Total Intravenous Anesthesia for Myocardial Protection and Preconditioning

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Perioperative myocardial injury is common after any major surgical procedure even with best possible anesthesia and surgical management. Organ preservation during surgical procedure prevents morbidity and mortality. The effect of ischemic preconditioning on myocardial as well as other organ protection is well known. A variety of other agents also shown to have preconditioning thus protective effect on myocardium during anesthesia and surgery. The beneficial effect of volatile anesthetic preconditioning is well studied. However, the effect of intravenous anesthetic agents on this context is still way to go. This review is an attempt to look into the latest available research regarding the preconditioning and myocardial protective effect of intravenous anesthetic agents.

Abstract

Perioperative myocardial injury is common after any major surgical procedure even with best possible anesthesia and surgical management. Organ preservation during surgical procedure prevents morbidity and mortality. The effect of ischemic preconditioning on myocardial as well as other organ protection is well known. A variety of other agents also shown to have preconditioning thus protective effect on myocardium during anesthesia and surgery. The beneficial effect of volatile anesthetic preconditioning is well studied. However, the effect of intravenous anesthetic agents on this context is still way to go. This review is an attempt to look into the latest available research regarding the preconditioning and myocardial protective effect of intravenous anesthetic agents.

Keywords

► total intravenous anesthesia
► myocardial protection
► preconditioning

Introduction

Perioperative myocardial injury is common after cardiac surgery even with best surgical procedure/anesthesia management. However, this injury is common after noncardiac surgery as well. The VISION study group in noncardiac surgery patients also noted that 8% of patients aging more that 45 years suffered from myocardial damage. The incidence of myocardial damage is again more in cases with comorbidities such as diabetes, ischemic heart disease, and/hypertension.

Perioperative organ protection is an important aspect of anesthesia and surgical management, and this is to prevent postoperative morbidity, mortality, and cost of hospital stay. Several methods have been described in literature to reduce organ damage in the perioperative period among which preconditioning is the most important one and considered to be the best.

Myocardial Injury and Preconditioning, General View, and Historical Aspect

Some degree of myocardial injury is inevitable in all kinds of surgery and that is more in cardiac surgical procedures.

Surgical trauma, mechanical stress, hemodilution, perfusion temperature, endotoxin release, ischemia-reperfusion injury, blood reaction with foreign material are the major stimuli those can give rise to ischemia, which leads to hypoxia and subsequently dysfunction of mitochondrial electron transport chain dysfunction. There occurs a decrease in adenosine triphosphate (ATP) production, induction of anaerobic metabolism, dysfunction of sodium-potassium pumps, detachment of ribosomes, and a decrease level of antioxidants in the cells. Retention of lactic acid may lead to lactic acidosis. Failure of Na+–K+ ATPase pump and Ca2+ATPase pump leads to accumulation of sodium, hydrogen, and calcium ions in the cell, leading to hyperosmolarity and cellular swelling. Sodium retention decreases cellular pH, leading to the impairment of enzymatic activity and clumping of cellular chromatin. Detachment of ribosome also leads to decrease in protein synthesis. There also occurs limitation of nitric oxide bioavailability followed by apoptosis of cardiac myocytes.

After the reperfusion stage, the restoration of blood flow to ischemic tissue resumes oxygenation. In parallel, there is generation of reactive oxygen species (ROS) due to decrease

DOI https://doi.org/10.1055/s-0041-1723932
ISSN 2457-0206.
concentration of antioxidants in the ischemic cells. This leads to endothelial dysfunction, damage to DNA and local inflammatory response. The mitochondrial damage and electrolyte imbalance in this stage promotes the oxidative stress from nicotinamide adenine dinucleotide phosphate-oxidase (NADPH) oxidative system, nitric oxide synthase system and xanthine oxidase system as well as mitochondrial electron transport system. There is activation of inflammatory cascade leading to a cytokine storm, and retention of ROS leading to cellular damage and cell death via mitoptosis, autophagy, necrosis, necroptosis as well as apoptosis. This reperfusion phase is dynamic and sometimes persists for several days. Understanding the detailed mechanism of ischemia-reperfusion injury may provide a strong foundation not only for novel therapeutic opportunities, but also for injury prevention.

In literary meaning, preconditioning (PC) is nothing but “adaptation,” in which a living entity is exposed to a form of stress or stimulus or environment to prepare that subject to be more resilient against the stimulus if it is encountered/ applied thereafter. The concept of myocardial preconditioning was narrated first by Murray et al way back in 1986. He with his team used ischemia as a stimulus and described ischemic preconditioning (IPC) in dog hearts. In these experiments, one group of dogs was preconditioned with four cycles (5 minutes each) of circumflex artery occlusions, each separated by 5 minutes of reperfusion and followed by continuous 40 minutes occlusion. The control group underwent a single 40 minutes occlusion only. The authors noted a reduction in infarct size (IS) to 25% when compared with the control group \( (p = 0.001) \).

Several cardioprotective strategies like cardioplegia, hypothermia, warm heart surgery, ischemic preconditioning, ischemic postconditioning, remote ischemic preconditioning, use of glucose-insulin in cardioplegia, and nitric oxide-L arginine supplemented cardioplegia are in use.\(^{14}\) The cardio protective effects of volatile anesthetics are widely studied by several authors in the past few decades. These investigators have shown that exposure to volatile anesthetics leads to a variety of changes in the protein structure of the myocardium. These changes in protein structure and their modified distribution after exposure to volatile anesthetic agents can mediate myocardial protection (MP) by preconditioning effect. There exist three windows where MP strategies can be implemented, for example, before ischemia (preconditioning), during ischemia, and after ischemia (postconditioning).\(^{5-8}\) There is a paucity of literature when myocardial preservation and preconditioning concerned with intravenous anesthetists. Intravenous anesthetics may be the future of cardioprotection; however, it is superiority to volatile anesthetics and other agents as well as ischemic preconditioning are yet to be proved. Fraßdorf et al in one of the reviews narrated the possible protective role of intravenous anesthetics against ischemia and reperfusion injuries.\(^{9}\) The main advantages of APC by anesthetic agents are that, unlike IPC, APC is not selective to myocardium only. The beneficial effects of these agents are for the entire organs of the body. APC is again easy way, less cumbersome because these agents are mandatory during any of the surgical procedures. This review is an attempt to reveal this concept with basic cellular mechanisms and recent trends.

**Myocardial Protection and Preconditioning by Intravenous Anesthetic Agents, Mechanisms to Clinical Outcome**

One of the frequent challenges of current day anesthesia practice is the prevention and treatment of myocardial ischemia and reperfusion injury. The primary goal in the therapy of myocardial ischemia-related injury is to restore perfusion to the ischemic tissues. The more lethal reperfusion injury can be reduced by modifications of conditions of reperfusion. Among all modifying agents, intravenous anesthetic agents are some. The mechanism involving anesthetic preconditioning (APC) is similar to reperfusion injury salvage kinase (RISK) that of IPC and ischemic postconditioning (IPoC). APC-MP is primarily mediated by RISK and survivor activating factor enhancement (SAFE) pathways. The activation of RISK pathway is via G-protein coupled cell surface receptor and that of SAFE pathway is via TNF-α receptor; both of which inhibit ischemia reperfusion injury (IRI) induced mitochondrial permeability transition pathway (mPTP) opening and activate the opening of KATP channels which subsequently protects cardiomyocyte from IRI induced cell death.

**Opioids and Its Derivatives**

Previous studies have demonstrated that opioid like agents bestow the ability of cardiac tissue to tolerate periods of ischemia and hypoxia.\(^{10}\) Morphine is one of the first agents to be tested for its cardioprotective effect by Schultz et al. In this experimental model, the authors elicited morphine induced PC by 5 minutes of drug infusion (100 μgm/kg IV) interspersed with 5 minutes drug free periods before the prolonged 30 minutes occlusion. The control group underwent three cycles of IPC. A similar reduction of IS to the area at risk happened in all the subjects. Their results indicate that the effect of morphine induced PC is most likely mediated via an opioid receptor-linked mechanism, which is similar to IPC.\(^{11}\) Murphy et al in one of the prospective randomized studies on coronary artery bypass grafting (CABG) patients, administered either morphine 40 mg or fentanyl 1,000 μgm before CPB. The morphine receivers showed an improvement of myocardial performance index 15 minutes post-CPB and end of surgery when compared with baseline and fentanyl group. However, this study does not comply with the strict definition of preconditioning.\(^{12}\) The protection against IRI to myocardium is offered by opioids mediated via stimulation of generation of ROS, which triggers and enhances the production of endogenous antioxidant enzymes and activates mitochondrial KATP channels, limiting myocardial infarction.\(^{13}\) Previous studies concluded the role of opioids in myocardial hibernation. Both endogenous and exogenous opioid agonists (morphine and remifentanil) reduce myocardial oxidative stress and \( \text{Ca}^{2+} \) overload attenuate myocardial IRI in patients undergoing cardiac surgery.\(^{12,13}\) Qiao et al in one of their initial experimental models show that remifentanil confers MP primarily via activation of JAK2/STAT3 signaling that can function independent of PI3K/AKT activation.\(^{14}\)
Propofol
The propofol induced myocardial preconditioning is mediated via its ROS scavenging properties, which enhances endogenous myocardial antioxidant capacity and thereby attenuates myocardial IRI. Few of the authors also suggested that propofol-induced MP may partly result from a direct effect on myocardial Ca²⁺ influx or from inhibition of mPTP. Opening of mPTP uncouples mitochondria and is involved in determining pathways that lead to apoptosis and necrosis. Inspite of the fact that propofol protects against IRP when given before onset of ischemia, its administration on reperfusion alone may be ineffective. Administration of propofol (120 µg/min for 10 minutes) before the commencement of CPB until 15 minutes after aortic cross clamp release, than 60 µg/min till the end of surgery, significantly attenuated myocardial injury as evidenced by a reduction in cardiac troponin I (CTnI) release as noted by Xia et al. Bulow et al compared dexmedetomidine 0.3 µg/kg/h in patients undergoing on-pump CABG to that with propofol 4 µg/mL/min. A reduced oxidative stress markers and inflammatory markers was found with both the drugs. The benefits of propofol as APC was demonstrated by several authors; however, few of the trials showed that no difference among patients receiving propofol or sevoflurane and propofol or desflurane in terms of CK-MB, CTnI level, and postoperative recovery parameters.

Ketamine
While one of the researchers reported that racemic mixture of ketamine blocks IPC of the myocardium, Hanouz et al found that both racemic and S+ isomer of ketamine induced preconditioning effect in isolated human myocardium. Their inference was ketamine-induced preconditioning involved activation of potassium adenosine triphosphate K (ATP) channels and stimulation of α and β adrenergic receptors.

In another experimental study, the authors found that higher dose of ketamine-xyaline (KX) (K: 200 mg/kg; X: 60 mg/kg or K: 85 mg/kg; X: 15 mg/kg) used to anesthetize guinea pigs led to reduction in myocardial IS and improved hemodynamics after experimental ischemia-reperfusion injury.

Table 1 The major randomized clinical trials of total intravenous anesthesia in myocardial protection and preconditioning

<table>
<thead>
<tr>
<th>Reference no.</th>
<th>Induction agents</th>
<th>Test drug for APC</th>
<th>Control drug</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>Sufentanil 0.5–1 µg/kg followed by 0.5–1 µg/kg/h</td>
<td>Dexmedetomidine 0.3 µg/kg/h</td>
<td>Propofol</td>
<td>Oxidative stress and inflammatory markers</td>
</tr>
<tr>
<td>23</td>
<td>Midazolam-propofol-fentanyl</td>
<td>Propofol</td>
<td>Sevoflurane</td>
<td>Postoperative lymphedema</td>
</tr>
<tr>
<td>24</td>
<td>Institutional protocol</td>
<td>Dexmedetomidine-Lidocaine</td>
<td>Isoflurane</td>
<td>CTnI and CK-MB</td>
</tr>
<tr>
<td>25</td>
<td>Fentanyl-Etomidate</td>
<td>Desflurane</td>
<td>Propofol</td>
<td>No difference in cardiac function, CTnI and CK-MB</td>
</tr>
<tr>
<td>26</td>
<td>Fentanyl-Midazolam</td>
<td>Sevoflurane</td>
<td>Propofol</td>
<td>No difference in CTnI</td>
</tr>
<tr>
<td>27</td>
<td>Etomidate-Midazolam-Fentanyl</td>
<td>Sevoflurane</td>
<td>Propofol</td>
<td>No difference in CTnI, CK-MB, NT-ProBNP, hemodynamics and duration of stay in hospital or intensive care unit</td>
</tr>
<tr>
<td>28</td>
<td>Etomidate-Sufentanil</td>
<td>Propofol-Isoflurane</td>
<td>Midazolam</td>
<td>CTnI is more in Propofol-Isoflurane group</td>
</tr>
<tr>
<td>29</td>
<td>Midazolam-Dexmedetomidine-Ketamine</td>
<td>Midazolam-Dexmedetomidine-Ketamine</td>
<td>Sevoflurane</td>
<td>CTnI and CK-MB</td>
</tr>
<tr>
<td>30</td>
<td>Thiopentone-Fentanyl</td>
<td>Isoflurane</td>
<td>Propofol</td>
<td>Similar in CTnI and CK-MB in both the groups</td>
</tr>
<tr>
<td>31</td>
<td>Fentanyl</td>
<td>Remifentanil till sternotomy-propofol</td>
<td>Normal saline till sternotomy-propofol</td>
<td>In CTnI, CK-MB and h-fatty acid binding protein in remifentanil recievers</td>
</tr>
<tr>
<td>32</td>
<td>Midazolam-Sufentanil</td>
<td>Ketamine-Sevoflurane-Fentanyl</td>
<td>Normal saline Sevoflurane-Fentanyl</td>
<td>No effect on pro-inflammatory cytokine release</td>
</tr>
<tr>
<td>33</td>
<td>Opioid-Isoflurane</td>
<td>Morphine</td>
<td>Fentanyl</td>
<td>Inflammatory response</td>
</tr>
<tr>
<td>34</td>
<td>Fentanyl-Isoflurane</td>
<td>Fentanyl-Isoflurane Propofol before aortic cross clamp release till 4 hours after reperfusion</td>
<td>Fentanyl-Isoflurane Normal before aortic cross clamp release till 4 hours after reperfusion</td>
<td>Free radical mediated lipid peroxidation and decreased systemic inflammation</td>
</tr>
<tr>
<td>16</td>
<td>Midazolam-Fentanyl</td>
<td>Propofol</td>
<td>Isoflurane</td>
<td>CTnI and oxidative stress markers</td>
</tr>
</tbody>
</table>

Abbreviations: APC, anesthetic preconditioning; |, decrease; CTnI, cardiac troponin I; CK-MB, creatinine kinase myocardial band; NT-Pro BN P, N-terminal pro-B natriuretic peptide.
Barbiturates
The ROS scavenging ability of barbiturates has been found in experimental models is lesser than that of propofol. Thiopental is the most potent agent among all the barbiturates for APC when renal, bowel, and neuronal ischemia is concerned, but there is migre literature concerning its effect on myocardial ischemia and reperfusion injury.21

Etomidate
This drug does not have any effect on adhesion of neutrophils to coronary endothelium in posts ischemic myocardium. There is no clinical report regarding its effect on PC of myocardium.22

Benzodiazepines
The impact of midazolam on ROS formation is much less than that of propofol and there are conflicting reports regarding the effect of benzodiazepines on MP. The following Table 1 enumerates some of the trials narrating the preconditioning effect of intravenous anesthetic agents.

Future Directives
We have achieved a bit in the field of MP and preconditioning by intravenous anesthetic agents. However, we have still miles to go. Volatile anesthetics are the first choice for APC both in noncardiac and cardiac surgical patients. However, there is growing evidence that few of the intravenous agents, especially opioids, propofol, and dexmedetomidine are good anesthetics for APC. Still, there is a lot of doubts that large-scale nonrandomized trials will be performed in the near future to tackle this question. The more challenging situation arises when age, diabetes, and myocardial remodeling diminishes APC. Again, there is significant interference in MP effect between sevoflurane and propofol, which should not be used concomitantly if possible. All the researchers are still waiting for a promising outcome with the best method and magic dose of IV anesthetic agents to provide APC in future.

Funding
None.

Conflict of Interest
None declared.

References
24 Kim HJ, Kim WH, Kim G, et al. A comparison among infusion of lidocaine and dexmedetomidine alone and in combination...


