Ischemia-Reperfusion Injury and Volatile Anesthetics

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Received 7 November 2013; Accepted 18 December 2013; Published 2 January 2014

Academic Editor: Ahmet Eroglu

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Ischemia-reperfusion injury (IRI) is induced as a result of reentry of the blood and oxygen to ischemic tissue. Antioxidant and some other drugs have protective effect on IRI. In many surgeries and clinical conditions IRI is counteract inevitable. Some anesthetic agents may have a protective role in this procedure. It is known that inhalational anesthetics possess protective effects against IRI. In this review the mechanism of preventive effects of volatile anesthetics and different ischemia-reperfusion models are discussed.

1. Introduction

After the ischemic period reentry of the blood to tissue causes massive release of oxygen free radicals. These free radicals trigger enzymatic reactions, such as peroxidation of polyunsaturated fatty acids or plasma lipoproteins, which leads to oxidative destruction of cell membranes and the productions of toxic reactive metabolites and cell injury involving DNA, proteins, and lipids [1]. All of these events are called ischemia-reperfusion injury (IRI).

2. Pathophysiology and Clinical Presentation

IRI occurred mostly during anesthesia and intensive care practice. In cardiac surgery or tourniquet application for extremity surgery, thromboembolic events and revascularization, severe hypotension, and restoration of hypovolemic shock, in organ transplantation, can cause IRI. During the ischemia anaerobic glycolysis is activated and then establishment of reperfusion accompanied by pro- and anti-inflammatory cytokine release, polymorphonuclear neutrophil activation, and platelet adhesion to the vascular endothelium occur with production of reactive oxygen species and release of vasoactive factors [2–4]. On the other hand, plasma concentration of some enzymes such as catalase, glutathione peroxidase, superoxide dismutase, lactated dehydrogenase, and some metabolites such as malonyldialdehyde (MDA), ischemia-modified albumin (IMA), lactate, and reactive oxygen species (ROS) increases during postreperfusion period. As a result of these pathophysiological phenomena, local and systemic inflammatory responses are formed by different mechanisms [5–7].

The total antioxidant status (TAS) of human body counteracts oxidative stress and reperfusion injury. It was found that while ROS increased, TAS decreased as a result of oxidative stress [8]. However, most patients do not counteract severe complication despite increasing ROS. It was explained that patients with normal TAS can tolerate these negative effects of oxidative stress. However, advanced age, severe ill, traumatic, or cancer patients have lower TAS in their plasma [9, 10]. In these patients oxidative stress may cause destruction of DNA and some structures with protein and lipid.

Severe systemic inflammatory reactions as a result of massive inflammatory mediator release and reperfusion injury may activate endothelial cells in remote organs which are not exposed to initial ischemic injury [11]. The distant effect of ischemia reperfusion causes microvascular injury with leukocyte invasion on endothelium [12]. These events may lead to multiorgan failure and increased postoperative morbidity and mortality. It was reported that IRI may cause cardiopulmonary complication such as tachyarrhythmia and hypoxia [13].

A lot of studies are conducted to prevent IRI. Some of these are related to anesthesia method such as regional anesthesia, inhalation general anesthesia, or total intravenous anesthesia.
3. The Mechanisms of Protective Effects of Volatile Anesthetics

The effects of volatile anesthetics on IRI were investigated for several years [14–17]. It is known that volatile anesthetics, especially halogenated, have a protective role against IRI. These protective effects have been attributed to pre- and post-conditioning effects with apoptosis. The mechanisms of these effects have been investigated, and new pathways are asserted continuously. Kowalski et al. [18] stated that polymorphonuclear neutrophils (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 postschismic 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. 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 IRI in other studies [17, 19].

However, protective effects of volatile anesthetics against IRI are wondered and some studies were carried out to explain the mechanism. Novalija et al. [20] performed anesthetic preconditioning with sevoflurane and gained positive outcomes with isolated guinea pig hearts. They explained the positive effect of sevoflurane with improved adenosine triphosphate synthesis and reduced ROS formation in mitochondrial KATP channel after ischemia by a redox dependent mechanism. Kersten et al. [21] stated that volatile anesthetics improved recovery of contractile function of postschismic, reperfused myocardium, and activated KATP channels. For the same purpose Zaugg et al. [22] studied to test whether volatile anesthetics mediate this effect by activation of the mitochondrial adenosine triphosphate-sensitive potassium (mitoKATP) or sarcoplasmic KATP channel in rat ventricular myocytes and to evaluate the signaling pathways involved. At the end of their study they found that volatile anesthetics mediate their protection in cardiomyocytes by selectively priming mitoKATP channels through multiple triggering protein kinase C-coupled signaling pathways. And also in another study Marinovic et al. [23] investigated "an innate" protective mechanism of volatile anesthetics against IRI. They made an effort to reveal whether KATP channels are triggers initiating the preconditioning signaling and/or effectors responsible for the cardioprotective memory and activation during ischemia reperfusion. Adult rat cardiomyocytes were exposed to oxidative stress. To induce preconditioning, the myocytes were pretreated with isoflurane. The involvement of sarcoplasmal and mitochondrial KATP channels was investigated using specific inhibitors. At the end of the study they concluded that both sarcoplasmal and mitochondrial KATP channels play essential and distinct roles in protection afforded by isoflurane. They also stated that sarcoplasmal KATP channel seemed to act as an effector of preconditioning, whereas mitochondrial KATP channel played a dual role as a trigger and an effector.

Lucchini et al. [24] explored in their study the effects of sevoflurane, propofol, and intralipid on metabolic flux rates of fatty acid oxidation (FOX) and glucose oxidation (GOX) in hearts exposed to ischemia and reperfusion. They studied on isolated, paced working rat hearts that were exposed to 20 min of ischemia and 30 min of reperfusion. Study groups were treated with sevoflurane or propofol. They observed that sevoflurane improved the recovery of left ventricular work and myocardial efficiency. This functional improvement was accompanied by reduced increases in postischemic diastolic and systolic intracellular Ca\(^{2+}\) concentrations. Sevoflurane increased GOX and decreased FOX in hearts exposed to ischemia and reperfusion. GLUT4 expression was markedly increased in lipid rafts of sevoflurane treated hearts. Increased GOX closely correlated with reduced Ca\(^{2+}\) overload. As a result of their study they concluded that enhanced glucose uptake via GLUT4 fuels recovery from Ca\(^{2+}\) overload after ischemia and reperfusion in sevoflurane treated hearts.

The protective effects of volatile anesthetics have been longstanding subject in many studies. It was shown that one of the mechanisms of IRI was an intracellular calcium overload. Volatile anesthetics might also protect the myocardium from IRI by altering myocardial calcium fluxes. They also preserve myocardial energetics and protect from ROS derived injury. Louvier and Lanc\’on stated that enfurane and halothane seemed to be more efficient than isoflurane. They explained these cardiovascular effects by a specific effect on myocardial cells. They also stated that halothane and enfurane mainly decreased intracellular calcium availability by a direct effect on sarcoplasmic reticulum, while isoflurane only decreased the transsarcolemmal calcium entry [25].

4. Organ Specific IRI Models and Volatile Anesthetics

Oxidative stress and reperfusion injury may develop in different ischemia-reperfusion models. In these models enzymatic reactions and cellular destructions can affect not only related system but also remote organ and system. Multiorgan involvement may occur as a result of IRI. The main organs in which IRI occurs are heart, lung, brain, liver, kidney, and intestine. Preconditioning and postconditioning with volatile anesthetics confer protection against reperfusion injury in these organs. There are a lot of studies that investigated protective effects of volatile anesthetics on these organs.

4.1. Heart Surgery and IRI. One of the most studied reperfusion model is open heart surgery. It was known that cardiac surgery using cardiopulmonary bypass is associated with release of inflammatory mediators and severe systemic inflammatory reactions. Cardiopulmonary bypass was performed and heart was exposed to ischemia in this surgery. After declamping the aorta ischemic tissue was reperfused and reoxygenated. Reperfusion and reoxygenation of the myocardium may lead to dysrhythmia or hypotension called "myocardial stunning." That is why the effects of volatile anesthetics on reperfusion injury were mostly studied on open heart surgery. On the other hand some antioxidative agents
were used for prevention of IRI in both clinical and experimental studies. Propofol is chemically similar to phenol based on free radical scavengers and endogenous antioxidant vitamin E [26, 27]. Therefore, it was used in many clinical and experimental reperfusion injury studies. In consequence of these studies, it was usually concluded that propofol shortens and attenuates oxidative stress and IRI [28–32]. As the protective effects of propofol is well known, some studies compared propofol and volatile anesthetics such as halothane, isoflurane, and sevoflurane carried out to exhibit the effect of volatile anesthetics on oxidative stress and IRI. Garcia et al. [35] stated at the end of their study that pharmacological preconditioning by sevoflurane provided protective role in cardiac events in coronary bypass patients. Conzen et al. [33] carried out a study on 20 patients scheduled to undergo elective offpump coronary artery bypass surgery. They maintained anesthesia with either sevoflurane or propofol. For assessing myocardial injury, troponin I and myocardial fraction of creatine kinase were determined during the postoperative 24 hours. They found that troponin I concentration increased significantly in propofol infusion group. They concluded that cardiac output improved with sevoflurane but not with propofol, suggesting better maintenance of myocardial function. In another study Julier et al. [34] investigated the effects of sevoflurane preconditioning on myocardial and renal function by measuring postoperative release of brain natriuretic peptide. They found that sevoflurane preconditioning significantly decreased postoperative release of brain natriuretic peptide and concluded that sevoflurane preconditioning preserves myocardial and renal function. Garcia et al. [35] stated at the end of their study that pharmacological preconditioning by sevoflurane provided protective role in cardiac events in coronary bypass patients.

4.2. Thoracic Surgery/One Lung Ventilation and IRI. One lung ventilation (OLV) is frequently used for thoracic and some other surgeries. During OLV, vessels in nonventilated lung (NVL) are constructed and blood flow mainly goes towards other lung lob. In such condition called hypoxic pulmonary vasoconstriction (HPV), while the blood flow of other lobe increases, perfusion and oxygenation of NVL decrease. As a result of this, tissue ischemia occurs in nonventilated site. After resuming 2-lung ventilation, reentry of the blood to ischemic tissue causes sudden and significant increase in ROS production leading to IRI.

We carried out a study to compare the preventive effects of sevoflurane and propofol from IRI in thoracic surgery with OLV by measuring blood gases, IMA, and MDA. We observed lower arterial oxygen pressure in sevoflurane group than in propofol group during OLV as a demonstration of HPV. IMA level at postoperative sixth hour was lower in sevoflurane group than in propofol group. We conclude that sevoflurane was superior in preventing in IRI compared to propofol [36]. Casanova et al. [14] emphasized importance of ischemia-reperfusion induced lung injury in thoracic surgery due to association with ventilation damage to one lung. They studied and evaluated the cytoprotective effects of sevoflurane compared with propofol in a pulmonary autotransplant model in pigs. They found increased oxidative stress markers and proinflammatory mediators in the propofol group. In a consequence of their study, they concluded that sevoflurane decreased the inflammatory response and oxidative stress and provided a protection in a live ischemia reperfusion lung model. In another study Liu et al. [37] investigated the effects of administration of isoflurane and sevoflurane before the intervention on ischemia-reperfusion induced lung injury in an isolated buffer-perfused rat lung model by measuring the coefficient of filtration of the lung, lactate dehydrogenase activity, tumor necrosis factor alpha, nitric oxide metabolites in the perfusate, and the wet-to-dry lung weight ratio. They found that administration of 1 MAC isoflurane or sevoflurane before ischemia significantly attenuates ischemia-reperfusion induced filtration and the wet-to-dry lung weight ratio. This 1 MAC inhibits increase of lactate dehydrogenase activity and tumor necrosis factor alpha in the perfusate and abrogates the decrease in nitric oxide metabolites in the perfusate. They concluded that isoflurane and sevoflurane administered before ischemia could attenuate ischemia-reperfusion induced injury in isolated rat lungs.

4.3. Tourniquet Induced Extremity IRI. Another frequently studied model is tourniquet induced ischemia-reperfusion model. Application of tourniquet is liberally used for providing bloodless surgical field and control of intraoperative bleeding in extremity surgery. Therefore, muscle ischemia occurs in distal area of tourniquet. IRI occurs after deflation of tourniquet and reoxygenation of ischemic tissue. It was stated that muscle ischemia is accompanied by hypoxic cellular challenge and anaerobic glycolysis, reperfusion by neutrophil activation, formation of reactive oxygen species, and release of vasoactive factors [2]. Carles et al. [38] investigated the effects of sevoflurane compared with propofol in tourniquet induced ischemia reperfusion by measuring with microdialysis probes interstitial metabolite levels of anaerobic glycolysis. They found that lactate, pyruvate, and glucose remained at a significantly higher level in the sevoflurane group during reperfusion. Their results indicated that there is a better availability of interstitial glycolysis metabolites in the skeletal muscle during ischemia and reperfusion after sevoflurane exposure. They concluded that sevoflurane had a potential preconditioning effect on tourniquet-induced skeletal muscle IRI. It may be considered that there is a more efficient anaerobic glycolysis after sevoflurane exposure because of higher availability of energetic substratum, that is, pyruvate, allowing higher production of lactate and therefore higher mitochondrial ATP [39, 40]. Higher interstitial glycolysis substratum levels resulting from sevoflurane exposure may participate in the preservation of ATP synthesis in the skeletal muscle.

4.4. Major Vascular Surgery and IRI. In some surgical procedures, such as aneurysm repair of big vessels, traumatic vessel injuries, and procedures related to artery being clamped to provide bloodless surgical area, volatile anesthetics were used to show their preventive effects from IRI in these procedures. Aortic ischemia and reperfusion may induce pulmonary sequestration of neutrophil granulocytes. Kalb et al. [41] investigated the effects of pre- or postconditioning with sevoflurane showing pulmonary neutrophil accumulation
after IRI of the aorta. Anesthetized and mechanically venti-
lated rats underwent laparotomy and developed ischemia by
clamping of the infrarenal aorta. Pre- and postconditioning
with sevoflurane were applied. Following reperfusion, the
lungs were removed for microscopic determination of neu-
trophil accumulation. They found that preconditioning, but
not postconditioning, with sevoflurane reduced pulmonary
neutrophil accumulation after IRI. They concluded that since
neutrophil accumulation played a major role in the patho-
physiology of acute lung injury, their data suggested a protec-
tive effect of sevoflurane preconditioning on remote pulmo-
nary IRI.

Annecke et al. [15] compared the effects of sevoflurane
with propofol on IRI after thoracic aortic occlusion in pigs.
The animals received sevoflurane or propofol anesthesia
before, during, and after lower body ischemia. Fluid and cat-
echolamine requirements were assessed. Serum samples and
intestinal tissue specimens were obtained. All animals dis-
played a severe reperfusion injury following 90 min occlusion
of the thoracic aorta. However, animals receiving sevoflurane
showed less signs of IRI as assessed by systemic hemody-
namic instability than animals receiving propofol for the
same intervention. Norepinephrine requirement in the
sevoflurane group was significantly reduced during reperfu-
sion. Animals tested with sevoflurane had a less pronounced
increase of serum enzyme activities indicative of tissue injury.
Serum activities of lactate dehydrogenase, aspartate transam-
inase, and alanine aminotransferase were lower with sevoflu-
rane. In a consequence of the study they concluded that use of
sevoflurane compared with propofol attenuated the hemo-
dynamic sequelae of IRI. Koşçu et al. [42] investigated the
effects of sevoflurane anesthesia combined with epidural
anesthesia on IRI in patients undergoing surgical revascu-
larization due to aortoiliac occlusive disease, by measuring
plasma MDA and IMA levels. They found that serum levels
of MDA and IMA were lower in study group compared to
control group. In consequence of their study, they concluded
that the sevoflurane anesthesia combined with epidural anes-
thesia might decrease the IRI in aortoiliac occlusive disease.

4.5. Cerebral Events and IRI. Cerebral IRI is encountered
from various neurological, vascular, and cardiovascular pro-
cedures. This typically causes a disorder of water homeostasis
and has been associated with oxidative stress, inflammatory
response, lipid peroxidation, and apoptosis [43–46]. Pre-
conditioning with volatile anesthetics can limit the cerebral
IRI. Bedirli et al. [47] carried out a study to examine the
effects of sevoflurane or isoflurane preconditioning on cere-
bral ischemia-reperfusion induced inflammation, oxidative
stress, and lipid peroxidation and test the hypothesis that the
underlining mechanism of the protective effect of precon-
ditioning involves changes in the apoptotic gene expression
profiles in an experimental model of middle cerebral artery
occlusion in rats. In consequence of their study they found
that sevoflurane and isoflurane preconditioning ameliorates
inflammation, cerebral lipid peroxidation, and histologic
injury. They also concluded that downregulation of proapop-
totic molecules and upregulation of antiapoptotic molecules
may be associated with this effect.

For the same purpose Wang et al. [48] investigated the
postconditioning neuroprotective effect of sevoflurane in rats with middle cerebral artery occlusion. They found that
postconditioning with sevoflurane not only reduced infarct
volume but also improved learning and memory. They con-
cluded that this neuroprotective effect may be partly due to
the activation of PI3K/Akt pathway and inhibiting neuronal
apoptosis. In another study, Ishiyama et al. [49] compared the
effects of sevoflurane with propofol on cerebral pial arterio-
lar and venular diameters during global brain ischemia and
reperfusion. Twenty rabbits were anesthetized with sevoflu-
rane or propofol and then global brain ischemia was induced
by clamping the brachiocephalic, left common carotid, and
left subclavian arteries. They observed pial microcircula-
tion microscopically through closed cranial windows and
measured using a digital video analyzer. They found that pial
arterioles and venules did not dilate immediately after reper-
fusion and subsequently constricted throughout the reperfu-
sion period in propofol group. In contrast, pial arterioles and
venules dilated temporarily and returned to baseline in
sevoflurane group. Adverse effects in sevoflurane group (pul-
monary edema and acute brain swelling) were higher than
propofol group. In addition, blood pressure, heart rate, and
plasma glucose were stable in sevoflurane group.

4.6. Liver and IRI. Temporary interruption of blood flow of
liver causes hepatic ischemia. IRI may cause removal of inter-
ruption and subsequent reperfusion in some surgical proce-
dures. Since volatile anesthetics are capable of providing rele-
vant organ protection from IRI, several studies are conducted
in this field [50, 51]. Bedirli et al. [52] investigated the effects of
isoflurane and sevoflurane in a warm liver ischemia-reper-
fusion model on cytokines, hepatic tissue blood flow, energy
content, and liver structure. They found that sevoflurane
given before, during, and after hepatic ischemia protected the
liver against IRI, whereas the effects of isoflurane on hepatic
IRI were not notable.

4.7. Kidney and IRI. Renal IRI is an inflammatory process
involving multiple cellular and systemic responses, includ-
ing complement activation, activation of proinflammatory
cytokines and chemokines, and infiltration by leukocytes
such as neutrophils, macrophages, and T cells [53]. Lee et al.
[54] reported that volatile anesthetics, including isoflurane,
protected from renal IRI injury by attenuating the inflam-
matory response as well as necrosis. Daqing et al. [55] used
preconditioning with noble gas, xenon, to show its protective
effect in renal IRI. They observed that xenon was a natural
inducer hypoxia-inducible factor 1a. Providing their data
confirmation in the clinical setting, they suggested that xenon
preconditioning before renal ischemia can prevent acute
renal failure arising from IRI. Guye et al. [56] examined a
possible protective effect of desflurane preconditioning on the
kidney in renal ischemia-reperfusion model in rabbits. They
investigated tubular cell damage histologically. They found
lower histological damage in desflurane group and concluded
that desflurane preconditioning reduced renal IRI.
4.8. Opposing Views. There are lots of studies in the literature investigating the effects of volatile anesthetics in other ischemia-reperfusion models. 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. However, some studies suggested that there is no protection [29, 57, 58], moreover harmful [59] effects of volatile anesthetics.

4.9. In the Future. IRI may occur in different clinical conditions without surgical intervention. After successful cardiopulmonary resuscitation, reperfusion is established in tissues and different organs that remained ischemic and hypoxic. As a result of reperfusion, IRI is inevitably encountered. On the other hand, severe hypotension connected with hypovolemic, hemorrhagic, or septic shocks also causes tissue hypoxemia. After treatment of these clinical conditions IRI may also occur.

Recently, tissue and organ transplantation is rapidly improved. As the transplanted organs are exposed to ischemia and reperfusion, IRI will be encountered more frequently. Therefore novel treatment modality will be offered to clinical practice. Perhaps usage of volatile anesthetics may be a part of this in the future.

5. Conclusion

Although there are a lot of studies in the literature suggesting potential protective effects of volatile anesthetics, further studies are required to show the effects of volatile anesthetics on IRI.

Conflict of Interests

The author declares that there is no conflict of interests regarding the publication of this paper.

References

[1] A. Akyol, H. Ulusoy, M. Imamoğlu et al., “Does propofol or caffeic acid phenethyl ester prevent lung injury after hindlimb ischemia-reperfusion in ventilated rats?” Injury, vol. 37, no. 5, pp. 380–387, 2006.
[2] U. Korth, G. Merkel, F. F. Fernandez et al., “Tourniquet-induced changes of energy metabolism in human skeletal muscle monitored by microdialysis,” Anesthesiology, vol. 93, no. 6, pp. 1407–1412, 2000.
[3] M. B. Welborn, H. S. A. Oldenburg, P. J. Hess et al., “The relationship between visceral ischemia, proinflammatory cytokines, and organ injury in patients undergoing thoracoabdominal aortic aneurysm repair,” Critical Care Medicine, vol. 28, no. 9, pp. 3191–3197, 2000.
[4] S. Gelman, “The pathophysiology of aortic cross-clamping and unclamping,” Anesthesiology, vol. 82, no. 4, pp. 1026–1060, 1995.
[5] J. Vinten-Johansen, “Involvement of neutrophils in the pathogenesis of lethal myocardial reperfusion injury,” Cardiovascular Research, vol. 61, no. 3, pp. 481–497, 2004.
[6] H. M. Piper, K. Meuter, and C. Schäfer, “Cellular mechanisms of ischemia-reperfusion injury,” Annals of Thoracic Surgery, vol. 75, no. 2, pp. S644–S648, 2003.
[7] M. T. Dirksen, G. J. Laarman, M. L. Simoons, and D. J. G. M. Duncker, “Reperfusion injury in humans: a review of clinical trials on reperfusion injury inhibitory strategies,” Cardiovascular Research, vol. 74, no. 3, pp. 343–355, 2007.
[8] Y.-J. Cheng, K.-C. Chan, C.-T. Chien, W.-Z. Sun, and C.-J. Lin, “Oxidative stress during 1-lung ventilation,” Journal of Thoracic and Cardiovascular Surgery, vol. 132, no. 3, pp. 513–518, 2006.
[9] K. Katsoulis, T. Kontakiotis, I. Leonardopoulos, A. Kotsovili, I. N. Legakis, and D. Patakas, “Serum total antioxidant status in severe exacerbation of asthma: correlation with the severity of the disease,” Journal of Asthma, vol. 40, no. 8, pp. 847–854, 2003.
[10] T. Miyazawa, T. Suzuki, K. Fujimoto, and M. Kinoshita, “Age-related change of phosphatidylcholine hydroperoxide and phosphatidylethanolamine hydroperoxide levels in normal human red blood cells,” Mechanisms of Ageing and Development, vol. 86, no. 3, pp. 145–150, 1996.
[11] D. L. Carden and D. N. Granger, “Pathophysiology of ischaemia-reperfusion injury,” The Journal of Pathology, vol. 190, pp. 255–266, 2000.
[12] J. Cremer, M. Martin, H. Redl et al., “Systemic inflammatory response syndrome after cardiac operations,” Annals of Thoracic Surgery, vol. 61, no. 6, pp. 1714–1720, 1996.
[13] T. Oxman, M. Arad, R. Klein, N. Avazov, and B. Rabinowitz, “Limb ischemia preconditioning the heart against reperfusion tachyarrhythmia,” American Journal of Physiology—Heart and Circulatory Physiology, vol. 273, no. 4, pp. H1707–H1712, 1997.
[14] J. Casanova, I. Garutti, C. Simon et al., “The effects of anesthetic preconditioning with sevoflurane in an experimental lung autotransplant model in pigs,” Anesthesia and Analgesia, vol. 113, no. 4, pp. 742–748, 2011.
[15] T. Annecke, J. C. Kubitz, S. Kahr et al., “Effects of sevoflurane and propofol on ischaemia-reperfusion injury after thoracic-aortic occlusion in pigs,” British Journal of Anaesthesia, vol. 98, no. 5, pp. 581–590, 2007.
[16] M. Carles, J. Dellamonica, J. Roux et al., “Sevoflurane but not propofol increases interstitial glycolysis metabolite availability during tourniquet-induced ischaemia-reperfusion,” British Journal of Anaesthesia, vol. 100, no. 1, pp. 29–35, 2008.
[17] B. Heindl, F. M. Reiche, S. Zahler, P. F. Conzen, and B. F. Becker, “Sevoflurane and isoflurane protect the reperfused guinea pig heart by reducing posts ischemic adhesion of polymorphonuclear neutrophils,” Anesthesiology, vol. 91, no. 2, pp. 521–530, 1999.
[18] C. Kowalski, S. Zahler, B. F. Becker et al., “Halothane, isoflurane, and sevoflurane reduce posts ischemic adhesion of neutrophils in the coronary system,” Anesthesiology, vol. 86, no. 1, pp. 188–195, 1997.
[19] J. Möbert, S. Zahler, B. F. Becker, and P. F. Conzen, “Inhibition of neutrophil activation by volatile anesthetics decreases adhesion to cultured human endothelial cells,” Anesthesiology, vol. 90, no. 5, pp. 1372–1381, 1999.
[20] E. Novalja, L. G. Kevin, J. T. Eells, M. M. Henry, and D. F. Stowe, “Anesthetic preconditioning improves adenosine triphosphate synthesis and reduces reactive oxygen species formation in mitochondria after ischemia by a redox dependent mechanism,” Anesthesiology, vol. 98, no. 5, pp. 1155–1163, 2003.
by isoflurane: role of adenosine triphosphate-regulated potassium (K(ATP)) channels,” Anesthesiology, vol. 85, no. 4, pp. 794–807, 1996.

[22] M. Zaugg, E. Lucchinetti, D. R. Spahn, T. Pasch, and M. C. Schaub, “Volatile anesthetics mimic cardiac preconditioning by priming the activation of mitochondrial KATP channels via multiple signaling pathways,” Anesthesiology, vol. 97, no. 1, pp. 4–14, 2002.

[23] J. Marinovic, Z. J. Bosnjak, and A. Stadnicka, “Distinct roles for sarcolemmal and mitochondrial adenosine triphosphate-sensitive potassium channels in isoflurane-induced protection against oxidative stress,” Anesthesiology, vol. 105, no. 1, pp. 98–104, 2006.

[24] Y.-J. Cheng, Y.-P. Wang, C.-T. Chien, and C.-F. Chen, “Small-channel chondrial death,” Science, vol. 305, no. 5684, pp. 626–629, 2004.

[25] C. Garcia, K. Julier, L. Bestmann et al., “Preconditioning with sevoflurane decreases PECAM-1 expression and improves one-year cardiovascular outcome in coronary artery bypass graft surgery,” British Journal of Anaesthesia, vol. 94, no. 2, pp. 159–165, 2005.

[30] R. Schmidt, E. Tritschler, A. Hoetzl et al., “Heme oxygenase-1 induction by the clinically used anesthetic isoflurane protects against oxidative stress,” Toxicon, vol. 46, no. 4, pp. 160–165, 2001.
rat livers from ischemia/reperfusion injury,” *Annals of Surgery*, vol. 245, no. 6, pp. 931–942, 2007.

[51] H. T. Lee, C. W. Emala, J. D. Joo, and M. Kim, “Isoflurane improves survival and protects against renal and hepatic injury in murine septic peritonitis,” *Shock*, vol. 27, no. 4, pp. 373–379, 2007.

[52] N. Bedirli, E. Ofluoglu, M. Kerem et al., “Hepatic energy metabolism and the differential protective effects of sevoflurane and isoflurane anesthesia in a rat hepatic ischemia-reperfusion injury model,” *Anesthesia and Analgesia*, vol. 106, no. 3, pp. 830–837, 2008.

[53] J. V. Bonventre and A. Zuk, “Ischemic acute renal failure: an inflammatory disease?” *Kidney International*, vol. 66, no. 2, pp. 480–485, 2004.

[54] H. T. Lee, A. Ota-Setlik, Y. Fu, S. H. Nasr, and C. W. Emala, “Differential protective effects of volatile anesthetics against renal ischemia-reperfusion injury in vivo,” *Anesthesiology*, vol. 101, no. 6, pp. 1313–1324, 2004.

[55] M. Daqing, T. Lim, J. Xu et al., “Xenon preconditioning protects against renal ischemic-reperfusion injury via hif-1α activation,” *Journal of the American Society of Nephrology*, vol. 20, no. 4, pp. 713–720, 2009.

[56] M.-L. Guye, B. McGregor, G. Weil, F. Arnal, and V. Piriou, “Ischaemic and pharmacologic preconditioning: desflurane reduces renal reperfusion injury in rabbits,” *Annales Francaises d’Anesthesie et de Reanimation*, vol. 29, no. 7-8, pp. 518–523, 2010.

[57] O. Aldemir, H. Celebi, C. Cevik, and E. Duzgun, “The effects of propofol or halothane on free radical production after tourniquet induced ischaemia-reperfusion injury during knee arthroplasty,” *Acta Anaesthesiologica Scandinavica*, vol. 45, no. 10, pp. 1221–1225, 2001.

[58] Y. Yamamoto, M. Kawaguchi, N. Kurita, M. Kakimoto, S. Inoue, and H. Furuaya, “Effects of xenon on ischemic spinal cord injury in rabbits: a comparison with propofol,” *Acta Anaesthesiologica Scandinavica*, vol. 54, no. 3, pp. 337–342, 2010.

[59] V. G. Nielsen, S. Tan, K. A. Kirk et al., “Halothane and xanthine oxidase increase hepatocellular enzyme release and circulating lactate after ischemia—reperfusion in rabbits,” *Anesthesiology*, vol. 87, no. 4, pp. 908–917, 1997.