anesthetics and the pathology of Alzheimer's disease, one randomized controlled trial failed to demonstrate the superiority of intravenous anesthetics to inhaled anesthetics for prevention of POD. Additionally, systematic administration of steroids with the expectation of anti-inflammatory properties were not found to be effective. Administration of S-ketamine, one of the optical isomers of ketamine, is of interest as another pharmacological intervention. A randomized trial that included 112 patients with a mean age of 52 years undergoing valve surgery showed that administration of S-ketamine was successful for reducing the incidence of delirium (hazard ratio: 0.45, 95% confidence interval: 0.23–0.89) [39].

Dexmedetomidine has been considered to be effective for preventing POD in the intensive care unit, but a meta-analysis including randomized controlled trials in which the primary outcome was the occurrence of POD revealed that the preventive effect of dexmedetomidine in cardiac surgery was limited [40]. Melatonin is a hormone that leads to a decrease in deep body temperature that induces sleep. In contrast, ramelteon, which is a highly selective melatonin receptor agonist, is widely available and effective for reducing the risk of POD [41]. Orexin is a hormone that maintains wakefulness and inhibits sleep, and two orexin receptor antagonists, suvorexant and lemborexant, are available in Japan as sleep-inducing drugs. Suvorexant has a positive impact on POD prevention during an acute hospitalization, but evidence regarding lemborexant has been poorly documented.

In conclusion, there is no effective treatment for POD, and prevention, including the identification of risk factors, is important. Preoperative optimization, S-ketamine, and sleep interventions are expected as measures to prevent POD.

Conclusions

In this symposium, we discussed the current evidence and concerns regarding pharmacological cardioprotective anesthetics, blood and hemostatic management, and postoperative delirium in cardiovascular anesthesia. We believe that the insights provided here will be beneficial for the daily management of clinical anesthesia and will encourage further research in this field.

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Declarations

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