Myocardial Protection by Desflurane: From Basic Mechanisms to Clinical Applications

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Abstract: Coronary heart disease is an affliction that is common and has an adverse effect on patients' quality of life and survival while also raising the risk of intraoperative anesthesia. Mitochondria are the organelles most closely associated with the pathogenesis, development, and prognosis of coronary heart disease. Ion abnormalities, an acidic environment, the production of reactive oxygen species, and other changes during abnormal myocardial metabolism cause the opening of mitochondrial permeability transition pores, which disrupts electron transport, impairs mitochondrial function, and even causes cell death. Differences in reliability and cost-effectiveness between desflurane and other volatile anesthetics are minor, but desflurane has shown better myocardial protective benefits in the surgical management of patients with coronary artery disease. The results of myocardial protection by desflurane are briefly summarized in this review, and biological functions of the mitochondrial permeability transition pore, mitochondrial electron transport chain, reactive oxygen species, adenosine triphosphate-dependent potassium channels, G protein–coupled receptors, and protein kinase C are discussed in relation to the protective mechanism of desflurane. This article also discusses the effects of desflurane on patient hemodynamics, myocardial function, and postoperative parameters during coronary artery bypass grafting. Although there are limited and insufficient clinical investigations, they do highlight the possible advantages of desflurane and offer additional suggestions for patients.

Key Words: coronary heart disease, desflurane, inhalation anesthetics, metabolism, mitochondria, myocardial protection, reactive oxygen species

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CORONARY HEART DISEASE

The Physiological Properties of the Heart

The heart is the organ with the highest oxygen and energy consumption, and its main energy sources include plasma free fatty acids (FFAs) and aerobic oxidation of carbohydrates.[1] FFAs and glucose maintain a relative balance under physiological conditions by metabolic competition.[2] Not only is glucose aerobically oxidized more efficiently than FFAs, in metabolites compared with fatty acid–induced myocardial diastolic dysfunction, glucose maintains cellular homeostasis and reduces myocardial injury after ischemia.[3] Myocardium is rich in mitochondria, which determine cell death and survival through multiple pathways.

The Pathophysiological Mechanisms of Ischemia-Reperfusion

During the progression of coronary heart disease (CHD), myocardial ischemia gradually worsens and even acute coronary artery occlusion occurs, requiring reperfusion therapy to restore blood circulation. In addition to coronary artery bypass grafting (CABG), the establishment and promotion of cardiac surgery extracorporeal circulation and organ transplantation have allowed tissues and organs to be reperfused with blood after ischemia. However, sometimes after restoring blood flow on the basis of ischemia, not only does it fail to restore tissue and organ functions, but also aggravates damage.

The area at risk is an area of the myocardium that is hypoperfused because of occlusion of the epicardial coronary arteries.[4] Massive necrosis happens when there are no collateral arteries or fast coronary reperfusion. The myocardial infarct area is determined by the duration of myocardial ischemia, the size of the area at risk, tissue temperature during ischemia, hemodynamics during ischemia, and residual blood flow through the branches.[5] Heart rate is the key hemodynamic parameter because it affects energy consumption and coronary blood flow.[6] However, hemodynamics can only slightly change infarct size. The myocardium has considerably lower demands as a result of the area's lack of contraction; therefore, the absence of blood and energy supply has less impact on the infarct's growth.[7]

Glucose transporter (GLUT) 4 is the main GLUT in cardiomyocytes.[8] Myocardial ischemia inhibited GLUT4 translocation leading to reduced myocardial glucose uptake, indicating that utilization efficiency and glycogen content were significantly associated with cardiac ischemia-reperfusion injury (IRI).[9] Some classical ischemia-reperfusion (IR) drugs ameliorate IRI by increasing GLUT4 mRNA expression and decreasing myocardial insulin resistance.[10] Anaerobic glycolysis not only leads to acidosis allowing Na^+ influx through the Na^+/H^+ exchanger, but the lack of adenosine triphosphate (ATP) also inhibits Na^+/K^+-ATPase, both of which promote

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the accumulation of intracellular Na^+.[7] Subsequently, the Na^+/Ca^{2+} exchanger works in reverse mode resulting in intracellular Ca^{2+} overload. Once reperfusion occurs, increased cytoplasmic Ca^{2+} accompanied by rapid normalization and reactivation of acidic pH induces the release-reuptake of Ca^{2+} from the sarcoplasmic reticulum and uncontrolled sarcoplasmic fiber hypercontraction.[11] Normalization of pH also activates calpain to digest the cytoskeleton and sarcolemma.[12] When the extracellular osmotic pressure immediately returns to normal through reperfusion, high Na^+ and Ca^{2+} levels can cause intracellular edema (Fig. 1). Excessive formation of reactive oxygen species (ROS) during abnormal myocardial metabolism can also lead to cell membrane disruption.[13]

Ischemic preconditioning (IP) and ischemic postconditioning are well-known protective strategies to reduce the size of the infarct. Research evidence suggests that all regulative strategies to protect myocardium and reduce infarct size are effective only when used in combination with eventual reperfusion, and that strategies to reduce IRI are critical.[14] Myocardial IRI is evident during cardiac surgery with extracorporeal circulation, and abnormal glucose metabolism is an important cause.[14] H^+ ion buildup, acidic environment, calcium overload, and ROS are all characteristics of IRI.[15] These alterations result in the opening of the mitochondrial permeability transition pore (mPTP), and the mobility and electron transport of the inner mitochondrial membrane are also impaired, exacerbating the dysfunction.[16] This vicious cycle causes cell death through releasing cytochrome C into the cytoplasm and activating the apoptosis-inducing cysteine aspartate protease system.[17]

The most important cellular organelles for cardiac energy metabolism, mitochondria are also crucial for a number of other cellular functions, such as the regulation of ROS generation, calcium homeostasis, and apoptosis. ROS is a major factor in the pathogenesis and progression of CHD. ROS is mainly from complexes I and III in the mitochondrial respiratory chain, and its production is strictly controlled by antioxidant enzymes under normal physiological conditions.[18] The damage caused by ROS includes the following: direct oxidative damage to proteins; impairment of proteins or phospholipids induced by the formation of lipid peroxidation products from oxidized lipids; involvement in DNA damage, especially in mitochondrial DNA; and damage to mitochondrial respiration by intracellular nitrosation, which is detrimental to cardiac health[18] (Fig. 2).

DESFLURANE

Comparison of Desflurane With Other Volatile Anesthetics

Desflurane, isoflurane, and sevoflurane are halogenated anesthetics commonly used in cardiac-related surgery. In view of the reliability and cost-effectiveness of anesthesia, no significant differences were found between desflurane, sevoflurane, and isoflurane in basic performance on liver and kidney function, respiratory parameters, and blood gas levels.[19,20] The type, duration, and frequency of exposure to volatile anesthetics before myocardial ischemia have been shown to be potentially relevant in in vitro experiments.[21] The ability of anesthetic

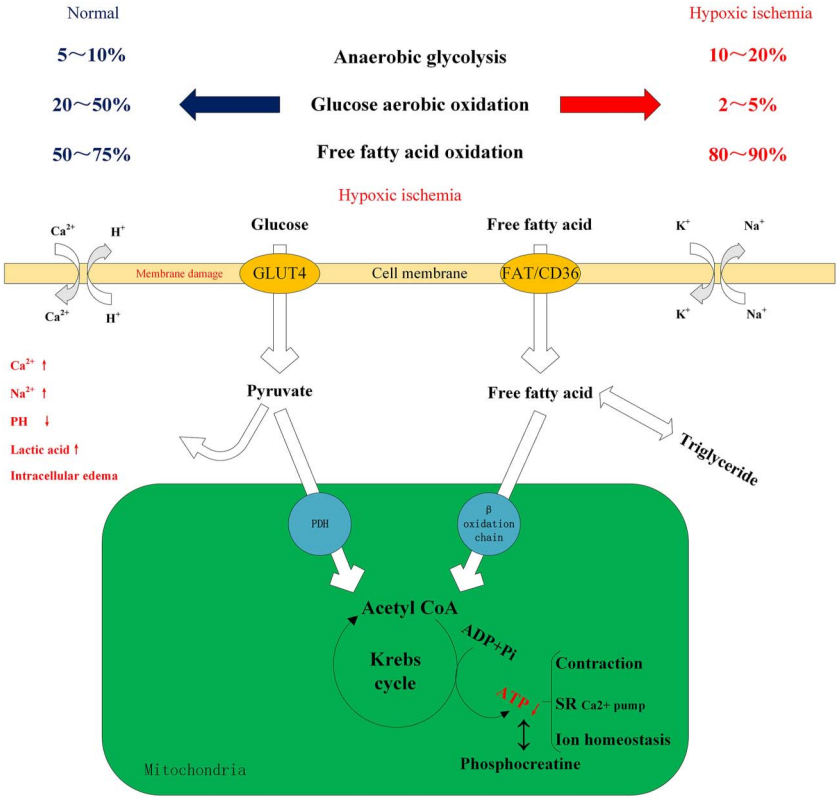

FIGURE 1. As a highly oxygen-depleted organ, aerobic oxidation of plasma free fatty acids and carbohydrates is the most important source of energy for the heart. Myocardial ischemia and hypoxia result in decreased production of adenosine triphosphate, disruption of myocardial contractile function, and homeostasis of ion electrical activity. Increased intracellular anaerobic glycolysis contributes to lower intracellular pH, calcium ion overload, and sodium/potassium-ATPase inhibition, whereas high cytoplasmic levels of sodium and calcium ions can cause intracellular edema.

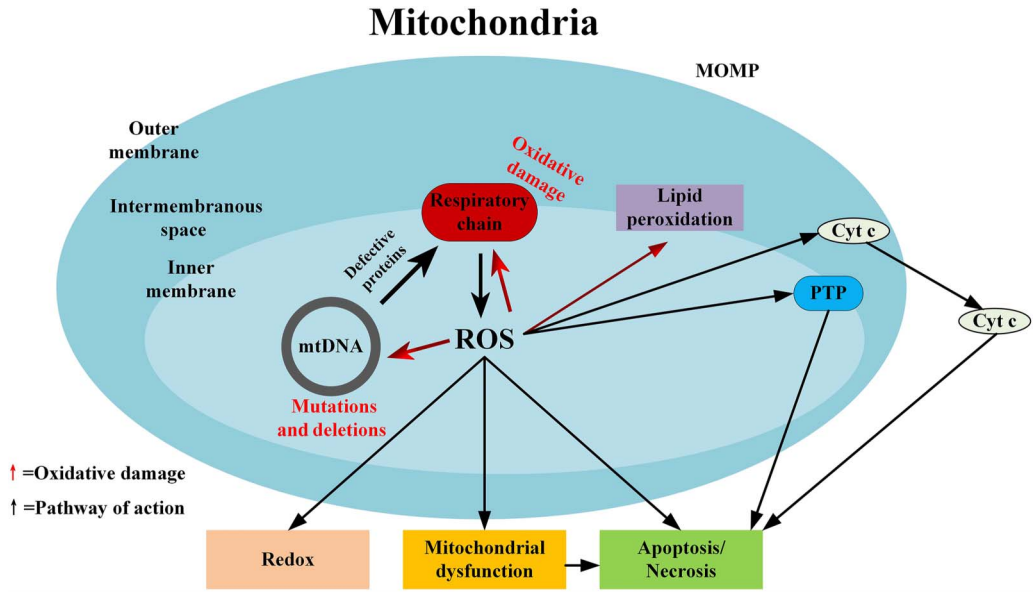

FIGURE 2. Mitochondrial ROS can be used as a tunable redox signal to reversibly affect the activities of a series of functions in the mitochondria, cytoplasm, and nucleus. However, excess ROS can cause oxidative damage to both mitochondrial proteins, cell membrane, and DNA, thereby reducing the ability of mitochondria to synthesize ATP. When mitochondria are oxidatively damaged, the outer mitochondrial membrane is permeabilized, releasing interstitial proteins such as cytochrome c into the cytoplasm, thereby activating apoptosis. In addition, mitochondrial ROS induces mPTP, causing the inner membrane to permeabilize small molecules in the presence of IRI.

preconditioning from isoflurane to sevoflurane to desflurane to protect the myocardium has been found to be significantly enhanced.[22] During stress state, patients with CHD have limited coronary and cardiac reserve capacity, such as a reduced ability to increase coronary blood flow and cardiac output. Anesthetic maintenance agents should be administered in a manner that minimizes circulatory changes. Hemodynamic effects from anesthetics such as tachycardia and hypotension may deplete subendocardial vasodilator reserves, thereby increasing the likelihood of pharmacologically induced coronary steal syndrome. Vascular hyperactivity is a common feature in patients with CHD, and the significant intraoperative changes in blood pressure that are common can lead to severe myocardial oxygen homeostasis and impaired left ventricular function.[23] Compared with volatile anesthetics such as sevoflurane and isoflurane, desflurane can rapidly control blood pressure without altering heart rate, systemic vascular resistance, etc.[24] Considering some of the advantages shown by desflurane over other halogenated anesthetics, we speculated that desflurane has a myocardial protective effect in patients with CHD and discussed the specific mechanism.

Desflurane in Experimental Researches

Desflurane could provide cardiac cytoprotection and prevent ischemic reperfusion events, whether used as anesthetic preconditioners or anesthetic agents (see **Table**, **Supplemental Digital Content 1**, http://links.lww.com/JCVP/A958).

Desflurane and the Mitochondrial Permeability Transition Pore

Animal studies have found a protective effect on myocardial IRI after treatment with inhaled anesthetic drugs.[25] The mPTP may be responsible for mitochondria-driven cell death after IRI.[26] Features of IRI such as accumulation of H^+ ions, acidic environment, calcium overload, and ROS formation lead to the opening of the mPTP, affecting electron transport and exacerbating mitochondrial dysfunction.[22] Desflurane acts as a downstream inhibitor of mPTP by preserving mitochondrial electron transport capability,[27] which is only partially elucidated in the myocardial protective effects of desflurane. For example, Piriou et al[28] found that desflurane increases the resistance of the mPTP to calcium-induced opening after preconditioning in rabbit hearts, causing the pore to close during cardiac reperfusion. Similar cardioprotective effects of desflurane were observed in another in vitro experiment on rat hearts by Heiberg et al.[29] Desflurane has also been shown to achieve inhibition of mPTP opening by reducing the expression of the proapoptotic protein Bax and improving the expression of Bcl-2 for anti-apoptosis and cardioprotection.[30] As mentioned earlier, the effects of desflurane on the mPTP may, indeed, be a class of effects in which it acts on the heart.

Desflurane and the Mitochondrial Electron Transport Chain

Researchers have observed that using volatile anesthetics on isolated mitochondria attenuates ischemia-related damage caused by the electron transport chain (ETC) in mitochondrial enzymes with a series of experimental results that corroborated this observation: Complex I inhibitors reduce mitochondrial electron flow when administered immediately before ischemia,[31] whereas volatile anesthetic pretreatment complements the action of complex I inhibitors

by decreasing electron transport and increasing nicotinamide adenine dinucleotide levels.[32] The presence of trace amounts of superoxide before the onset of ischemia eliminates cytotoxic superoxide bursts that normally occur during ischemia and reperfusion. Moreover, it has been shown that the applying volatile anesthetics before ischemia stimulates the production of preischemic superoxide and, thus, exerts a protective effect, which is diminished by the simultaneous application of superoxide and the nitric oxide scavenger.[33] Extrapolation from a range of indirect evidence leads to the conclusion that volatile anesthetic preconditioning triggers protective effects on mitochondrial enzymes through the respiratory chain and mediates myocardial protection through substances such as ROS, superoxide, and nitric oxide free radicals. Conversely, reaction products, such as ROS, send positive feedback signals and feedback damage status at complex I by mediating volatile anesthetic-induced attenuation of mitochondrial electron transport,[34] which in turn increases ROS production, triggers anesthetic preconditioning secondary to altered mitochondrial function, and modulates net mitochondrial electron transport[32] (Fig. 3).

Once mitochondria can be reactivated during reperfusion and electron transport resumed in time, this would prevent the production of cytotoxic superoxide and further prevent the opening of the mPTP (which corroborates the previous part), a process that requires the coupling efficiency of electron transport that may be ensured by the aforementioned hypothesis. As a result, another powerful measure of the protective effect of desflurane may be the scavenging of substances such as superoxide and peroxynitrite radicals, which are induced during its cardioprotection.

Deflurane and Reactive Oxygen Species

ROS are intracellular signaling molecules from the mitochondrial ETC that trigger early and delayed cardioprotection. Cellular ROS levels are elevated after mitochondrial exposure to sublethal oxidative stress (preconditioning stimulus). During myocardial protection induced by volatile anesthetic preconditioning, ROS play a key role in the oxidative signaling cascade: The oxidative signaling cascade may trigger desflurane preconditioning; desflurane preconditioning may induce superoxide production; and the production of ROS-containing superoxide in turn triggers the second messenger mechanism responsible for preconditioning such as inositol triphosphate, Ca^{2+}, and nitric oxide.[33] ROS activation of protein kinases, various ion channels, hypoxia-inducible factors, and other multiple transcription factors leads to cardioprotection and amplifies preconditioning stimuli through phospholipase C and protein kinase C (PKC).[35]

In a study on rats, pretreatment of isolated adult rat ventricular cardiomyocytes with desflurane significantly reduced cell death induced by oxidative stress.[36] When cardioprotection is induced by volatile anesthetics, IP, or endogenous substances, the beneficial effects of early IP can be blocked once a free radical scavenger is given before ischemia.[37] Sun et al[35] reported evidence for an important role of ROS in late preconditioning. Thus, the generation of ROS during preconditioning initiation is an important trigger for early and delayed cardioprotection. Although desflurane exerts myocardial protection in volatile anesthetic preconditioning by inducing ROS production,[38] excessive ROS in turn can cause damage to mitochondria. Desflurane also exerts cardioprotection by attenuating the toxic effects of excessive ROS.[39]

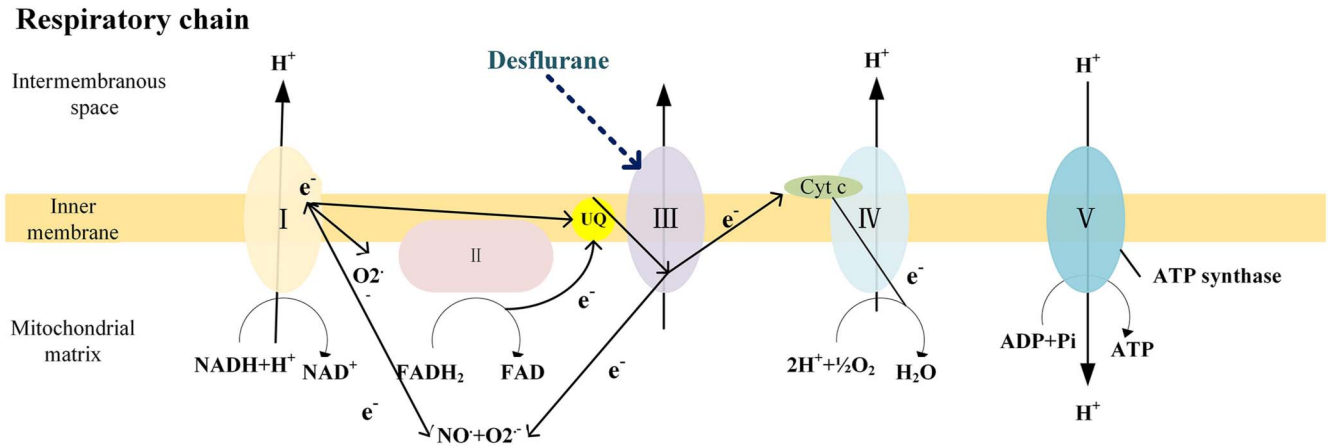

FIGURE 3. In complexes I and II of electron transport, reduced nicotinamide adenine dinucleotide and reduced flavin adenine dinucleotide are reoxidized to nicotinamide adenine dinucleotide and flavin adenine dinucleotide, respectively, which provides electrons for the reduction of oxygen to water in complex IV. Ubiquitin, complex III, cytochrome c, and complex IV pump protons from the mitochondrial matrix into the membrane gap through electrons from complex I or II, creating a proton gradient and building a membrane potential across the inner mitochondrial membrane that allows protons to re-enter the mitochondrial matrix and synthesize ATP through complex V. Superoxide ($O2^-$) from complexes I and III can react with nitric oxide (NO) to form peroxynitrite ($ONOO^-$), weakening electron transfer from complex I and leading to increased formation of $O2^-$. Desflurane impairs electron transport in complex III, leading to an increase in reduced nicotinamide adenine dinucleotide/reduced flavin adenine dinucleotide levels and a decrease in nicotinamide adenine dinucleotide/flavin adenine dinucleotide levels; the opening of K_{ATP} channels leads to the opposite change.

Deflurane and ATP-Dependent Potassium Channels

In a study involving the mechanisms of the cardioprotective effects of desflurane during reperfusion, Lemoine et al[40] found that the ATP-dependent potassium (K_{ATP}) channels on the mitochondrial membrane also worked in ischemic postconditioning. Nonspecific blockers identify the role for mitochondrial and sarcolemmal K_{ATP} channels in volatile anesthetics-induced preconditioning.[41] Hanouz et al[42] discovered that selective mitochondrial K_{ATP} channel inhibitors but not selective sarcolemmal K_{ATP} channel inhibitors suppressed desflurane-induced preconditioning. Toller et al[43] found that both K_{ATP} channels may be involved in desflurane-mediated preconditioning in an in vivo dog model of local ischemia. The negative inotropic effect of desflurane may be related to intramyocardial catecholamine release. In the presence of α- and β-adrenoceptor blockade, this effect was less than that induced by desflurane alone.[44] Lange et al[45] found that desflurane preconditioning reduced myocardial infarct size and its effect was inhibited by esmolol. Coupled with evidence that the preconditioning effects of desflurane are triggered by multiple signaling cascades, it is hypothesized that the different sequential activation of the 2 K_{ATP} channels is due to the activation of different signaling pathways by low and high concentrations of desflurane. Overall, desflurane increases mitochondrial K_{ATP} and sarcolemmal K_{ATP} channel activity, and the protective effect on IR myocardium is mainly mediated by the former.

There is substantial crosstalk between sarcolemmal and mitochondrial K_{ATP} channels, but they play different roles in preconditioning. Mitochondrial K_{ATP} channels are mainly responsible for infarct size reduction, whereas sarcolemmal K_{ATP} channels restore heart rate and other functions.[46] Mitochondrial K_{ATP} channels not only prevent cardiomyocyte apoptosis and delay preconditioning protection, but are also critical for mitochondrial respiration. Opening mitochondrial K_{ATP} channels reduced ischemia-related mitochondrial gap swelling and maintained functional coupling between adenosine nucleotide transporter enzymes and mitochondrial creatine kinase.[47] Desflurane has been shown to inhibit mitochondrial swelling, increase membrane potential, and improve mitochondrial respiratory complex I + III and IV function.[48] This allows the transport of newly synthesized ATP from the ATP synthase production site on the inner mitochondrial membrane to the energy-depletion site. Mitochondrial K_{ATP} channels also exert an indirect protective effect by increasing ROS formation (in the pro-oxidant environment of the cytochrome b-c1 fragment of ETC complex III).[49]

Desflurane and G Protein–Coupled Receptors and Protein Kinase C

G protein–coupled receptors (GPCRs) and PKC are also important targets for myocardial protection during IP. In a volatile anesthetic preconditioning model, the reperfusion injury remediation kinase pathway of GPCRs directs cardioprotection from cell surface receptors to mitochondria.[50] GPCRs inhibit Ca^{2+} inward flow, regulate cellular metabolism, and activate K_{ATP} channels during ischemia.[51] Direct activation of phospholipase by G proteins under stimulation releases Ca^{2+} from the sarcoplasmic reticulum through the formation of inositol triphosphate and receptor binding and activates different isoforms of PKC. PKC can be activated by mitochondrial-generated ROS during transient ischemia or subsequent repetitive reperfusion. Activated PKC leads to translocation of isoform PKC and phosphorylation, which activates sarcolemmal and mitochondrial K_{ATP} channels.[52] Desflurane selectively enhances myocardial protection mediated by mitochondrial K_{ATP} channels through multiple PKC-coupled signaling pathways.[53] After IP, PKC activity was reduced in the cytoplasm and increased in the nucleus, mitochondria, and membrane.[54]

GPCRs includes β1- and β2-adrenergic receptors as well as adenosine-A1 receptors. Desflurane mainly stimulates β-adrenergic receptors for preconditioning and postconditioning.[55] Desflurane stabilizes the open state of mitochondrial K_{ATP} channels and sarcolemma K_{ATP} channels by stimulating adenosine receptors to activate PKC as well as increasing nitric oxide (NO) and ROS formation and further by phosphorylation.[40] The opening of K_{ATP} channels ultimately reduces cytosolic and mitochondrial Ca^{2+} overload, cell death, and improving myocardial survival.

In conclusion, mitochondria play a fundamental role in the protective effect of desflurane on the myocardium. By using mitochondria as a direct target, desflurane ultimately leads to a reduction in cellular oxygen demand, reduces inflammatory mediators, and prevents mitochondrial calcium overload through multiple mechanisms. Desflurane induces mitochondrial inner membrane depolarization, maintains mitochondrial volume and endostasis to reduce excessive ROS production and mitochondrial calcium accumulation, provides an optimal medium for ATP production, and inhibits the opening of the mPTP pore. The gold standard endpoint for assessing preconditioning status and its protection is the reduction in infarct size,[56] which is the ultimate goal common to the above mechanisms of action. Desflurane reduced biomarkers of myocardial injury, decreased the size of myocardial infarction, and promoted recovery of myocardial contractility after hypoxia in animal models.[57,58]

Desflurane in Clinical Application

At least 2 characteristics should be present in an ideal anesthetic for patients with CHD: First, the associated cardiovascular changes have no adverse effect on myocardial oxygen balance; second, the associated cardiovascular changes have no effect on left ventricular function. Desflurane has cardiac depressant properties that reduce myocardial oxygen demand and improve myocardial oxygen balance in ischemic patients; moreover, its pharmacological properties unrelated to anesthetic or hemodynamic effects may directly protect against ischemic myocardial injury, making it a potentially suitable anesthetic for patients with CHD.[23] In this section, in addition to focusing on the role of desflurane in CABG, we also discussed its effects in other surgeries requiring ischemia-reperfusion (see **Table**, **Supplemental Digital Content 2**, http://links.lww.com/JCVP/A959).

Myocardial Conditioning With Desflurane: Meta-analyses

At the 2018 International Consensus Conference, volatile anesthetics were confirmed as a nonsurgical

intervention for reducing mortality in patients undergoing heart surgery.[59] A risk-adjusted analysis of CABG involving 34,310 patients found a lower 30-day mortality in the volatile anesthetic group and weak correlation with 30-day mortality.[60] However, which volatile anesthetic has better protection is not clarified. Based on previous studies, this review focused on CABG surgery and analyzed whether desflurane provides benefit to patients.

A comprehensive review of global meta-analyses on the results of randomized clinical trials involving desflurane revealed that volatile anesthetics were found to be associated with a significant reduction in myocardial infarction. The cardioprotective effect of desflurane was demonstrated by comparing the results of perioperative cardiac surgery patients anesthetized with desflurane or propofol, which had a 2-fold and 4-fold lower incidence of myocardial infarction and mortality than propofol, respectively.[61] Compared with total intravenous anesthesia (TIVA), desflurane alone was associated with a reduction in cardiac surgical mortality, with results confirmed in trials with low risk of bias, in large trials, and when including only CABG studies.[62] Other meta-analyses also supported the findings that the use of desflurane in cardiac surgery led to a reduction in mortality and a reduction in the incidence of pulmonary complications.[63,64] Pulmonary complications were the most common complication. In summary, these results showed that desflurane enhanced myocardial protection and reduced the incidence of perioperative death, myocardial infarction, and myocardial dysfunction, consistent with the observations of medium-sized randomized controlled trials.[65] However, the results of clinical studies vary widely; therefore, meta-analyses sometimes reach different conclusions. For example, the same authors did not observe any beneficial effects when comparing desflurane anesthesia with intravenous anesthesia in high-risk cardiac surgery, which involved prolonged intensive care unit (ICU) stay, mortality, or a composite endpoint of both.[66] As mentioned earlier, in cardiac surgery, desflurane offer some key benefits, whereas in noncardiac surgery, a more common type, the outcomes were not encouraging,[63,67] suggesting that this question has not been conclusively addressed.

Desflurane in CABG

In high-risk patients, desflurane was found to be efficient in controlling the patient's blood pressure response to surgical stimuli and maintaining the cardiac index and pulmonary capillary wedge pressure at the same level before and after induction, demonstrating that the hemodynamic response because of noxious stimuli during the perioperative period can be attenuated by desflurane.[68] Desflurane maintained mean arterial pressure and contractility better than isoflurane at similar anesthetic concentrations in CABG.[69] The better control of blood pressure in the desflurane group appears to be due to the pharmacokinetic properties of the drug rather than to differential effects on cardiac contractility or loading conditions.[70] However, in noncardiac surgery, desflurane has more potent vasodilatory properties than sevoflurane at equivalent doses, resulting in higher perfusion index and lower blood pressure.[71] The difference in blood pressure control outcomes in cardiac and noncardiac surgeries require further studies to explain.

The regulation of myocardial function is a fundamental strategy for the management of myocardial IRI desflurane can promote the recovery of reoxygenation myocardium after hypoxia.[40,72] Like other volatile anesthetics, desflurane had no adverse effects on diastolic function in patients undergoing CABG with preoperative diagnosis of diastolic dysfunction.[73] But in patients undergoing cardiac surgery, administration of sevoflurane dose-dependently reduced left ventricular systolic performance by reducing peak systolic tissue Doppler velocity (S′) in the lateral mitral annulus.[74] Isoflurane similarly dose-dependently reduced left ventricular systolic long-axis performance during cardiac surgery with preserved preoperative systolic function.[75] Desflurane had no adverse effect on length-dependent regulation of left ventricular function and preserved left ventricular function after extracorporeal circulation in patients undergoing high-risk (>70 years, with three-vessel disease, ejection fraction <50%, and impaired length-dependent regulation of myocardial function) coronary artery surgery.[76] After CABG, patients on desflurane had lower troponin I and NT-proBNP levels, and fewer patients required inotropic medications.[56,77] A comparative study of myocardial protection between sevoflurane and desflurane was conducted by Sivanna et al,[78] who measured Trop-T, creatine phosphokinase-MB, and myocardial performance index preoperatively and 4 hours postoperatively and found a significant decrease in postoperative myocardial performance index in the sevoflurane group and concluded that desflurane exerted better cardioprotection during CABG.

Postoperative observations such as length of stay, complication rates, and mortality rates are also important indicators for evaluation. Hert et al[79] found that under a desflurane-remifentanil–based anesthetic regimen, not only was the patient's postoperative cardiac function better protected, but also ICU and hospital length of stay were shortened. The beneficial effects of desflurane were also supported by the later findings of Guarracino et al[77] on hospital stay in patients after CABG. A study on the effect of anesthetic regimens on postoperative complications of CABG found that volatile anesthetics (desflurane, isoflurane, and sevoflurane) may be associated with lower rates of postoperative myocardial infarction and hemodynamic complications in patients compared with TIVA.[80] Postoperative mechanical ventilation provides essential ventilatory support, but the duration of ventilation is closely related to the chance of patients developing complications such as impaired respiratory function. Zhang et al[64] found that volatile anesthetics, including desflurane, shortened the duration of mechanical ventilation. In a multicenter randomized controlled study, desflurane reduced the need for postoperative inotropic support and tended to reduce the duration of mechanical ventilation in patients compared with those receiving propofol.[81] Early postoperative cognitive impairment is also a common complication after CABG, and desflurane also presented a beneficial effect compared with propofol.[82] A cohort study involving 34,310 patients found that volatile anesthetics, including desflurane, were associated with a significant reduction in risk-adjusted 30-day mortality.[83] Another longer mortality

study found lower 1-year mortality in the desflurane (DES) group compared with the TIVA group (6.9% vs. 12.3%).[65] Although evidences support the use of desflurane as a factor in reducing morbidity and mortality, such as the difference in the incidence rates of serious cardiac complications observed 1 year after cardiac surgery of 8.3% and 24.4% in the desflurane and propofol groups, respectively, the high complication rate is not well explained.[61]

General anesthesia does not contain only a single drug, but a combination of drugs. High-dose propofol given during cardiopulmonary bypass reduced postoperative cardiomyocyte injury compared with isoflurane or low-dose propofol anesthesia.[84] In studies of adults undergoing on-pump or off-pump CABG, the use of desflurane had the least effect on cardiac index compared with propofol.[85] Johan et al demonstrated that both desflurane and propofol are cardioprotective and that the former is more potent; however, the additional benefit of desflurane disappears if used concurrently with propofol (35 mg/kg/h).[29,86] Some studies also observed that volatile anesthetics can exert beneficial effects or enhance myocardial protection even under conditions where the 2 are combined.[65,87] Onk et al[88] found that low-dose propofol (2–3 mg/kg/h) and continuous desflurane inhalation were more effective than propofol alone (5–6 mg/kg/h) or a short course of desflurane in CABG. These evidence suggest that the cardioprotection of desflurane with other drugs is a complex matter, showing different effects under different conditions of drug concentration, time of administration, etc. The mechanisms underlying this difference in action require further study. And, it is well known that etomidate has a more modest effect on cardiovascular function and hemodynamic stability for high-risk patients. What effect would it have if propofol were replaced by etomidate when used in combination with desflurane? Researches in this area are much needed.

The similar pretreatment cardioprotective effects of opioids may also conceal the effects of volatile drugs, but the doses of opioids for anesthesia are considerably lower than the doses for cardioprotection. For example, 3 intravenous injections of 5 mg of morphine at 5 minutes intervals each pretreatment can significantly reduce the extent of myocardial infarction after cardiac IR in rats; however, the dose commonly used for analgesia in anesthesia is about 5 mg.[89] This may explain why intraoperative opioid dosing regimens have not been confined or designated in studies on the benefits of volatile drugs. Extra care also needs to be taken in these 3 situations involving old age,[90] diabetes,[91] or the concomitant use of sulfonylureas[92] because their attenuating effect on volatile anesthetics can lead to intractable problems.

Several modes of administration ranging from single exposure to desflurane for 5 minutes before myocardial ischemia to total inhalation anesthesia have been studied in previous studies.[56,80] Combining the various possible strategies, it seems that the idea proposed by Landoni et al[93] may be promising for clinical application by holding volatile anesthetics for clinical and pretreatment purposes at a minimum level of 1.0 minimum alveolar concentration (MAC) for a minimum of 30 minutes, discontinuing volatile agents for 15 minutes or more before extracorporeal circulation, and going through at least 3 wash-in and wash-out periods when using volatile anesthetics, with the wash-in period being at a minimum of 0.5 MAC for 10 minutes and the wash-out period lasting 10 minutes or longer. These strategies for potentially enhancing the cardioprotective effects of desflurane provide ideas for subsequent clinical studies on cardioprotection. More clinical studies will be needed to determine which strategy is more effective.

Desflurane in Valve Surgery

Landoni et al[94] randomly assigned 59 patients undergoing mitral valve surgery to receive desflurane for 30 minutes before cardiopulmonary bypass. Although the postoperative peak troponin I phase was not significantly lower in patients receiving desflurane, in the subgroup of patients with combined coronary artery disease, the expected reduction in peak troponin I phase was achieved in patients receiving desflurane compared with those receiving propofol. In meta-analysis[95] and randomized controlled study[96] involving patients undergoing heart valve surgery, inhalation anesthetics were found to have no significant differences in mortality and major postoperative complications compared with TIVA. However, in aortic valve replacement, Kapoor et al[97] found that patients in the desflurane group had significantly shorter ICU and hospital stays and postoperative mechanical ventilation times compared with the TIVA group. The difference in these results may lie in the fact that different types of valve disease (with different degrees of myocardial ischemia) respond differently to desflurane. In the study of mortality and major postoperative complications, it was a study of inhaled anesthetics including desflurane as a whole, but different inhaled anesthetics have different effects on the heart. More studies focusing on desflurane in valve surgeries and measuring cardiac biomarkers, mortality, and postoperative complication rates are needed to further objectively confirm the role of desflurane.

Desflurane in Organ Transplantation

Early graft dysfunction in organ transplantation is mainly manifested by IRI, which causes an inflammatory response that leads to different clinical outcomes. Volatile anesthetics used during surgery have immunomodulatory effects that may also affect postoperative outcomes. General anesthesia protocols for organ transplantation usually use a combined intravenous and inhalation anesthesia. Shin found no significant differences in outcomes between the desflurane and desflurane-propofol groups by comparing liver transaminase levels, creatinine levels, inflammatory factor levels, and postoperative complication rates at different time points.[98] Toprak et al[99] compared the effects of desflurane and isoflurane on postoperative liver function in right hepatectomy living donors and found that international normalized ratio and postoperative liver tests such as aspartate aminotransferase and alanine aminotransferase were better with desflurane at the same dose. This finding also was supported by the results of Mangus et al.[100] In the study comparing desflurane and sevoflurane, Lee et al[101] found a significant reduction in postperfusion syndrome (PRS) in the sevoflurane group in liver transplant patients. The reason for the higher

incidence of PRS in the desflurane group might be the significantly higher blood loss. Although there was a significant difference in the incidence of PRS between the 2 groups, there was no difference in perioperative laboratory data or postoperative course, suggesting that mild PRS may be benign, similar to patients without PRS, with few clinical consequences.

The glomerular filtration rate is an important factor affecting the function of the transplanted kidney. Lee et al[102] comparing the effects of different volatile anesthetics on renal function in transplants found that glomerular filtration rate was greater in the desflurane group than in the sevoflurane or isoflurane groups before postoperative day 7; in the further comparison of desflurane and propofol, no significant improvement in renal function was found. Another, more detailed study evaluated hemodynamics, creatinine, glomerular filtration rate, and inflammatory factors and supported the finding that desflurane had no adverse effect on transplanted kidney function.[103] In comparisons between desflurane and sevoflurane, desflurane may be more beneficial in renal transplantation in regulatory T cells (Tregs).[104] And, in studies of pancreas transplantation, desflurane significantly increased early graft survival and reduced post-transplant clinical outcomes associated with IRI.[105]

Desflurane in Noncardiac Surgery

Although animal studies and clinical studies of cardiac surgery supported the view that desflurane is cardioprotective, there were no significant results in noncardiac surgery.[63] In 2019, Kwon et al[67] found that volatile anesthetics and TIVA exhibited equivalent effects in patients without preoperative myocardial injury in the observation of myocardial injury after noncardiac surgery. Later, Park et al[106] found that noncardiac surgery patients with preoperative myocardial injury and elevated cardiac troponin demonstrated significantly improved survival with intraoperative volatile anesthetics. However, this study was on volatile anesthetics and not specifically on the protective effects of desflurane, so we need further studies to confirm this beneficial effect of desflurane. Perhaps, because patients with CHD who undergo noncardiac surgery have greater myocardial self-regulation than those who undergo cardiac surgery. The former may be less dependent on the additional protective effects of drugs such as desflurane; however, it cannot be assumed that patients with CHD who undergo noncardiac surgery do not require this additional myocardial protection.

Adverse Events of Desflurane

The current studies focused on the overall adverse event (AE) rates for all types of surgeries with desflurane, but not specifically on AE rates when desflurane was administered to surgical patients undergoing cardiac-related surgeries or with CHD. Although the safety of desflurane is generally accepted, there have been some AEs reported during the 3 decades of clinical use. According to the food and drug administration (FDA) Adverse Event Reporting System database, desflurane produced a total of 1140 AEs between 1996 and December 2019, much lower than sevoflurane's 4,977.[107] Of these 1140 AEs, cardiac AE was the second most common category with an incidence of 23.9%, and the most common subcategories included bradycardia, cardiac arrest, and tachycardia. Desflurane increases the release of catecholamines in the heart muscle, which may lead to arrhythmias.[108] In healthy young volunteers, increased sympathetic activity because of desflurane may lead to transient hypertension and tachycardia, but this effect is transient and only occurs at desflurane concentrations greater than 7%.[109] However, in elderly patients at risk of CHD, the incidence of sympathetic activation was low.[23] Desflurane lowers blood pressure,[71] and for those patients with CHD who are at risk because of elevated heart rate and blood pressure, the likelihood of sympathetic overactivity during desflurane anesthesia observed in clinical practice is not high.

Relevant History of Desflurane in Surgical Applications

With more than 300 million patients undergoing major surgery worldwide each year, international consensus conferences have identified volatile anesthetics as key nonsurgical interventions based on their cardioprotective properties, with the primary aim of improving survival.[59] Guidelines from the European Society for Cardiothoracic Surgery have likewise advised that this feature should be applied to the anesthetic management of patients undergoing cardiac surgery.[110] Volatile anesthetics were advocated in the 2007 American College of Cardiology/American Heart Association (ACC/AHA) cardiovascular care guidelines to sustain general anesthesia in noncardiac surgical patients who are hemodynamically stable but at high risk of myocardial ischemia.[111] Because of the absence of appreciable benefits of volatile anesthetics versus propofol during noncardiac surgery, the ACC/AHA guidelines amended recommendations for selecting anesthetics for noncardiac surgery in 2014.[112]

There have been various reports on the cardiac effects of halogenated anesthetics in the past, but this review focuses on a group of studies on desflurane. Unlike other conventional preconditioning induction agents that must be administered directly into the coronary arteries, desflurane can be administered nonselectively. Desflurane-mediated or facilitated cardiac preconditioning is particularly beneficial during times of surgical stress in patients with high-risk cardiac disease. And, routine IP is clinically high risk. It is challenging to determine the optimal time of ischemia for each patient and to achieve cardioprotection without inducing cardiac ischemia, but desflurane is not required to induce a favorable oxygen supply-to-demand ratio because volatile anesthetic-induced protection also occurs at the time of arrest. Whatever the surgery, no single technique can easily overcome all the challenges that surgery brings to high-risk patients. If the mere application of a drug may improve cardiac function and reduce perioperative cardiac injury, it should be considered to support its use. With this review, we aim to initiate additional clinical studies to further demonstrate the clinical utility of desflurane for cardioprotection in surgical patients.

OUTLOOK

Desflurane not only provided strong protection in defined IRI models, it is safer for clinical use because it does not involve additional drug administration or any mechanical intervention. Desflurane might be effective in reducing mortality and the frequency of long-term cardiovascular complications in patients undergoing surgery for CHD, but the experimental data pertaining to myocardial protection have not been well translated into clinical practice and appropriately applied to other categories of surgical patients with underlying cardiac disease. Additional laboratory research and clinical trials are required to better overcome these issues. Understanding and overcoming the barriers associated with the concomitant conditions of myocardial injury in CHD and the conditions of targeted application seem to be key to the successful further application of desflurane-induced protection in clinical practice.

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