Anesthetic-induced myocardial protection in cardiac surgery: relevant mechanisms and clinical translation
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Cardiac surgery is still associated with complications such as adverse perioperative cardiovascular events. Over the past two decades, many studies have shown that volatile anesthetics and opioids provide myocardial protection against ischemia-reperfusion injury in a similar manner as ischemic conditioning. First (1–2 hours) and second (24–72 hours) windows of protection are provided, the underlying mechanisms for which involve activation of G-protein-coupled receptors, protein kinases, and the opening of adenosine triphosphate-sensitive potassium channels. These processes ultimately result in inhibition of the mitochondrial permeability transition pore. Post-conditioning can also be effective when treatment is applied in the proximity of reperfusion. Although propofol lacks these conditioning effects, it acts as a strong antioxidant and protects the myocardium by attenuating oxidative stress related to reperfusion injury. Clinical evidence favors the use of volatile anesthetics over propofol in terms of reduced cardiac enzyme release, length of hospital stay, and mortality. However, the existing evidence level is insufficient to draw a definite conclusion regarding the mortality benefit of one anesthetic over the others. In addition, many common clinical conditions, such as advanced age, hyperglycemia/diabetes, and hypertrophy, have been shown to mitigate the protective efficacy of the anesthetics, although this effect also lacks clinical validation. Propofol may also abolish the protective effects of volatile anesthetics and opioids by scavenging reactive oxygen species, an essential trigger for pre-conditioning. The following review addresses these issues from a clinical perspective.

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sympathetic response. Moreover, anesthetics have been shown to have direct myocardial protective effects providing tolerance to ischemia-reperfusion (I-R) injury [1]. Anesthetics have also been shown to enable better myocardial functional recovery in terms of contractile function and arrhythmia after I-R injury [2].

Among the various anesthetics in current use, volatile anesthetics have been experimentally shown to have the most beneficial influence in terms of reducing infarct size against myocardial I-R injury via pre- and post-conditioning effects [2,3]. Propofol and opioids have also been shown to provide myocardial protection against I-R injury by both similar and different mechanisms of actions compared to volatile anesthetics [4,5]. With the advent of sophisticated target-controlled infusion models, along with the favorable pharmacokinetic profiles of propofol and remifentanil, total intravenous anesthesia (TIVA) has gained increased popularity in cardiac anesthesia. Thus, the anesthetic regimen for cardiac surgery has changed from high-dose narcotic-based ones to balanced anesthesia using either volatile anesthetics or propofol in combination with opioids. However, the ideal choice of anesthetics remains to be validated.

The present review article discusses the underlying mechanisms of action by which each anesthetic confers myocardial protection, the evidence regarding their clinical utility and drawbacks, potential interactions between anesthetics, and future clinical perspectives regarding their use and validation.

MYOCARDIAL PROTECTION VIA CONDITIONING INDUCED BY VOLATILE ANESTHETICS

Anesthetic pre-conditioning

Since the introduction of the evolutionary concepts of pre- and post-conditioning, numerous therapies providing myocardial protection have been experimentally evaluated. However, there has been limited success in the clinical translation of these therapies. Among experimentally proven methods, ischemic pre-conditioning has yielded the most consistent results regarding infarct size reduction across various animal species in different myocardial I-R injury models. While early translational studies have shown promising results, ischemic pre-conditioning is not always feasible in clinical settings.

In 1997, Kersten et al. [1] demonstrated that similar infarct size reduction could be obtained with isoflurane, which later led to the widely accepted concept of anesthetic pre-conditioning. Numerous subsequent studies have addressed anesthetic pre-conditioning effects on the myocardium using enflurane, isoflurane, sevoflurane, and desflurane, aiming to also elucidate the underlying mechanisms for such effects. Thus far, evidence suggests that anesthetic pre-conditioning shares fundamental characteristics with ischemic pre-conditioning, providing early and delayed windows of myocardial protection [6,7]. In addition, anesthetic and ischemic pre-conditioning share many of the same molecular processes involved in myocardial protection, such as G-protein-coupled cell membrane receptors, mediation via multiple protein kinases, and the opening of adenosine triphosphate-sensitive potassium (K_{ATP}) channels [2,6,7].

In anesthetic pre-conditioning, as in ischemic pre-conditioning, the first window of protection is provided for approximately 1–2 hours via various cytosolic signaling pathways, including reperfusion injury salvage kinase (RISK) and survivor-activating factor enhancement (SAFE) pathways. The RISK pathway is activated mainly by G-protein-coupled cell surface receptors that activate phosphatidylinositol (4,5)-biphosphate 3-kinase (PI3K), protein kinase B, and extracellular-regulated kinase to promote cell survival [8]. The SAFE pathway mainly involves tumor necrosis factor (TNF)-α and signal transducer and activator of transcription (STAT)-3 to attenuate apoptotic cell death [9]. Both pathways are also known to have close interactions with each other, and with either pathway, protection in the mitochondria is conveyed by the inhibition of mitochondrial permeability transition pore (mPTP) and the activation (opening) of the K_{ATP} channel [10,11]. The second window of protection appears after 24–48 hours, and lasts up to 72 hours. It involves increased expression of protective proteins in response to acute signaling, including protein kinase C (PKC)-ε, STAT, and nuclear factor-κB [2]. Major upregulated proteins involved in delayed myocardial protection include inducible nitric oxide synthase, cyclooxygenase-2, superoxide dismutase, aldose reductase, and heme oxygenase. It has also been suggested that activation of sarcolemmal K_{ATP} along with the mitochondrial K_{ATP} channel, subsequently alleviates cytosolic calcium overload in the second window of protection [12,13].
Importance of mitochondrial mechanisms: the mPTP and K\textsubscript{ATP} channel

It is noteworthy that the mitochondria are the molecular center for various cardioprotective signaling processes, and mPTP is a major point of convergence for these various signals. Indeed, opening of mPTP during reperfusion is deleterious in terms of cell survival. Transient opening of mPTP may be a physiological function related to the homeostasis of reactive oxygen species (ROS) and calcium release, which has been shown to provide cardioprotection during ischemic pre-conditioning [12]. However, prolonged opening of mPTP results in matrix swelling, rupture of the mitochondrial membrane, and the release of proapoptotic cytochrome C into the cytosol, where it triggers apoptotic cell death. Therefore, mPTP inhibition is critical in modulating the balance of the cell-survival and apoptotic pathways [10].

The mitochondrial K\textsubscript{ATP} channel is a critical determinant of mitochondria respiration. Its opening induces inner mitochondrial membrane depolarization, preserving mitochondrial volume and homeostasis. This attenuates excessive ROS generation and mitochondrial calcium accumulation, provides the optimal milieu for ATP production, and inhibits mPTP. This channel is a direct target of volatile anesthetics, and is linked to mitochondrial respiration through nicotinamide adenine dinucleotide [11]. It also confers protection via a positive feedback loop with PKC-\(\varepsilon\) activation [14].

Considering their importance in mediating myocardial protection induced by volatile anesthetics, it is critical to elucidate the pathways that initiate or contribute to the activation of the mitochondrial K\textsubscript{ATP} channel and the inhibition of mPTP. Indeed, many co-morbidities, currently used medications, and the concomitant use of propofol may interfere with these mechanisms. In brief, cardioprotective signaling by volatile anesthetics is mainly initiated by G-protein-coupled cell membrane receptors, which include \(\beta_1\)- and \(\beta_2\)-adrenergic receptors and adenosine-A1 receptor [2,7]. The role of adrenergic receptors seems to be of particular importance in desflurane-induced pre-conditioning [15].

The generation of a small amount of ROS is essential in triggering myocardial protection induced by volatile anesthetics, while excessive oxidative stress and the production of large amounts of ROS are harmful [16]. Volatile anesthetics cause a small degree of subclinical harm (e.g., ROS generation) to trigger protective signaling against persistent and clinically harmful I-R injury, which can be viewed as pre-conditioning. Consequently, volatile anesthetics attenuate the generation of excessive ROS production after I-R, and thus alleviate the hazardous oxidative stress that triggers reperfusion injury [17].

Anesthetic post-conditioning and other direct cardioprotective effects

Volatile anesthetics also provide post-conditioning effects, with efficacies similar to those of pre-conditioning in terms of reducing infarct size, when given within the first 30 seconds of reperfusion [18]. Myocardial protection is not observed when post-conditioning with volatile anesthetics is performed 3–10 minutes after the onset of reperfusion. The underlying mechanisms are similar to those of pre-conditioning, and involve the activation of G-protein-coupled cell membrane receptors and the stimulation of downstream pathways. As in pre-conditioning, the major pathways involved are the RISK and SAFE pathways. These ultimately inhibit the opening of the mPTP, which is thought to be achieved mainly by PKC-\(\varepsilon\), which is involved in the activation of mitochondrial K\textsubscript{ATP} channel) [2,7].

Apart from their pre- or post-conditioning effects, volatile anesthetics also provide direct endothelial protection that may also be linked to myocardial protection. Volatile anesthetics attenuate the degradation of the endothelial glyocalyx layer following I-R injury [19], the integrity of which plays a vital role in preventing leukocyte and platelet adhesion thereby mitigating inflammation and tissue edema [20]. Various experiments, including some performed in human umbilical vein tissue, have demonstrated inhibition of the expression of TNF-\(\alpha\)-induced adhesion molecule by volatile anesthetics that may facilitate further recruitment of inflammatory cells [21].
clinical dose range, apart from their central vagotonic effects. Even in terms of pharmacokinetics, the modern opioid congeners sufentanil and remifentanil do not interfere with early awakening of the patient after surgery. Thus they enable fast-track anesthesia, if necessary. The role of endogenous opioid peptides (such as enkephalins, dynorphins, and endorphins) as anti-inflammatory factors in response to stress has long been acknowledged [22]. The role of G-protein-coupled opioid receptors in conveying the protective signaling in ischemic pre-conditioning of the myocardium has also been scrutinized [12]. Of note, externally administered opioids have also been shown to provide myocardial protection against I-R injury in a manner mimicking the effects of ischemic pre-conditioning [5].

Molecular pathways involved in opioid-induced myocardial protection are conveyed mostly through δ and κ opioid receptors. Downstream signaling is relayed by G-protein-coupled signal transduction, PKCs, and PI3K, similar to the mechanisms of pre-conditioning induced by volatile anesthetics. As with volatile anesthetics, early and late windows of myocardial protection are provided, with similar mechanisms and time frames [23]. The first window of protection is ultimately provided by the activation of the mitochondrial KATP channel and the inhibition of mPTP, whereas the second window of protection requires modulation of cardioprotective transcription factors and the expression of relevant genes. Notably, small bursts of ROS production due to the opening of the mitochondrial KATP channel seem to be as pivotal in the further induction and amplification of opioid-induced cardioprotective signaling as they are in ischemic and volatile anesthetic induced pre-conditioning [24]. In addition, opioids have post-conditioning effects when administered in close proximity to reperfusion [25]. The underlying mechanisms share many of the signaling processes involved in pre-conditioning, which ultimately lead to the opening of the mitochondrial KATP channel and the inhibition of mPTP [23].

Because opioid-induced myocardial protection shares many of the features related to ischemic pre-conditioning and pre-conditioning induced by volatile anesthetics, it is also subject to potential abrogation by advanced age, diabetes/hyperglycemia, and myocardial hypertrophy. Indeed, experimental data have demonstrated negative changes in opioid receptor responses related to pre- and post-conditioning with age and the aforementioned comorbidities [26].

**Propofol**

Compared to volatile anesthetics, propofol may preserve myocardial contractility and the arrhythmogenic threshold at clinically relevant concentrations [27]. Along with its pharmacokinetic advantage of providing a reliable context-sensitive half-life and its superb antiemetic properties, TIVA consisting of propofol and remifentanil has rapidly gained interest as an anesthetic technique for cardiac surgery, particularly in conjunction with fast-track anesthesia.

On the other hand, propofol may act as a mitochondrial toxin by interfering with oxidative phosphorylation and electron transport in a dose-dependent manner, resulting in the inhibition of ATP synthesis [28]. Although rare, these potentially adverse features are present in propofol infusion syndrome, which mimics mitochondrial myopathies caused by the disruption of fatty-acid oxidation and the respiratory chain [29]. Nonetheless, propofol has consistently been shown experimentally to provide cardioprotection against I-R injury [4,30].

Propofol is similar in structure to phenol-based radical scavengers such as the endogenous antioxidant vitamin E. Excessive ROS generation related to myocardial I-R, representing oxidative stress, plays a critical role in the pathogenesis of myocardial contractile dysfunction, dysrhythmia, microvascular damage, and cell death either by necrosis or apoptosis [31]. In that context, propofol acts as a strong antioxidant. It scavenges oxygen free radicals through the formation of phenoxy radicals, which is the key mechanism involved in propofol-induced myocardial protection against I-R injury [4,30]. It also provides mitochondrial membrane stabilization via decreased mitochondrial calcium uptake and direct inhibition of mPTP [32]. In contrast to volatile anesthetics and opioids, its mechanism of action suggests that it does not trigger signaling pathways related to pre- or post-conditioning, and thus lacks any conditioning effect in terms of myocardial protection against I-R injury [33]. Propofol’s ability to preserve myocardial function after I-R injury may be attributable to the compensatory hypercontractile state of the non-ischemic region, whereas isoflurane is able to preserve the contractile function in the ischemic region [34]. Overall, the degree of myocardial protection against I-R injury provid-
ed by propofol seems to be somewhat less than that of preconditioning induced by volatile anesthetics [6,7].

**CLINICAL TRANSLATION OF EXPERIMENTAL DATA**

Based on experimental data, anesthetic conditioning has been translated into clinical practice, mostly in the cardiac surgical setting. While a number of studies with limited sample sizes have reported beneficial effects of volatile anesthetics in terms of myocardial enzyme release, function recovery, and length of hospital stay, there is not yet conclusive evidence to support a reduction in mortality. The two largest randomized controlled trials conducted to date involved 414 patients (De Hert et al. [35]) and 868 patients (Likhvantsev et al. [36]) undergoing coronary artery bypass graft surgery (CABG). De Hert et al. [35] compared sevoflurane or desflurane administered at > 0.5 minimum alveolar concentration (MAC) to propofol in a multicenter, randomized trial, and found no difference in postoperative peak troponin T levels associated with the anesthetic regimen. However, they observed reduced length of hospital stay in the volatile anesthetic group compared to the propofol group, and reduced 1-year mortality for sevoflurane (3.3%) and desflurane (6.7%) versus propofol (12.3%). Likhvantsev et al. [36] compared sevoflurane to propofol administered via bispectral index score guidance (between 40–60) in a multicenter, randomized trial, and reported reduced length of hospital stay, troponin T release, and 1-year mortality (17.8% vs. 24.8%) in the sevoflurane group versus the propofol group. However, their mortality rates were unconventionally high, considering that the median EuroSCORE II of the patients ranged from 0.75 to 0.77.

Not surprisingly, meta-analyses including mainly small single-center studies of volatile anesthetics [37–40] have found conflicting results. The most recent meta-analysis [38] involved 3,966 patients from 38 trials, and reported a significant 50% reduction in mortality (1.3% vs. 2.6%) in the volatile anesthetic group versus the propofol group. Other meta-analyses have reported 47% reductions in myocardial infarction, 69% reductions in postoperative inotrope use [37], and 36.6% reductions in cardiac enzyme release [39].

Two longitudinal retrospective studies have been carried out, in Italy (n = 34,310) [41] and Denmark (n = 10,535) [42]. They included patients undergoing only CABG and CABG plus other cardiac surgeries, respectively. Both studies suggested that reduced mortality was associated with the use of volatile anesthetics. However, the results of these studies were inconsistent: the Italian study demonstrated a reduced risk-adjusted mortality rate with the use of volatile anesthetics versus TIVA, while only isoflurane was associated with reduced mortality, not sevoflurane or desflurane [41]. In the Danish study [42], overall 30-day mortality was lower in a sevoflurane group compared to a TIVA group, but the results were not statistically significant (2.84% vs. 3.30%, P = 0.18). Statistically significant mortality benefits of sevoflurane versus TIVA were observed only in patients without unstable angina or recent myocardial infarction. Conversely, the mortality rate was similar between the anesthetics in patients with unstable angina or recent myocardial infarction, which indicates no additive protection by volatile conditioning to the ischemic conditioning. Interestingly, urgent CABG surgery was associated with six-fold higher mortality than elective CABG, and propofol was associated with significantly lower mortality compared to the sevoflurane in this subset of patients (8.19% vs. 16.23%, P = 0.031).

Nevertheless, no large-scale, multicenter, randomized trials have clearly demonstrated that volatile anesthetics reduce mortality. Such studies would require a large number of patients (at least 5,000, assuming a mortality rate of 2%) considering the current low mortality rate in developed countries. Furthermore, the data mainly involve CABG patients, and ischemic symptoms before surgery may mimic ischemic pre-conditioning, confounding the observed results [42]. Evidence is even more scarce for patients without coronary artery disease undergoing cardiac surgeries other than CABG.

Major drawbacks limiting the clinical efficacy of volatile anesthetics include co-morbidities and associated medications. Most experimental evidence has been collected using young animals without any co-morbid diseases. Indeed, advanced age, concentric hypertrophy, diabetes, and the presence of transient hyperglycemia (commonly encountered features in the cardiac surgical setting) have all been experimentally shown to abolish the cardioprotective effects of volatile anesthetics [7]. In addition to the well-known negative effects of sulfonylurea on anesthetic preconditioning, the use of beta-blockers has also been shown to mitigate myocardial protection, while the use of angiotensin-converting enzyme inhibi-
tors/angiotensin receptor blockers may enhance protection [12]. The interactions among these conditions and medications have not yet been clinically validated; for example, β-blockers do not seem to interfere with volatile-induced anesthetic conditioning clinically [43].

Another major drawback is the lack of an established consensus regarding the dosing or administration protocol for anesthetics. Even in experimental studies, there are controversies over the minimum requirement (0.3 vs. 0.5 MAC) or the administration protocol (multiple versus single cycle with wash-out periods versus continuous administration) [6,7]. Experimental evidence suggests that there exists a dose-response effect with a ceiling effect reached at 2 MAC [44]. Clinically, however, the administration of 2 MAC volatile anesthetics may not be feasible in cardiac surgical patients without the concomitant use of adrenergic stimulants, which may compromise anesthetic pre-conditioning. Clinical evidence is also inconclusive regarding the optimal administration protocol. Two studies involving small numbers of patients undergoing CABG advocated the use of multiple cycles of volatile anesthetic administration, interspersed with wash-out periods to attenuate myocardial damage [45,46]. However, concerns were raised regarding the potential delay of cardiopulmonary bypass required to wait for the wash-out period. More importantly, providing wash-out periods may not be feasible as anesthesia must be ensured to patients throughout the surgery. Nonetheless, the use of volatile anesthetics in a practical manner (e.g., guided by bispectral index score) has beneficial effects in patients undergoing CABG [36].

Regarding the use of propofol-based TIVA, it is important to note that its oxygen free radical scavenging property may actually prevent other pre-conditioning effects [16,24]. Indeed, one of the triggers of anesthetic pre-conditioning is the formation of ROS species that can be inhibited by propofol. Accordingly, concomitant use of propofol with volatile anesthetics has been shown to abrogate the cardioprotective effects of anesthetic pre- and post-conditioning [7]. Clinically, the use of propofol may be a major factor mitigating the myocardial protective efficacy of remote ischemic pre-conditioning, which shares many protective signaling pathways with ischemic or anesthetic pre-conditioning [47]. Likhvantsev et al. [36] recently found that avoiding propofol was associated with decreased cardiac enzyme release and reduced length of hospital stay, even in patients who received propofol at anesthetic induction while sevoflurane was administered throughout the surgery.

Interestingly, one study has suggested superior myocardial protection in patients undergoing CABG using a combination of isoflurane before cardiopulmonary bypass and propofol thereafter, compared to isoflurane or propofol anesthesia alone [48]. Although performed on a small number of patients, this study implicates the potential for combining pre-conditioning induced by volatile anesthetics with the free radical scavenging properties of propofol. However, volatile anesthetics must always be administered before propofol. Finally, the use of an opioid (remifentanil) in conjunction with volatile anesthetics has been clinically shown to provide additive myocardial protection [7,23].

**CONCLUSIONS AND PERSPECTIVES**

Although the current literature suggests a beneficial role for volatile anesthetics over propofol in terms of myocardial enzyme release, length of hospital stay, and mortality, the level of evidence is insufficient. One must also acknowledge emerging evidence for the potential neurotoxicity of volatile anesthetics, particularly in the developing brain and in patients with Alzheimer’s disease. By contrast, propofol has well-validated antiemetic efficacy and is not known to be associated with the formation of neurofibrillary tangles or amyloid plaques related to the progression of Alzheimer’s disease [49]. Therefore, based on current evidence, both anesthetic regimens can be employed depending on patients’ comorbidities.

Considering that ROS production is essential in triggering the pre-conditioning effects of volatile anesthetics and opioids, it is reasonable to use volatile anesthetics in combination with opioids before aortic cross-clamp application to maximize their pre-conditioning stimuli. TIVA can be used after reperfusion to reduce oxidative stress and reperfusion injury without hindering the early and late windows of myocardial protection provided by pre-conditioning. In addition, it may be beneficial to discontinue oral hypoglycemic agents that may interfere with the opening of the mitochondrial K\textsubscript{ATP} channel, and to avoid desflurane in patients receiving β-blockers. In selected patients with acute coronary syndrome presenting for urgent or salvage CABG, TIVA may be considered.
The optimal regimen for myocardial protection and patient outcome must be validated through large-scale, randomized, multicenter studies. Likewise, appropriate studies should be conducted to determine whether TIVA is more beneficial than volatile anesthetics in patients with advanced age, hypertrophy, or diabetes. Above all, we should bear in mind that anesthetics cannot prevent myocardial cell death from ischemia. They merely delay it by providing increased ischemic tolerance; thus, timely reperfusion therapy should always be a top priority in cases of suspected myocardial ischemia during the perioperative period.

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