Mechanisms of Volatile Anesthetic-Induced Myocardial Protection

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ABSTRACT

Volatile anesthetics protect myocardium against reversible and irreversible ischemic injury. Experimental evidence from several in vitro and in vivo animal models demonstrates that volatile agents enhance the recovery of stunned myocardium and reduce the size of myocardial infarction after brief or prolonged coronary artery occlusion and reperfusion, respectively. This protective effect persists after the anesthetic has been discontinued, a phenomenon known as anesthetic-induced preconditioning (APC). Recent clinical data also demonstrates evidence of APC in patients during cardiac surgery. Thus, administration of volatile anesthetics may represent a novel therapeutic approach that reduces morbidity and mortality associated with perioperative myocardial ischemia and infarction.

The mechanisms responsible for APC appear to be similar to those implicated in ischemic preconditioning, but nonetheless have subtle differences. Accumulating evidence indicates that APC is characterized by complex signal transduction pathways that may include adenosine receptors, G proteins, protein kinase C, reactive oxygen species, and sarcolemmal or mitochondrial KATP channels. Opioid analgesics may further enhance APC as well. This article will review recent advances in the understanding of mechanisms responsible for volatile anesthetic-induced myocardial protection.

INTRODUCTION

A growing body of experimental and clinical evidence indicates that volatile anesthetics protect myocardium against ischemic injury. Delineating the mechanisms that mediate this beneficial anti-ischemic effect has been a difficult task because volatile agents profoundly affect cardiovascular function. Volatile anesthetics cause dose-related depression of myocardial contractility, reduce arterial and coronary perfusion pressure, produce coronary vasodilation, affect electrophysiological function, and modify autonomic nervous system activity to varying degrees. The anti-ischemic effects of volatile anesthetics may be partially attributed to a favorable reduction in myocardial oxygen consumption, preservation of energy-dependent cellular functions, and increases in coronary blood flow. Nevertheless, it is highly unlikely that alterations in myocardial metabolism and coronary perfusion are solely responsible for myocardial protection during administration of these drugs. Multiple endogenous signal transduction pathways, all of which appear to act through the adenosine triphosphate-sensitive
potassium (K\textsubscript{ATP}) channel as an integral component, have been implicated in mediating the salutary effects of volatile anesthetics. In this review, we will discuss recent developments in the understanding of mechanisms responsible for volatile anesthetic-induced myocardial protection.

**BACKGROUND**

Laboratory investigations performed over the past 15 years repeatedly demonstrated that volatile anesthetics attenuate reversible and irreversible damage associated with myocardial ischemia. Halothane was shown to reduce ST segment elevation during brief coronary artery occlusion [1], consistent with a decrease in acute ischemic injury. Halothane also preserved contractile function and ultrastructural integrity during cardioplegic arrest [2]. Enflurane decreased lactate production during coronary artery stenosis when perfusion pressure was maintained [3], and preservation of high-energy phosphate levels was coupled to these protective effects [4]. Isoflurane and sevoflurane enhanced left ventricular diastolic function during acute coronary artery occlusion [5]. Halothane [6, 7, 8], enflurane [6, 9, 10], isoflurane [6, 7, 9], and sevoflurane [11] were shown to improve the functional recovery of isolated hearts subjected to global ischemia and reperfusion. Halothane and isoflurane also enhanced the functional recovery of stunned myocardium in vivo [12, 13]. Halothane [14] and isoflurane [15] reduced myocardial infarct size in dogs, and this protective effect persisted despite discontinuation of the volatile agent before prolonged coronary artery occlusion [15]. This phenomenon (figure 1) was termed “anesthetic-induced preconditioning” (APC), and was characterized by a short-term memory phase similar to that of ischemic preconditioning (IPC). APC has also been described in rats [16] and rabbits [17]. Sevoflurane decreased the time threshold level of the ischemic stimulus required to protect against infarction during IPC [18]. These results suggested that volatile agents and brief ischemic episodes may produce synergistic protection against subsequent irreversible ischemic damage. Volatile anesthetics may also exert...
beneficial actions on coronary collateral perfusion to ischemic myocardium. Volatile anesthetics produce coronary vasodilation by activating K$_{ATP}$ channels [11, 19, 20, 21, 22, 23] or by favorably affecting intracellular Ca$^{2+}$ handling in vascular smooth muscle cells [24]. Halothane has been shown to attenuate reductions in coronary collateral perfusion associated with acute coronary occlusion [25]. Halothane also enhances the ratio of myocardial oxygen delivery to consumption in collateral-dependent myocardium [25]. Sevoflurane increases coronary collateral blood flow to ischemic myocardium when perfusion pressure is maintained at a constant level [23, 26]. Sevoflurane also improves functional recovery of coronary vascular reactivity and nitric oxide release in isolated hearts after global ischemia [11]. Halothane has been shown to reduce cyclical changes in coronary blood flow and prevent the development of platelet thrombi in the presence of a critical coronary artery stenosis [27]. Volatile anesthetics attenuate neutrophil and platelet aggregation [28] and also inhibit cytokine-induced cell death [29] after ischemia-reperfusion injury in coronary vessels.

The precise mechanisms responsible for anesthetic-induced myocardial protection against ischemia remain unclear despite extensive study. While it is clear that volatile anesthetics produce complex cardiovascular actions that may improve the myocardial oxygen supply and demand relationship, it is equally clear that such salutary alterations in the determinants of myocardial metabolism and coronary perfusion are not solely responsible for the anti-ischemic actions of these agents. For example, halothane confers protection during cardioplegic arrest [2] and upon reperfusion [30], circumstances in which myocardial metabolism plays little if any role. Isoflurane and sevoflurane also increase viability of isolated cardiac myocytes exposed to a cellular model of ischemia [31]. These results were initially attributed to reductions in excessive intracellular Ca$^{2+}$ during ischemia and reperfusion [32] by partial inhibition of Ca$^{2+}$ channel activity during administration of these drugs [33, 34, 35, 36]. However, these data did not address specific mechanisms by which anesthetics produced protection nor did they provide insight into the intracellular processes responsible for these beneficial effects.

**MITOCHONDRIAL K$_{ATP}$ CHANNELS: MEDIATORS OF IPC**

K$_{ATP}$ channels are heteromultimeric complexes consisting of an inward-rectifying K$^+$ channel (Kir) and a sulfonylurea receptor (SUR) [37]. Pharmacological and recombinant techniques indicate that the cardiac sarcolemmal K$_{ATP}$ channel [38] is composed of the Kir6.2/SUR2A isoforms. In contrast, the mitochondrial K$_{ATP}$ channel [39] consists of the Kir6.1/SUR1 isoforms [40]. It was originally hypothesized that opening of sarcolemmal K$_{ATP}$ channels protects ischemic myocardium by shortening the action potential duration and preventing intracellular Ca$^{2+}$ overload [38]. However, other studies indicated that the beneficial actions of K$_{ATP}$ channel activation occurred independent of the action potential duration [41, 42]. In fact, the vast majority of recent evidence suggests that mitochondrial K$_{ATP}$ channels are the dominant mediators of IPC [43] and further, that preservation of mitochondrial bioenergetic function is vital for cytoprotection against myocardial ischemia [44, 45, 46, 47]. Mitochondrial K$_{ATP}$ channel openers maintain intracellular Ca$^{2+}$ homeostasis and inhibit mitochondrial Ca$^{2+}$ overload [46, 47]. These actions may enhance myocyte survival by preventing tissue necrosis or apoptosis [48]. Opening of mitochondrial K$_{ATP}$ channels has been shown to inhibit apoptosis in rat ventricular myocytes [49] by attenuating oxidant stress upon reperfusion [50]. Alteration of the mitochondrial redox state by K$_{ATP}$ channel opening may also promote cellular protection [47, 51]. Experiments conducted in isolated cardiac mitochondria [47] indicate that membrane depolarization, matrix swelling, and the uncoupling of ATP synthesis that occurs as a result of increased oxygen consumption are effects associated with the opening of mitochondrial K$_{ATP}$ channels that may mediate cellular viability during IPC [51]. Opening of mitochondrial K$_{ATP}$ channels depolarizes the inner mitochondrial membrane and causes a
transient swelling of the mitochondrial matrix [52], resulting from a shift in the ionic balance [53].

Mitochondrial KATP channel opening initially reduces ATP production as a result of membrane depolarization [47], but also subsequently stimulates a compensatory increase in respiration that optimizes oxidative phosphorylation efficiency in part through energy-dependent matrix volume regulation [54]. Thus, a moderate disturbance of mitochondrial homeostasis may promote myocardial tolerance to ischemic stress by altering energetic systems to reduce Ca overload, prevent the activation of necrotic or apoptotic pathways, or attenuate oxidant stress.

**SIGNAL TRANSDUCTION IN APC**

**KATP CHANNELS**

Experimental evidence accumulated in the past seven years indicates that the endogenous mechanisms involved in APC bear striking similarity to those identified during IPC. It is hypothesized that a "trigger" initiates a cascade of signaling events leading to activation of an "end-effector" that is responsible for resistance to injury. KATP channel activation has been implicated as the end-effector (figure 2) in this protective scheme during APC, as these channels have been shown to play a fundamental role in mediating myocardial protection during IPC [55, 56, 57]. A recent investigation using a cellular model of ischemia reported that administration of isoflurane and sevoflurane preserved myocyte viability compared to cells that were not exposed to a volatile agent. This protective effect was abolished by the selective mitochondrial KATP channel antagonist 5-hydroxydecanoic acid (5-HD).

**Figure 2.** Schematic diagram illustrating volatile anesthetic-induced stimulation of endogenous signaling mechanisms responsible for myocardial protection. A "trigger" initiates a cascade of signal transduction events resulting in the activation of an "end-effector" that promotes resistance against cellular injury. Mitochondrial KATP channels have been implicated as the end-effector in this protective scheme, but sarcolemmal KATP channels may also play a role. Volatile anesthetics signal through adenosine and opioid receptors, modulate G proteins, or activate protein kinase C (PKC) and other intracellular kinases that subsequently open KATP channels. Volatile anesthetics also directly generate reactive oxygen species (ROS) in mitochondria that modulate KATP channel activity.
but not the selective sarcolemmal $K_{\text{ATP}}$ channel antagonist HMR-1098 [31]. The nonselective $K_{\text{ATP}}$ channel blocker glyburide completely attenuated the recovery of contractile function produced by isoflurane in stunned myocardium [13, 58]. Isoflurane-induced reductions in canine myocardial infarct size [15] and the ATP-sparing effects of this agent [58] are also abolished by glyburide. 5-HD inhibits preconditioning by isoflurane in vivo in rats [16], rabbits [60], and isolated human atria [61, 62]. Both HMR-1098 and 5-HD abolished the protective effects of desflurane in dogs [63], supporting a role for both sarcolemmal and mitochondrial $K_{\text{ATP}}$ channels in APC. These latter data contrast to some degree with findings that implicate mitochondrial $K_{\text{ATP}}$ channels alone as the predominant mediators of IPC [43].

Results from carefully conducted in vitro experiments using pharmacological techniques strongly suggested that volatile anesthetics directly activate $K_{\text{ATP}}$ channels. Isoflurane stimulated outward $K^+$ current through sarcolemmal $K_{\text{ATP}}$ channels in isolated ventricular myocytes during patch-clamping [64, 65]. Volatile anesthetics also reduced sarcolemmal $K_{\text{ATP}}$ channel sensitivity to inhibition by ATP, thereby increasing the open state probability [66]. In contrast, other studies indicate volatile anesthetics alone were unable to elicit channel opening, but these agents did enhance sarcolemmal $K_{\text{ATP}}$ channel current by facilitating channel opening after initial activation [64, 65]. Isoflurane and sevoflurane increased mitochondrial flavoprotein oxidation, an index of mitochondrial $K_{\text{ATP}}$ channel activity, in guinea pig cardiac myocytes, and this endogenous autofluorescence was inhibited by 5-HD [67]. Isoflurane and sevoflurane also enhanced diazoxide-induced flavoprotein fluorescence in isolated rat ventricular myocytes [31]. Interestingly, isoflurane failed to augment $K_{\text{ATP}}$ channel current in excised membrane patches [64]. These data suggest that volatile anesthetics may not directly interact with sarcolemmal $K_{\text{ATP}}$ channels, but instead act upon other intracellular signaling elements that modulate $K_{\text{ATP}}$ channel activity. In contrast to the findings with isoflurane, halothane had no effect on pinacidil-induced increases in sarcolemmal $K_{\text{ATP}}$ channel current. Halothane also inhibited $K_{\text{ATP}}$ channel current that had been maximally activated by 2,4-dinitrophenol [65]. Thus, the preponderance of evidence collected to date suggest that volatile anesthetics may not directly open $K_{\text{ATP}}$ channels, but instead prime the activation of these channels in both sarcolemmal and mitochondrial membranes. This hypothesis is partially supported by the observation during IPC that adenosine facilitates $K_{\text{ATP}}$ channel activation during myocardial ischemia through a PKC-dependent mechanism [59]. Taken as a whole, the experimental results with volatile anesthetics are consistent with previous findings demonstrating that pharmacological stimulation of $K_{\text{ATP}}$ channels with other drugs mimics the conditions present during IPC [69].

Volatile anesthetics may activate parallel or redundant signal transduction pathways that involve $K_{\text{ATP}}$ channel opening to generate a physiologically-meaningful cellular response. The sequential activation of several intracellular elements within a given transduction pathway may facilitate signal amplification and interaction between other redundant signaling systems. For example, administration of isoflurane in the presence of the $K_{\text{ATP}}$ channel opener nicorandil [70] or diazoxide [71] markedly enhances protection against ischemic injury beyond that observed with either drug alone. Interestingly, the combination of isoflurane and a selective $\delta$-opioid receptor agonist amplifies the preconditioning response in the rat [71]. This effect is synergistic, and is sensitive to inhibition by glyburide [71]. Recent experiments also demonstrate that combined administration of isoflurane and morphine also markedly reduces infarct size in vivo. This enhanced protective effect is abolished by 5-HD [16]. These data suggest that combined administration of a volatile anesthetic and an opioid may stimulate similar or cooperative signaling cascades that amplify $K_{\text{ATP}}$ channel activation to profoundly augment myocardial protection beyond that produced by either drug alone.

$K_{\text{ATP}}$ channels in vascular smooth muscle cells have been shown to be essential regulators...
of coronary vascular tone when ATP production is reduced [72]. Volatile anesthetic-induced coronary vasodilation [11, 19, 20, 21, 22, 23] is attenuated by glyburide, indicating an important role for KATP channels in this process. Thus, it remains possible that the beneficial actions of APC may be partially attributed to increased oxygen supply mediated by KATP channel-dependent coronary vasodilation. However, sevoflurane increases coronary collateral blood flow in the presence of glyburide in vivo, indicating that volatile anesthetics enhance coronary collateral blood flow independent of KATP channel activation [23]. In fact, we have recently shown that sevoflurane-induced increases in collateral perfusion occurs as a result of Ca2+-regulated potassium (BKCa) and not KATP channel activation [73]. In addition, isoflurane and sevoflurane directly activate mitochondrial KATP channels in isolated cardiac myocytes, and this action is linked to enhanced cell viability [31]. Based on these data, it appears highly unlikely that myocardial protection produced by volatile anesthetics is solely related to favorable alterations in coronary vascular tone mediated by KATP channels.

ADENOSINE AND OTHER G-PROTEIN COUPLED RECEPTORS

Several receptor-mediated events and intracellular signaling elements that converge on the KATP channel have been implicated in APC. Pertussis toxin abolished reductions in infarct size produced by isoflurane, indicating that inhibitory guanine (G) nucleotide-binding proteins are linked to the signal transduction pathways that mediate APC [74]. In contrast, pertussis toxin did not prevent the beneficial effects of direct KATP channel opening produced by nicorandil. These data strongly supported the contention that volatile anesthetics modulate KATP channel activity through a second messenger. Halothane-induced protection against infarction was completely abolished by blockade of the adenosine type 1 (A1) receptor [6], and a selective A1 receptor antagonist also partially attenuated the beneficial effects of isoflurane in stunned myocardium [75]. Isoflurane eliminated increases in interstitial adenosine during repetitive periods of coronary artery occlusion and reperfusion as demonstrated using a myocardial microdialysis technique [75]. These novel findings suggest that ATP preservation and a subsequent reduction of adenosine released into the interstitium occur during isoflurane anesthesia. The results are also very similar to findings during IPC [76] and pharmacological preconditioning produced by bimakalim [77]. The results further indicate that volatile anesthetics may either directly activate A1 receptors or indirectly enhance A1 receptor sensitivity to diminished endogenous adenosine concentrations [75]. The preservation of cardiac myocyte viability during ischemia produced by volatile anesthetics is also sensitive to adenosine receptor and G protein-mediated signaling blockade [31]. Additional findings indicate that the nonselective opioid antagonist naloxone abolishes isoflurane-induced preconditioning in the rat [16]. These intriguing data suggest an important link between volatile anesthetics and another family of G protein-coupled receptors. In fact, new evidence reveals that volatile agents competitively inhibit the ligand-binding site of G protein-coupled receptors [78]. Thus, APC appears to be associated with the activation of at least two separate receptor-mediated pathways (A1 and δ-opioid) that are linked to G proteins.

PROTEIN KINASE C

APC may also produce translocation and phosphorylation of several protein kinases involved in signal transduction [79, 80, 81]. PKC is an essential component of the signaling pathway involved in protecting the myocardium against cell death after ischemia and reperfusion [82]. The diverse PKC isomform family is a large group of serine/threonine protein kinases that are distinguished by variable regulatory domains and cofactors, and also display diverse tissue and species distributions [83]. Volatile anesthetics stimulate PKC translocation and activity [84], possibly by interacting with the regulatory domain of the enzyme[85]. Inhibition of PKC attenuates isoflurane-induced augmentation of the functional recovery of stunned myocardium in dogs [86]. The beneficial actions of halothane are entirely blocked by selective PKC antagonism in rabbits [6]. The microtubule depolymerizing drug, colchicine, prevents isoflurane-induced reductions
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in myocardial infarct size in rabbits [87]. This
interesting result suggests that an intact
cytoskeleton may be essential for translocation of
these protein kinases to occur.

Recent findings strongly suggest that
volatile anesthetic-induced PKC translocation and
activation is required to open K\textsubscript{ATP} channels and
produce myocardial protection. For example, the
nonselective PKC antagonist chelerythrine
abolished sevoflurane-induced increases in
mitochondrial K\textsubscript{ATP} channel activity in rat
ventricular myocytes [31] and prevents protection
from ischemic damage. Patch-clamp
experiments demonstrate that isoflurane does not
facilitate K\textsubscript{ATP} channel opening in excised
membrane patches, but enhances K\textsubscript{ATP} channel
current in a whole-cell configuration concomitant
with PKC stimulation [64]. These observations are
supported by additional evidence illustrating that
both adenosine and PKC enhance K\textsubscript{ATP} channel
activity [71, 88, 89, 90, 91]. In fact, specific PKC
consensus sites are located on K\textsubscript{ATP} channels,
indicating a molecular basis for phosphorylation
and activation of the channel by the enzyme [92].
Mitochondrial K\textsubscript{ATP} channel opening occurs after
PKC activation during IPC in isolated rabbit hearts
[93]. Other intracellular kinases may also be
involved in the signaling pathways mediating the
cellular response to ischemia because PKC
stimulates tyrosine [94] and mitogen-activated
protein (MAP) kinases [95] as well. Thus, volatile
anesthetics also appear to modulate several
critical intracellular signaling proteins independent
of direct receptor activation (figure 2).

**Reactive Oxygen Species**

Reperfusion of ischemic myocardium is
associated with the release of large quantities of
reactive oxygen species (ROS) [96, 97, 98] that
disrupt intracellular homeostasis, depress
contractility, and produce tissue injury. Halothane,
isoflurane, and enflurane has been shown to
attenuate the toxic effects of oxygen-derived free
radicals on left ventricular pressure development
in isolated hearts [99]. Isoflurane decreases
hydroxyl radical generation in the ischemic rat
heart [100] and halothane has a similar effect in
dogs [101]. The protective effects of sevoflurane
are associated with reduced dityrosine formation,
an indirect marker of reactive oxygen and nitrogen
species [102]. These results support the
contention that volatile anesthetics may reduce the
release of deleterious quantities of reactive
oxygen species immediately after coronary artery
occlusion.

In contrast to these data implicating a
pathological role of large amounts of ROS, new
evidence strongly suggests that a variety of
preconditioning stimuli, including brief ischemia,
mitochondrial K\textsubscript{ATP} channel openers, opioids, and
volatile anesthetics, stimulate a small burst of
ROS that paradoxically appears to initiate
downstream signaling events and produce
protection from subsequent ischemic injury. The
beneficial actions of sevoflurane against ischemic
damage are abolished by scavengers of
superoxide and inhibition of nitric oxide synthase
[102]. These results suggest that superoxide may
act to trigger APC and also indicate that nitric
oxide may scavenge superoxide upon reperfusion
to reduce injury. ROS scavengers attenuate
isoflurane-induced reductions in myocardial infarct
size in rabbits [103, 104] as shown in figure 3, and
also inhibit the salutary effects of IPC [105, 106]
or mitochondrial K\textsubscript{ATP} channel activation [107]. We
have recently demonstrated that isoflurane directly
increases superoxide formation in vivo [104]
independent of ischemia and reperfusion [104].
These data [104] indicate that volatile anesthetics
are capable of producing small amounts of ROS
that may exert protective effects during
subsequent ischemia. Notably, pretreatment with
low concentrations of ROS mimic the beneficial
actions of IPC and reduce infarct size through a
PKC-mediated mechanism [108]. These reports
provide compelling evidence that small quantities
of ROS play a critical role in APC.

Activation of mitochondrial K\textsubscript{ATP} channels
is associated with the ROS generation [109].
Mitochondrial K\textsubscript{ATP} channel opening produced by
selective agonists generates ROS that appear to
be essential for activation of MAP kinase [110] and
beneficial effects on myocardium [111]. Morphine
increases cardiac myocyte viability and the
fluorescence intensity of the hydrogen peroxide-
sensitive probe, 2,7'-dichlorofluorescin. These
actions are blocked by 5-HD [112], suggesting that
activation of mitochondrial K\textsubscript{ATP} channels by
Figure 3. Histogram depicting myocardial infarct size expressed as the percentage of the left ventricular area at risk (AAR) in rabbits exposed to isoflurane in the presence and absence of the reactive oxygen species (ROS) scavengers N-acetylcysteine (NAC) and 2-mercapto-propan-2-ylglycine (2-MPG). NAC and 2-MPG attenuated isoflurane-induced myocardial protection (ISO + NAC and ISO + 2-MPG, respectively). Other groups: control (CON), isoflurane alone (ISO), NAC alone (NAC), 2-MPG alone (2-MPG). (Adapted with permission of authors and publisher [104].)

Figure 4. Photomicrographs demonstrating superoxide anion production using dihydroethidium fluorescence in rabbits. Isoflurane significantly (P < 0.05) increased fluorescence intensity of stained myocardial nuclei compared to control. (Adapted with permission of authors and publisher [104].)
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Mitochondria have been hypothesized to be a source of ROS production [106, 113, 114, 115, 116], but whether opening of mitochondrial K<sub>ATP</sub> channels directly contribute to free radical generation remains unknown. Conversely, ROS may also modulate K<sub>ATP</sub> channel activity [117] to provide a beneficial effect.

The identities of the ROS involved in APC and IPC and the signaling cascades that are modulated by these free radicals also remain unclear. ROS have been shown to activate PKC, restore contractility, and limit the extent of myocardial infarction [108]. Hydrogen peroxide stimulates tyrosine kinase-dependent activation of phospholipase C (PLC) in mouse embryonic fibroblasts, rendering these cells resistant to stress [118]. ROS may also directly stimulate PLC activity [119] or indirectly enhance the activity of the enzyme by activation of PLC [118].

Interestingly, hydrogen peroxide activates G<sub>α</sub> and G<sub>β</sub> proteins [120, 121], as well as other protein kinases involved in reducing cellular injury [110, 122, 123, 124]. Recent evidence suggests that hydrogen peroxide may be converted to more reactive species that modify cysteine residues specific to G<sub>α</sub> and G<sub>β</sub>, resulting in selective activation of these proteins [120]. Therefore, volatile anesthetic-induced production of ROS may directly activate intracellular mediators of endogenous protection against ischemic injury (figure 2). This tantalizing hypothesis will require further research to confirm.

**MYOCARDIAL PROTECTION BY VOLATILE ANESTHETICS IN HUMANS**

Evidence accumulated to date strongly suggests that APC occurs in human myocardium, but evaluation of this process in patients is complicated by alterations in systemic and coronary hemodynamics, the use of other anesthetics, analgesics, or vasoactive drugs, preexisting disease states, and the influence of surgery on cardiovascular homeostasis. Isoflurane [62] and desflurane [125] enhance the recovery of contractile function of human atrial trabeculae by stimulation of adenosine receptors and opening of K<sub>ATP</sub> channels [62]. Other studies have previously demonstrated a role for adenosine receptors, MAP kinases [61], and ROS [126] in other forms of preconditioning in human atrial myocytes concomitant with opening of mitochondrial K<sub>ATP</sub> channels. Isoflurane increases the tolerance to pacing-induced ischemia in patients with coronary artery disease [127]. Isoflurane also decreases postoperative release of troponin I and creatine kinase-MB in patients undergoing coronary artery bypass graft (CABG) surgery, suggesting a reduction in the severity of myocardial necrosis [128]. Administration of enfurane before cardioplegic arrest also enhances postischemic contractile functional recovery in CABG patients [129]. Most recently, sevoflurane but not the intravenous anesthetic propofol was shown to preserve myocardial function in patients undergoing CABG concomitant with a reduction in troponin I release [130]. This compelling evidence emphasizes that volatile anesthetics exert beneficial effects against ischemic injury in humans and dispels the previously held contention that these agents may produce adverse redistribution of coronary collateral blood flow away from ischemic myocardium ("coronary steal") in certain patients with coronary artery disease. It has become increasingly clear that preexisting ischemia on arrival to the operating room and not anesthetic technique is the strongest predictor of intraoperative ischemia [131, 132]. However, volatile anesthetics may represent an important therapeutic modality to reduce the risk of perioperative myocardial ischemia and infarction [133], although this conclusion has yet to be confirmed in a large-scale, randomized, clinical trial.

**SUMMARY**

Experimental and clinical evidence indicates that volatile anesthetics exhibit important anti-ischemic actions that reduce the sequelae of reversible and irreversible ischemic injury. Several endogenous signaling elements mediate APC, but the mitochondrial K<sub>ATP</sub> channel appears to be a central feature involved in maintaining function and promoting myocyte survival. Preservation of mitochondrial integrity and metabolic homeostasis by volatile anesthetics may ultimately enhance tolerance to myocardial ischemia. Translation of strong experimental data...
about the protective effects of volatile anesthetics and other protective drugs, including opioids, into therapeutic approaches to reduce morbidity and mortality in patients with coronary artery disease remains to be established.

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