Review Article

Intra-operative anesthetic induced myocardial protection during cardiothoracic surgery: a literature review

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Background and Objective: Myocardial protection involves limiting the metabolic activity and oxygen consumption of the heart, thus enabling surgery to proceed with minimal blood loss while reducing the level of ischemic injury. It was this concept that allowed for the development of the open-heart surgical technique. We know myocardial ischemia and reperfusion injury are both detrimental, thus developing strategies to mitigate this can help reduce peri-operative morbidity and mortality. In this review, we will mainly be addressing the anesthetic considerations for myocardial protection, along with discussing potential future research which can help expand the field.

Methods: We searched the PubMed database for relevant studies dating from 2004–2022. In total, 18 studies were deemed suitable for this literature review.

Key Content and Findings: Studies have demonstrated cardioprotective effects with use of the volatile agents and propofol, mainly with respect to lower levels of inflammatory markers such as creatine kinase (CK)-MB and troponin I (TnI)/troponin T (TnT). The data is lacking regarding protective effects of dexmedetomidine and lidocaine, hence we cannot recommend either agent at present.

Conclusions: Myocardial protection with respect to the anesthetic agents have been extensively studied over the past two decades, some routinely used drugs such as the volatile agents, propofol and opiates have demonstrated a cardioprotective role. The ideal dosing regimen and duration are areas of research that can be studied further. The data for the other anesthetic adjuncts such as lidocaine, dexmedetomidine along with use of regional anesthesia is still equivocal. Alongside advances in anesthesia, we believe surgical research looking into optimal cardioplegia solutions will also help improve myocardial protection in the future.

Keywords: Myocardial protection; ischemic-reperfusion injury; cardiac surgery; cardiothoracic anesthesia

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Introduction

Myocardial protection strategies begin with the preparation of the myocardium in the pre-bypass phase. During this phase, the anesthesiologist prepares the myocardium to tolerate ischemic arrest. Myocardial optimization during this phase is achieved by controlling hemodynamic perturbations, ensuring rehydration, absence of dyselectrolytemia, and adequate euglycemia.

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Several pharmacological interventions, such as utilization of vasopressors/inotropes, may be necessary to optimize coronary perfusion pressure and possibly reduce perioperative organ injury. Next, the phase of myocardial protection occurs with initiation of the bypass period. The primary method of myocardial preservation remains the utilization of cardioplegia and the institution of hypothermia. From the initial proposal by Bigelow in 1950 via use of hypothermic cooling, the strategies for myocardial protection have changed drastically over the years (1). Advances include electrochemical arrest via potassium solutions as described by Melrose, the incorporation of blood-based cardioplegia during cardiopulmonary bypass (CPB), increased recognition of ischemic-reperfusion injury, recognition of the protective role of preconditioning and the cardioprotective effects of various systemic pharmacologic agents (2,3).

Before we discuss myocardial protection further, we must first define ischemic pre-conditioning, as this is one of the key phenomena at play here. Ischemic pre-conditioning describes a phenomenon whereby brief periods of ischemia can trigger pathways that ultimately help preserve myocardial function when longer periods of ischemia take place. This is of particular importance during cardiothoracic surgery when the heart can undergo extensive periods of ischemia. The concept of myocardial protection involving ischemic pre-conditioning was first described in 1986 by Murry *et al.* (4). The process of 'pre-conditioning' can be undertaken with pharmacological treatment or with direct ischemic intervention, prior to the insult occurring. Once an insult occurs, the process is known as post-conditioning.

The purpose of myocardial protection is to ultimately prevent myocardial ischemia reperfusion injury, there are a plethora of mechanisms responsible for this entity. Examples include build-up of intracellular calcium, opening of the mitochondrial permeability transition pore (mPTP), disruption of nitric oxide production and metabolism and complement activation (especially C5 complement) (5). While this list is not exhaustive, it just highlights the multiple active molecular mechanisms during cardiac surgery.

Over the last several decades, there have been numerous reports looking into myocardial protection with respect to the anesthetic pharmacological treatment such as propofol, opioids, and volatile anesthetics (6,7). While many studies favor these agents with respect to limiting the degree of cardiac ischemia-reperfusion injury, there is still more research to be done and questions that need answering (8). The focus of this review will be on utilization of anesthetic agents, however we would like to acknowledge the importance of non-pharmacologic factors such as the type and composition of cardioplegic solution, use of myocardial cooling (9), and ventricular unloading. The latter is becoming more prevalent with increasing use of ventricular assist devices prior to reperfusion that can help unload the ventricle and thus attenuate the degree the reperfusion injury. We present this article in accordance with the Narrative Review reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1101/rc).

Methods

We searched the PubMed database for relevant studies over the time period 2004–2022. We used the following mesh terms to help aid our search: 'cardiac surgery' AND 'ischemic-reperfusion injury' AND 'anesthetics' AND 'myocardial protection' AND 'adults' OR 'volatile anesthetics' OR 'propofol' OR 'opioids' OR 'dexmedetomidine' OR 'regional anesthesia' OR 'lidocaine' OR 'lidocaine infusion' OR 'mechanism' OR 'pathophysiology'. We only included literature published in English, specifically systematic reviews, randomized controlled trials (RCTs), and narrative reviews from 2004–2022. We excluded any editorials, commentary, abstracts, letters to the editor, and non-human studies. A detailed search summary is seen in *Table 1*.

Anesthetic agents

Volatile anesthetics

Volatile anesthetics have been used extensively during cardiac surgery for decades, with many studies reporting better preserved myocardial function with inhalational anesthetic usage (10) (*Table 2*).

Yang *et al.* (11) performed a study looking at use of sevoflurane *vs.* propofol with respect to myocardial protection during cardiac valve replacement surgery. The team tracked serum levels of troponin I (TnI) and creatine kinase (CK)-MB at various time intervals ranging from before induction to 48 hours post-operatively. Their results revealed the sevoflurane group had lower levels of the above inflammatory markers, furthermore this group has a shorter length of overall hospital stay (12 *vs.* 16 days, $P<0.05$). De Hert *et al.* conducted a study looking at the use of propofol, midazolam, sevoflurane, or desflurane during elective cardiac surgery. The primary outcome was

Table 1 Search strategy

Items	Specification
Date of search	1st June 2023
Databases	PubMed
Search terms used	'Cardiac surgery' AND 'ischemic-reperfusion injury' AND 'anesthetics' AND 'myocardial protection' AND 'adults' OR 'volatile anesthetics' OR 'propofol' OR 'opioids' OR 'dexmedetomidine' OR 'regional anesthesia' OR 'lidocaine' OR 'lidocaine infusion' OR 'mechanism' OR 'pathophysiology'
Timeframe	2004–2022
Inclusion and exclusion criteria	Inclusion: English as the primary language, systematic reviews, RCTs, and narrative reviews
	Exclusion: editorials, commentary, abstracts, letters to the editor, and non-human studies
Selection process	Two authors independently reviewed the preliminary studies, in total 54 studies. Of these 18 were chosen for this literature review

RCT, randomized controlled trial.

Table 2 Studies involving the volatile agents

Study	Protocol	Result
De Hert *et al.*, 2004	Propofol (n=80) *vs.* midazolam (n=80) *vs.* sevoflurane (n=80) *vs.* desflurane (n=80). Elective coronary surgery. Each agent administered continuously intra-operatively with a remifentanil infusion	Sevoflurane and desflurane groups—overall shorter hospital and ICU stay, number of patients needing ICU stay beyond 48 h significantly lower (P<0.01, propofol: n=31, midazolam: n=34, sevoflurane: n=10, desflurane: n=15)
Huang *et al.*, 2011	Propofol (n=30) *vs.* isoflurane (n=30), *vs.* isoflurane and propofol (n=30). Elective CABG surgery	Isoflurane and propofol—lower pro-inflammatory cytokine levels compared to each agent alone
Steurer *et al.*, 2012	Propofol (n=56), sevoflurane (n=46). Post-cardiac surgery. Upon arrival to ICU, propofol infusion/ sevoflurane regimen commenced	Sevoflurane group—on POD1, TnT levels significantly lower (adjusted mean was 0.2 μg/L lower, P=0.03)
Yang *et al.*, 2017	Propofol (n=37) *vs.* sevoflurane (n=36). Valve replacement surgery. Each agent administered continuously intra-operatively	Sevoflurane group—lower TnI and CK-MB levels from 30 min post-aortic unclamping to 48 h post-operatively, shorter length of ICU and hospital stay (12 *vs.* 16 days, P<0.05)
Landoni *et al.*, 2019	Volatile (n=2,709) *vs.* TIVA (n=2,691). Elective CABG surgery. Desflurane/isoflurane/sevoflurane used, TIVA with propofol mainly, also midazolam	No difference in death from any cause at 30 days or 1 year (P=0.71)

ICU, intensive care unit; CABG, coronary artery bypass grafting; POD, post-operative day; TnT, troponin T; TnI, troponin I; CK-MB, creatine kinase-MB; TIVA, total intravenous anesthesia.

length of hospital and intensive care unit (ICU) stay. The results revealed the sevoflurane and desflurane groups were associated with a shorter hospital and ICU stay. In addition, the number of patients who needed ICU stay for beyond 48 hours was also significantly lower for the volatile group (P<0.01; propofol: n=31, midazolam: n=34, sevoflurane: n=10, desflurane: n=15) (12).

Steurer *et al.* administered either propofol or sevoflurane as sedation to post-cardiac surgery patients for at least 4 hours upon arrival into the ICU. On post-operative day 1, the troponin T (TnT) levels in the sevoflurane group were significantly lower than the propofol group (adjusted mean was 0.2 μg/L lower, P=0.03) (13). This study supports the notion that volatile anesthetics may confer post-conditioning myocardial protective benefits. Huang *et al.* investigated isoflurane use pre-CPB and propofol use post-CPB, they compared this with sole use of propofol or isoflurane. Their results demonstrated that preconditioning with isoflurane and post-conditioning with propofol in combination helped limit the degree of myocardial injury than use of each agent alone (14).

Of note, there is some inconsistency amongst studies

on this topic, for example Landoni *et al.* compared total intravenous anesthesia (TIVA) *vs.* inhalational anesthetic technique during coronary bypass surgery and found no significant differences in morbidity and mortality (15).

The MYRIAD trial (15) was an international multi-center trial looking into volatile anesthetic *vs.* TIVA for patients undergoing coronary artery bypass grafting (CABG) surgery. Of note, patients assigned to the TIVA group did not receive any volatile anesthetic, hence there was no agent mixing in this study. The primary outcome of the MYRIAD trial was death from any cause at 1 year, the secondary outcomes included death at 30 days, death from a cardiac cause at 1 year, hospital and ICU length of stay. The team found no significant differences with respect to the primary or secondary outcomes (15).

While use of volatile anesthetics appears to be beneficial as per several small studies, it is unclear which volatile anesthetic best preserves myocardial function, in addition more research needs to be conducted on optimal duration of the volatile anesthetic. In many studies, the inhalational agent is usually co-administered with other intravenous agents such as propofol and remifentanil. We do not know how much confounding impact these intravenous drugs have on the overall myocardial protection. Furthermore, many of the volatile agents and intravenous agents were started either pre-CPB, during or post-CPB. Despite the lack of consistency across all studies, volatiles typically are still the mainstay maintenance anesthetic of choice during cardiac surgery. We believe it is worthwhile using these agents considering the positive outcomes seen albeit in smaller sized studies (*Table 2*).

One of the proposed biological mechanisms of action of the volatile agents (isoflurane and sevoflurane) includes minimizing production of reactive oxygen species by inhibiting complex 1 of the electron transport chain. This mechanism appears to be beneficial for both the ischemic and reperfusion periods of the surgery (16). The mPTP is a membrane protein that opens during ischemia-reperfusion injury. This results in mitochondrial swelling, adenosine triphosphate (ATP) depletion, and cellular apoptosis. Volatile anesthetics may delay or inhibit mPTP opening, thus minimizing the degree the ischemia-reperfusion injury. Please see *Table 3* for downstream molecular pathways associated with volatile anesthetics.

Propofol

Studies have demonstrated propofol helps attenuate the degree of myocardial damage, possibly due to its antioxidant and anti-inflammatory effects. Huang *et al.* postulate that excessive production of peroxynitrite ($ONOO^-$) may contribute to myocardial injury, this is thought to be an important causative molecule in the pathophysiology of heart failure (14). Propofol is a known scavenger of $ONOO^-$; this may be particularly important during reperfusion, when $ONOO^-$ levels are increased (19). Similar to the volatile agents, some authors suggest the cardioprotective effect of propofol can be attributed to inhibition of mPTP. He *et al.* (20) conducted *in vitro* research looking at use of propofol and sevoflurane post-reperfusion of the heart, thus targeting the post-conditioning state. The authors also postulate the myocardial protective effects of both drugs may be attributed to inhibition of mPTP opening (20). Interestingly, Rogers *et al.* (21) conducted a RCT whereby they supplemented conventional cardioplegia solution during cardiac surgery with propofol *vs.* intralipid (placebo). The authors found the propofol group had lower levels of TnT in the first 48 hours post-operatively (primary outcome). This study also demonstrates the myocardial protective benefits of propofol however this was a single-center trial. The results do pose an interesting question as to whether propofol should be mixed in with cardioplegia as standard of care for the future.

While most studies seem to be in favor of propofol, there are studies which found no protective benefits. It appears higher doses of propofol infusion confer greater cardioprotective benefits, however clinically this must be balanced with hemodynamic stability. Xia *et al.* (22) advocate high-dose propofol, 120 mcg/kg/min^{-1} at select times prior to CPB and post-aortic unclamping *vs.* low-dose propofol at 60 mcg/kg/min^{-1} throughout surgery. The team found the high-dose propofol group was associated with lower inotropic support when weaning of CPB (n=2 *vs.* n=5 in low-dose propofol group, $P<0.05$), furthermore lower TnI levels and shorter ICU stay was noted (34 *vs.* 48 hours, $P<0.05$).

In summary, propofol does appear to help limit the degree of ischemia-reperfusion injury, especially at higher doses. Further research needs to be conducted on when best to start the propofol infusion, along with its synergistic effects with volatile usage.

Opiates

There are several studies that support the notion that opiates help attenuate myocardial infarction size when

Table 3 Downstream molecular pathways of several anesthetic agents

Agent	Receptor/target	Mechanism of action
Volatile anesthetic	K_{ATP}	Increased opening of mitochondrial K_{ATP} channels
		Decreased mPTP opening
		Increased phosphorylation of Akt, decreased apoptosis, decreased Ca^{2+} accumulation following reperfusion
		Decreased NF-κB (activation) (17)
Propofol	$ONOO^-$	Direct scavenging of free $ONOO^-$
	mPTP	Decreased channel opening during ischemia/reperfusion, decreased cellular swelling, ATP depletion, and apoptosis
Opioids	δ/κ	Direct myocardial signal modulation via Gi/o coupled receptors (18)
		Activation of mitochondrial and sarcolemmal K_{ATP} channels
		Modulatory effects on following proteins:
		PKC
		GSK-3β
		mTOR
		iNOS
		JAK/STAT
		COX-2
	μ	Attenuation of the sympathetic nervous system through direct CNS effect
		Possible direct myocardial protective effect shared with δ and κ receptors

K_{ATP}, ATP-sensitive potassium; ATP, adenosine triphosphate; mPTP, mitochondrial permeability transition pore; NF-κB, nuclear factor-kappa B; $ONOO^-$, peroxynitrite; PKC, protein kinase C; GSK-3β, glycogen synthase kinase-3 beta; mTOR, mechanistic target of rapamycin; iNOS, inducible nitric oxide synthase; JAK/STAT, Janus kinase/signal transducers and activators of transcription; COX-2, cyclooxygenase-2; CNS, central nervous system.

exposed to ischemia. The generally accepted theory behind this phenomenon is direct myocardial preconditioning mediated by δ and κ opiate receptors present in myocardial tissue which seemingly lacks μ receptors. Surprisingly though, μ-receptor specific opioids without significant δ and κ such as remifentanil have demonstrated similarly reduced infarction size (18). This is thought to be due to a central nervous system (CNS) mediated reduction in sympathetic tone or a relative increase in parasympathetic tone, reducing myocardial oxygen demand. Supporting this hypothesis, Gross *et al.* showed that opioid antagonists that cross the blood-brain barrier, such as naloxone hydrochloride, have blocked this beneficial response in the presence of a μ receptor agonist, while those with only peripheral activity preserved the reduction in infarction size (23). Please see *Table 3* for additional receptor activation information for the anesthetic agents.

Other anesthetic adjuncts

Aside from volatile anesthetics, propofol, and opiates, there are other pharmacological agents that have the potential to be used during cardiac surgery. One such example is dexmedetomidine, an alpha-2 agonist commonly used for its anxiolytic properties along with use during sedation cases. Chen *et al.* (24) conducted a meta-analysis gathering studies that compared dexmedetomidine with normal saline during cardiac surgery, in total nine studies were analyzed. Using the concentration of CK-MB as a surrogate for myocardial injury, the dexmedetomidine groups had lower levels of CK-MB. Furthermore, the dexmedetomidine groups had lower levels of interleukin-6 (IL-6) and tumor necrosis factor (TNF)-alpha, these are known pro-inflammatory cytokines that are induced during cardiac surgery (25). The most common dosing regimen consisted of a loading

dose of 1 mcg/kg over 10 minutes before initiation of CPB followed by an infusion of 0.5 mcg/kg/h for the rest of surgery. Given its superior hemodynamic stability profile when compared to propofol, it may be a useful alternative agent for providers.

We must also look into use of local anesthetics, specifically, lidocaine infusions. Lidocaine is a sodium channel blocker, thought to exert its myocardial protective mechanisms by limiting the degree of intracellular sodium build-up, and thus limiting the degree of calcium release. We know the latter is a key culprit with respect to myocardial ischemia and reperfusion injury. Lee *et al.* (26) conducted a RCT whereby patients received a bolus of 2% lidocaine on induction, followed by an infusion of 2 mg/kg/h. This was conducted during off pump CABG. The lidocaine cohort had lower levels of TnI and CK-MB at the 24-hour post-operative mark. Interestingly, there were no differences in inflammatory markers such as C-reactive protein (CRP), this poses another question, maybe there are pathways that we are yet to consolidate that can also prevent CK-MB and TnI rise aside from the conventional inflammatory pathways (26). Of note, this study was conducted in patients with normal ejection fraction hence one must be cognizant of supratherapeutic lidocaine levels in those unstable patients with poor ejection fraction. Furthermore, the CPB circuit was eliminated in this study, this must also be factored into the interplay of cytokine and inflammatory mediator release. As of now, we do not know the optimal dosing regimen, and cannot recommend routine use of lidocaine infusions during cardiac surgery (27).

While the concept of fast-track anesthesia is ideal, it is harder to universally implement in cardiac surgery given patient and surgical factors. The regional anesthetic of choice is typically thoracic epidural analgesia, while it does provide good post-operative analgesia, thus helping with respiratory mechanics, the cardiac outcomes have been mixed. A 2019 Cochrane review (28) looked into use of epidural analgesia *vs.* other modalities of analgesia in patients having cardiac surgery under general anesthesia. The team found no 30-day mortality difference [risk difference (RD): 0.00] along with a small decrease in incidence of myocardial infarction (RD: –0.01). Of note, the Cochrane review did acknowledge this data was obtained from low-quality studies. Given the use of system anti-coagulation, one must also weigh the risks of an epidural hematoma which may go unidentified for hours whilst the patient is under general anesthesia and sedation post-operatively (29).

Conclusions

In conclusion, we have established certain strategies and methods to help preserve myocardial function, thus enabling high-risk patients to successfully undergo cardiac surgery. Alongside advances in research pertaining to pharmacological treatment, the surgical approach with respect to cardioplegia solution, timing, and delivery is also important. There are still unanswered questions with respect to the ideal anesthetic regimen, along with optimal duration and dosing. The data as of now suggests volatile usage during cardiac surgery is beneficial given the reduced hospital and ICU length of stay, along with attenuation of myocardial damage. The cardioprotective effects of propofol appear to be dose dependent, however hemodynamic instability may be a concern with larger doses. The use of opiates appears beneficial, possibly due to the whole host of downstream protein modulation. In addition, dexmedetomidine appears to be a valid, alternative agent to propofol, mainly owing to its hemodynamic stability, and possible myocardial protective effects. As of now, there is very limited clinical data looking into the cardioprotective effects of etomidate, benzodiazepines or lidocaine, hence further studies are warranted. Of note, lidocaine specifically must be used with caution in those with hepatic failure or low ejection fraction given the concern of local anesthetic toxicity. Another area of interest is use of regional anesthesia, while thoracic epidurals certainly help with post-operative analgesia, there is insufficient evidence to universally recommend them. The risk of hematoma given system anti-coagulation also remains a concern (30). At our home institution, we typically use volatile anesthetic as the maintenance agent of choice, and start a propofol infusion post-CPB. Depending on the surgery and surgical preference, we tend to perform bilateral pecto-intercostal fascial plane blocks prior to transport to the ICU. We do not place thoracic epidurals for our cardiac surgery patients.

We believe the greatest advances in myocardial protection will come from other determinants, such as optimizing the various cardioplegia solutions. While this has been extensively studied in the literature, we are still experimenting with cardioplegia additives such as ‘esmolol’ and ‘diltiazem’. Finally, other avenues of research include use of exogenous nitric oxide considering animal studies have demonstrated endogenous nitric oxide decreasing myocardial infarction size (31). In addition, use of anti-C5 complement antibodies (pexelizumab), this specific drug is off the market due to variable results, however

pharmacologic agents targeting the complement system are a pathway for further research (32).

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Footnote

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