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Inhalation Anesthetics and Cardiovascular Protection [Version 1, 1 Approved, 1 Approved with Reservation]

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Abstract

Cardiovascular surgeries are associated with significant risks of perioperative morbid events including: ischemia, diverse arrhythmias, reperfusion injury and cardiac revascularization. Increasing preclinical evidence demonstrated that administration of inhalant anesthetics - before and during surgery - reduces the degree of ischemia and reperfusion injury to the heart and attenuate revascularization to the vessel. A number of studies reports have indicated administration of volatile anesthetics shows protective effects on cardiovascular system through manipulation of multiple signaling pathways. In this review, it covers the inhalant anesthetics beneficial effect on cardiovascular system and narrated the possible involved mechanism. Meanwhile, as not all studies have demonstrated improved outcomes, the risks for undesirable hemodynamic effects must be weighed against the possible benefits of using volatile anesthetics as a means to provide cardiovascular protection in patients with cardiovascular disease.

Keywords

Inhalant Anesthetic; Cardiovascular Surgery; Mechanism; Cardiovascular Protection

Introduction

Perioperative myocardial ischemia, reperfusion, revascularization are the serious acute or long term adverse events that can increase morbidity and mortality after cardiovascular surgery. It has been reported that there are more than 50% of patients with diabetes or coronary arterial disease undergoing surgery experiencing perioperative myocardial ischemia or revascularization [1,2]. Treatment approaches that prevent or lessen cardiovascular complications during and after surgery have been proposed [3]. Most of these approaches are directed towards modulation of the oxygen supply-demand ratio and reduction of super oxide generation, although the clinical benefit of these approaches remains to be demonstrated.

The use of particular anesthetics for the induction and maintenance of general anesthesia is one approach to protect against the adverse effects of cardiovascular system. Experimental data indicate that volatile anesthetics have cardiovascular protective effects against cardiac and vascular injury that are independent of their hemodynamic effects.

At present, the most widely used inhalant anesthetics are the halogenated, inflammable vapors halothane, sevoflurane and desflurane, enflurane, isoflurane and the gas nitrous oxide. The anesthetic effect of these agents is related to their tension or partial pressure in the brain, represented at equilibrium by the alveolar concentration. There are lots of studies in the literature investigating the effects of volatile anesthetics in cardiovascular disease model. However, recently, many of these studies have been performed with sevoflurane and isoflurane. Halothane and enflurane are no longer investigated for this purpose due to decreased usage of these agents. In general, ideal inhalation anesthetics offers smooth and reliable induction and maintenance of general anesthesia with minimal effects on other organ systems [4]. During the major surgery on heart or vessel, when inhalant anesthetics is applied, cardiovascular system function was mainly to protect and keep in good shape.

However, despite all of the medications, resources, and efforts available to investigate how the inhalant anesthetic exert their function, the incidence of controlled and properly treated strategy which the mechanism can lead to remains low. The inhalant anesthetic that has been known to cause agitation and delirium. It is not clear if this can be prevented.

Therefore, to figure out all the inhalant anesthetics influence to cardiovascular function and cardiovascular properties remains unclear. From this review, we will predominantly focus on the clinic inhalant anesthetics application and delineate their function and involved mechanism in cardiovascular protection aspects.

Volatile Anesthetics Application

The inhalant anesthetics application to human was first used by Pracelsus in 1540. He applied sweet oil of vitriol to fowl. Subsequently, 40 years later, Giabattista Delia Porta demonstrated the use of ether on human although it was not employed for any surgical anesthesia [5]. The volatile anesthetic agents share the property of being liquid at room temperature, but evaporating easily for administration by inhalation. All of these agents share the property of being quite hydrophobic. In addition it is odorless or pleasant to inhale; safe for all ages and in pregnancy; not metabolized; rapid in onset and offset; potent; and safe for exposure to operating room staff. Although none of the agents currently in use are ideal, many of them have some of the desirable characteristics. For example, sevoflurane is pleasant to inhale and is rapid in onset and offset. It is also safe for all ages. However, it is expensive (approximately 3 to 5 times more expensive than isoflurane), and approximately half as potent as isoflurane [5-8]. We listed below the advantage and disadvantage of inhalant anesthetics for the referencing.

Advantages of inhalation anesthetics

- Fulfill objectives of anesthesia:

  > Causes unconsciousness

  > Muscle relaxation

  > Rapid ventilatory function recovery

  > Dose-related reduction in ventricular work/ oxygen consumption

- Easily reversible
- Amnesia
- Titratable myocardial depression
- Attenuation of autonomic [9] response to surgical stimulation and cardiopulmonary bypass

Disadvantages of inhalation anesthetics

- Myocardial depression-excessive under some conditions
- Hypotension, secondary to either vasodilation or reduced by myocardial contractility
- Incomplete suppression of sympathetic responses to noxious/painful stimulation
- Absence of postoperative analgesia
- Post-operative shivering, secondary to peripheral vasodilation -- would be accompanied by increased oxygen demand because of excessive heat loss

Inhalant Anesthetics and Cardioprotective Effects

In clinic, general anesthetic requires four main components: hypnosis, analgesia, amnesia and muscle relaxation. In practice, although many if agents are capable of producing

more than one of these effects, it is logical that drugs producing these effects are given in combination to achieves the most beneficial effect. Inhalant anesthetics alone are capable of producing all of the conditions necessary to safely anesthetize the patient during cardiac surgery. The inhalant anesthetics physiological and pharmacological effects have been well documented. Most of these volatile agents cause some degree of myocardial depression, skeletal muscle relaxation, and an increase in renal vascular tone and hepatic blood flow [10]. Volatile anesthetics may reduce ischemic myocardial damage similar to ischemic preconditioning [11-15]. The degree of myocardial protection and the deleterious outcomes of inhalational agents are variable and depend on the specific agent and the concentration used.

All inhalant anesthetics reduce mean arterial pressure and cardiac output in a dose-dependent manner. The reduction in mean arterial pressure by sevoflurane, and isoflurane is primarily determined by the reduction in systemic vascular resistance. However, sevoflurane has fewer respiratory and cardiovascular depressant effects than halothane and may be a future alternative for pediatric anesthesia. Sevoflurane may prolong the QT interval and should be administered with caution in patients with long QT interval syndrome. Overall, the arrhythmogenic potential of sevoflurane is lower than that of isoflurane [15,16]. Ischemic preconditioning with inhalant anesthetics may also reduce perioperative myocardial injury [17].

The effects of volatile anesthetics on cardiovascular ischemia and reperfusion were investigated for several years [18-22]. It is known that volatile anesthetics, especially sevoflurane, have a protective role against ischemia and reperfusion injury. These protective effects have been attributed to pre- and post-conditioning effects with apoptosis. The mechanisms of these effects have been investigated, and new path ways are asserted continuously. Kowalski et al. [23] stated that polymorphonuclearneutrophils (PMN) lead to reperfusion injury in many organs and tissues via adhesioning to vascular endothelial cells. They investigated the effects of halothane, isoflurane, and sevoflurane on post ischemic adhesion of human PMN in the intact coronary system of isolated perfused guinea pig hearts. As a result of this study they found that volatile anesthetics had inhibitory effect on ischemia induced adhesion of PMN and concluded that it may be beneficial for the heart during general anesthesia [23,24]. Similarly, it was stated that volatile anesthetics were able to modulate the interaction of PMN with the endothelial cell, and this may play a crucial role in the initiation of cardiac injury in other studies [25,26].

In contrast to halothane, the ether-based anesthetics (isoflurane, enflurane, sevoflurane, and desflurane) have not predisposed patients to ventricular arrhythmias, nor sensitized the heart to the arrhythmogenic effects of epinephrine. Some of the differences between volatile anesthetics in their ability to promote arrhythmias can be attributed to their direct effects on cardiac pacemaker cells and conduction pathways [27,28].

Although many mechanism has been discovered, the exact mechanism of the action of volatile anesthetics have not been fully delineated. Sevoflurane is thought to potentially act as a positive allosteric modulator of the GABAA receptor [29]. However, it also acts as an NMDA receptor antagonist, [30] potentiates glycine receptor currents, [29] and inhibits nACh [31,32] and 5-HT3 receptor currents [33,34].

In addition, the observation that anesthetic cardioprotection with sevoflurane is also observed during off-pump coronary surgery, suggesting that this phenomenon is also present in patients at risk of myocardial events undergoing surgical procedures[35]. The risks associated with noncardiac surgical procedures were evaluated in the American College of Cardiology/ American Heart Association practice guidelines on perioperative cardiovascular evaluation for noncardiac surgery [36]. The guidelines identified a number of procedures with a more than 5% risk of perioperative cardiac morbidity: major emergency operations, particularly in the elderly; aortic and other major vascular surgery; peripheral vascular surgery; and anticipated prolonged surgical procedures associated with large fluid shifts or blood loss.

Inhalant Anesthetics and Vascular Beneficial Function

Recently, accumulated preclinical data has supported that volatile anesthetics implementing clinically, have beneficial effects found in some studies of patients undergoing coronary artery bypass graft surgery. Not only limited in this, the vascular effects of the volatile anesthetics have been carefully defined by a number of studies carried out in human volunteers. A common effect of the potent volatile anesthetics has been a dose related decrease in arterial blood pressure, with essentially no differences between the volatile anesthetics at steady state, equi-anesthetic concentrations [37,38]. However, the mechanism by which they decrease arterial blood pressure is somewhat more specific for each anesthetic. Desflurane, sevoflurane and isoflurane are known to maintain cardiac output, whilst halothane is most noted for its decrease in cardiac output and contributes to its blood pressure lowering effect [39]. The mechanism by which halothane decreases cardiac output is primarily a result of a profound depression of myocardial contractility and has been associated with an increase in right arterial pressure [40,41]. However, the sevoflurane and desflurane's primary mechanism to decrease blood pressure with increasing dose is related to their potent effects on regional and systemic vascular resistance [39,42].

The Mechanisms of Protective Effects of Volatile Anesthetics

The absence of clinically straightforward data from volatile anesthetics studies has prompted researchers to investigate the reason of volatile anesthetics' protective effect during en-

tire surgical procedure, by which it would really have an impact on cardiovascular outcomes in depth. Because the potent volatile anesthetics relax vascular smooth muscle and lead to vasodilation, there has been a concern related to abnormal distribution of blood flow in coronary blood vessels of patients with ischemic heart disease. What they called this effect is coronary steal and became a concern with the introduction of isoflurane to clinical practice. Isoflurane (and most other potent volatile anesthetics) increases coronary blood flow many times beyond that of the myocardial oxygen demand, thereby creating potential for steal [43-45]. Steal is the diversion of blood from a myocardial bed with limited or inadequate perfusion to a bed with more adequate perfusion, especially one that has a remaining element of autoregulation [46,47]. In instrumented animal models, the pronounced coronary vasodilation produced by isoflurane was shown to cause steal and early patient studies provided additional support [48,49]. However, more recent work in a chronically instrumented, canine model of multivessel coronary artery obstruction has shown that neither isoflurane, sevoflurane, nor desflurane at concentrations up to 1.5 MAC resulted in abnormal collateral coronary blood flow redistribution (steal), whereas adenosine, a potent coronary vasodilator, clearly resulted in abnormal flow distribution [50]. Interestingly, sevoflurane favorably increased (rather than decreased) collateral coronary blood flow in this instrumented animal model when aortic pressure was held constant (similar to what might be seen with systemic blood pressure support) [50].

The study compared the stress response in patients with coronary artery disease undergoing myocardial revascularization anesthetized with either sufentanil and oxygen or enflurane-nitrous oxide and oxygen 51-54]. Throughout induction and maintenance of anesthesia, and while the patients were in the intensive care unit, hemodynamics plus plasma catecholamine, sufentanil, and enflurane concentrations were recorded and compared, suggesting that higher blood levels of sufentanil can attenuate, but not eliminate, the stress response to CPB, as can enflurane, and that both the narcotic and inhalation anesthetic techniques for patients with coronary artery disease were quite satisfactory [51-55].

The cardioprotective effects of a volatile anesthetic regimen were also observed subsequently in cardiac surgery. Conzen et al. found significantly better cardiac function in patients who received sevoflurane for maintenance of anesthesia during surgery compared with patients who received propofol maintenance anesthesia [35]. Administration of volatile anesthetic gases was protective for patients undergoing cardiac surgery through manipulation of the potassium ATP (KATP) channel, mitochondrial permeability transition pore (mPTP), reactive oxygen species (ROS) production, [56-59] as well as through cytoprotective Akt and extracellular-signal kinases (ERK) pathways [57- 60] (Figure 1).

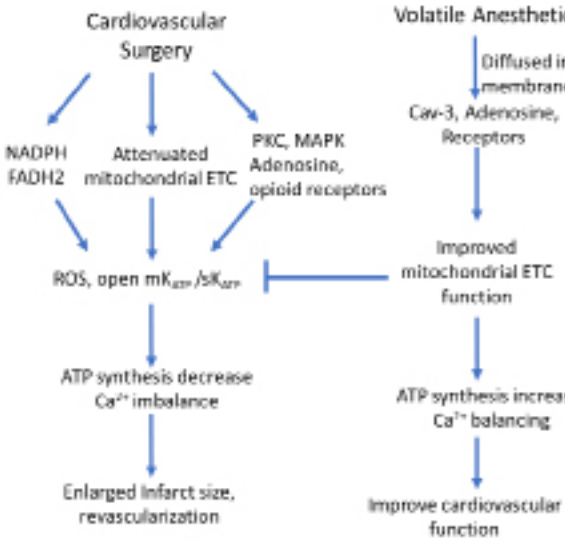

Figure 1: Possible protective mechanism for volatile anesthetic in the cardiovascular system. Note the several signal pathways that may lead to cardiovascular injury by priming of mitochondrial (m) $_{KATP}$ channels and ROS generation beginning with ROS generation resources (NADPH, FADH2) through sarcolemmal and mitochondrial membranes. Volatile Anesthetics are slowed mitochondrial respiration, decreased production of oxygen-derived radicals, which leads to balance m$_{KATP}$ and sarcolemmal sK$_{ATP}$ channel with down regulation of overactivated mitochondrial function.

NADPH-Nicotinamide Adenine Dinucleotide Phosphate; FADH2-Reduced Flavin Adenine Dinucleotide; ETC-Electron Transport Chain; Cav-3-Caveolin-3; PKC-Protein Kinase C; MAPK- Mitogen Activated Protein Kinase

The authors of a study observed that the length of stay in the intensive care unit seemed to be related to the choice of anesthetic regimen [61,62]. The use of a volatile anesthetic regimen during cardiovascular surgery was associated with a decreased incidence of prolonged stay (>48 h) in the intensive care unit compared with use of a total IV anesthetic regimen. The individual variables responsible for a prolonged length of stay were occurrence of atrial fibrillation, increase in postoperative troponin I levels >4 ng/mL, and the need for prolonged inotropic support (>12 h). Although the incidence of atrial fibrillation was similar with all anesthetics studied, the number of patients with an increased troponin I level >4 ng/mL and those receiving prolonged inotropic support were significantly less

with the volatile anesthetic regimens compared with the total IV anesthetic regimens. These clinical results suggest that the cardioprotective effects of volatile anesthetics well described in animal studies do appear to translate to the clinical setting [61,62].

In the Future

Abounding evidence has shown that pretreatment with volatile anesthetics protects against cardiovascular injury including ischemia reperfusion and vascular surgery in both animal and clinical studies. Future investigations need to evaluate the most optimal anesthetic agent, concentration and administration approach for the best cardiovascular protective benefits of pretreatment or treatment, as studies have noted that there is a difference in cardioprotection dependent upon pretreatment protocol with inhalant anesthetics. Additionally, a comprehensive mechanistic model needs to be elicited that integrates all mechanisms evaluated thus far. However, further studies are needed to explore and confirm these mechanisms, which include: volatile anesthetics sensor recipient, cell membrane distributor sensor for volatile anesthetics, signaling responsory for volatile anesthetics and the nuclear sensor.

Another important area of clinical research is determination of whether the organ protective effects observed in the myocardium also apply to other tissues. Experimental evidence is emerging that volatile anesthetics may also offer a degree of protection against the effects of ischemia and reperfusion in the brain [63,64], the resuscitation [65] and the kidney [66].

The cardioprotective effect of volatile anesthetics has been supported by studies in patients during coronary surgery. However, further investigation is needed to determine whether the observed experimental and clinical cardioprotective effects of volatile anesthetics indeed translate into decreased morbidity and mortality in patients undergoing cardiac and noncardiac surgery.

We conclude the results of laboratory studies provide mechanistic pathways supporting the cardiovascular protective effect of pretreatment with inhalant anesthetics. Our opinion is these effects should be beneficial to patients with cardiovascular system injured disease who are undergoing surgery. Tailoring of inhalational agents to the patients' needs, based on patients cardiac and vascular conditions and their cardiac performance to make the anesthetics optimal option, is a balancing between desirable features and disadvantages. However, the optimum dose and timing of inhaled anesthetics administration for it must be further personalized and investigated.

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