

Cardioprotection with Anesthetic Agents: Myth or Reality?

BY STEFAN G. DE HERT, MD, PHD

With the aging of the population, anesthesiologists are increasingly treating patients with ischemic heart disease. The presence or development of myocardial ischemia may be an important cause of perioperative complications. A recent study analyzed the incidence of complications in 3970 patients aged ≥ 50 years who were scheduled for major noncardiac procedures.¹ Cardiac complications occurred in 2%, while noncardiac complications occurred in 13%. In addition, patients with cardiac complications were more likely to suffer noncardiac complications than those without cardiac complications (odds ratio = 6.4; 95 % confidence interval (CI), 3.9-10.6). Conversely, patients with noncardiac complications were more likely to suffer cardiac complications than those without complications (odds ratio = 5.3; 95 % CI, 3.2 - 8.8). The occurrence of both cardiac and noncardiac complications was associated with a markedly increased length of hospital stay (11 vs 4 days). Preventing and/or treating myocardial ischemic events is therefore an integral part of the anesthesiologist's job. This issue of *Anesthesiology Rounds* provides insight into the mechanisms involved in myocardial ischemia and the potential therapeutic approaches that are mandatory for professionals involved in the perioperative care of patients.

ISCHEMIA-REPERFUSION INJURY

Tissue damage caused by ischemia is termed "ischemic injury" and its extent depends on the duration of the ischemic period. If ischemia lasts >20 minutes, myocardial necrosis occurs and spreads as the duration of ischemia increases (Figure 1). Reperfusion terminates the ischemic episode and is essential for tissue to survive and resume normal functioning. The transient period of myocardial dysfunction after ischemia, in the absence of myocardial cell death, is termed "stunning." This phase may be associated with severe functional disturbances that are referred to as "reperfusion injury." Therefore, in both early reperfusion and in delayed or absent reperfusion, myocardial dysfunction will occur, usually necessitating supportive interventions to maintain adequate cardiac function.

PRECONDITIONING

The body has a number of intrinsic compensatory mechanisms that allows the preservation of tissue homeostasis in the presence of different forms of stress or injury.

Ischemic preconditioning

Ischemic preconditioning is a mechanism that helps protect against ischemia and reperfusion injury. The term "preconditioning" refers to the phenomenon whereby pretreatment with a potentially noxious stress-stimulus increases cellular tolerance to subsequent stress-stimuli. At the level of the myocardium, ischemic preconditioning represents an adaptive endogenous response to brief sub-lethal episodes of ischemia, leading to a paradoxical pronounced protection against subsequent lethal ischemia.

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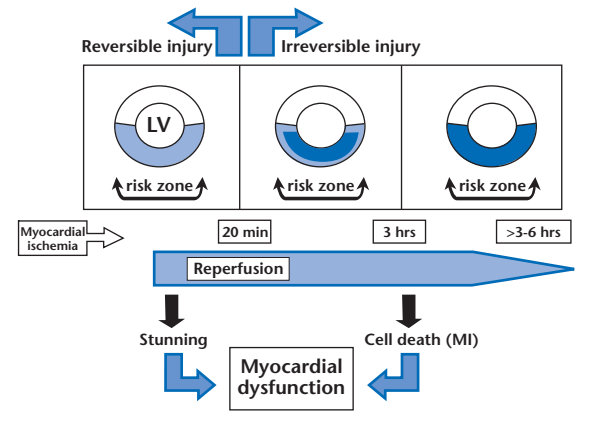
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FIGURE 1: Evolution of myocardial ischemia leading to myocardial dysfunction. When reperfusion starts early enough, the cells survive, but suffer transient dysfunction (stunning). If ischemia is longlasting, ultimately irreversible injury will occur and myocardial cells will die, resulting in myocardial infarction (MI). The extent of MI depends on the duration of ischemia.



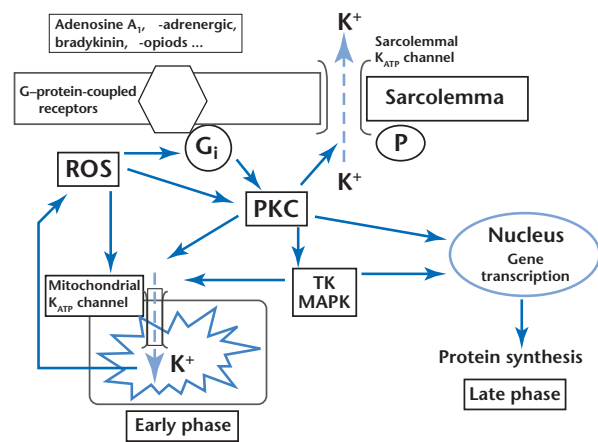
The protective effects offered by ischemic preconditioning are of limited duration and can typically be divided into two phases:

- the *early phase* occurs immediately and induces strong protection, but has a limited duration of 1 to 2 hours
- the *late phase* occurs about 24 hours after the initial stimulus, induces less protection, but lasts for as long as 3 days.

The underlying mechanisms involved in preconditioning remain to be definitively elucidated. Initially, it was postulated that preconditioning reduced metabolic activity during the prolonged ischemic period so that cellular adenosine triphosphate stores were better preserved. However, it became apparent that this was, at best, an oversimplification of the situation. The hypothesis now is that stimulation of a number of signalling pathways is induced by a various triggers that activate several mediators which, in turn, activate one or more end-effectors, ultimately resulting in protection against prolonged ischemia.

Recent reviews summarize the present knowledge concerning the underlying mechanisms involved in ischemia-reperfusion injury and preconditioning.^{2,3} Briefly, signaling substances bind to inhibitory G-protein coupled receptors and trigger the activation of several intracellular signaling pathways. These pathways mainly involve a post-translational modification of proteins (translocation and phosphorylation). Protein kinase C plays a central role as an intracellular mediator, but tyrosin kinase and mitogen-activated protein kinases are also involved. During the early phase of preconditioning, the cellular memory is believed to relate to the translocation of protein kinase C from cytosol to the different cel-

FIGURE 2: Schematic illustration of the proposed pathways involved in ischemic preconditioning.



Gi = G inhibitory protein, P = phospholipase, TK = tyrosine kinases, PKC = protein kinase C, MAPK = mitogen-activated kinases, ROS = reactive oxygen species

lular membranes; this results in a more rapid activation of protein kinase C during the prolonged ischemic period. Several structures have been involved as end-effectors; however, the majority of experimental findings now indicate that the preservation of mitochondrial function that occurs as a consequence of mitochondrial K_{ATP} channel activation (opening) is of pivotal importance for the cardioprotective effect against ischemia. It remains an open question as to whether the mitochondria constitute the final end-effectors of the preconditioning pathway or if, instead, mitochondrial K_{ATP} channel opening merely serves as a trigger for preconditioning. The subsequent release of reactive oxygen species would then stimulate the activation of a number of transcription factors, ultimately leading to cardioprotection (Figure 2).

The increased tolerance to myocardial ischemic damage has been attributed to a reduction in calcium overload, better preservation of energy stores, prevention of the activation of necrotic or apoptotic pathways, and an influence on the extent of oxidative stress. During the *late phase* of preconditioning, cellular memory is thought to be related to the synthesis or activation of proteins that have a cytoprotective effect, such as the induction of several antioxidant enzymes, or the synthesis of heat-shock proteins that are involved in the stabilization of the cytoskeleton.

Pharmacological preconditioning

Different experimental studies have demonstrated that ischemic preconditioning can be abolished or mimicked by administrating pharmacological agents that either block or stimulate certain steps in the intracellular cascade of events. This has

led to the concept of “pharmacological preconditioning.” From a clinical aspect, preconditioning with pharmacological agents is preferred above ischemic preconditioning because it eliminates the risk of further jeopardizing diseased myocardium by making it transiently ischemic. However, the current use of pharmacological agents to induce preconditioning is limited by unwanted side-effects (eg, hypotension [adenosine], arrhythmias [adenosine, K_{ATP} channel openers], or possible carcinogenic effects [protein kinase activators]).

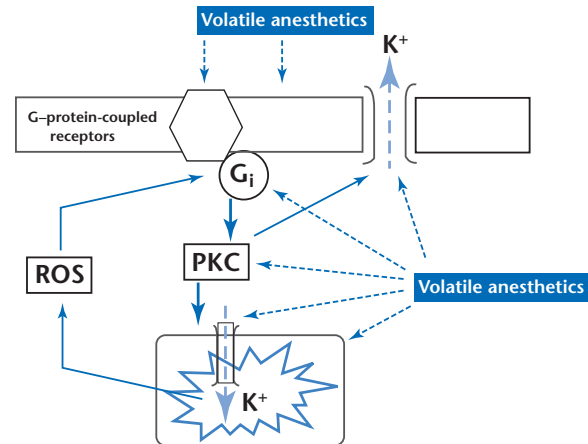
Anesthetic preconditioning

During the past few years, a number of important experimental studies have indicated that volatile anesthetics protect against ischemic myocardial dysfunction. This cardioprotective effect is not related to effects on myocardial oxygen balance, instead it appears that volatile anesthetics induce protection in the myocardium via pharmacological preconditioning. The mechanisms involved in anesthetic preconditioning strongly resemble those involved in ischemic preconditioning and are the subject of different recent reviews.^{4,7}

The signal transduction pathway involved in anesthetic preconditioning (Figure 3) has indeed been shown to involve, among others, the adenosine receptor, the inhibitory guanine nucleotide-binding proteins, protein kinase C, protein tyrosine kinase, and sarcolemmal and mitochondrial K_{ATP} channel activity. The relative importance of the different proposed intracellular pathways remains to be established. It appears that volatile anesthetics do not directly open mitochondrial K_{ATP} channels, instead, they “prime” mitochondrial K_{ATP} channel activity.

Anesthetic preconditioning has been shown to be initiated by an increase in reactive oxygen species (ROS). This increase in ROS appears to be mediated by a partial inhibition of the electron transport chain, the component of respiration that oxidizes nicotinamide adenine dinucleotide (NADH) and results in the release of partially oxidized free radicals. The sequence of events between ROS release and anesthetic preconditioning is not fully understood, but there is evidence for activation or translocation of protein kinase C, tyrosine kinases and p38 mitogen activated protein kinase. Interestingly, although ischemic and anesthetic preconditioning share a number of common pathways, they may also have distinctly different pathways. The final target of anesthetic preconditioning is the opening of the mitochondrial K_{ATP} channels, resulting in depolarization of the mitochondrial membrane potential with an improvement of mitochondrial bioenergetics. It is suggested that mitochondrial ROS formation during anesthetic preconditioning has 2 key roles. First,

FIGURE 3: Schematic illustration of the proposed pathways involved in anesthetic preconditioning



there is an early component of ROS generated by mitochondria during anesthetic exposure, leading to a triggering of signaling pathways that induce anesthetic preconditioning. Subsequently, this results in a decrease in the large amount of ROS normally formed during reperfusion after ischemia. The ultimate result is a reduction in cytosolic and mitochondrial calcium loading, with better structural and functional preservation.

In addition to the direct effects on myocytes, both *ischemic and anesthetic* preconditioning also protect endothelial cells in the coronary (and other) vasculature. One of the major features of this endothelial protection appears to be the ability to generate nitric oxide and mediate vasodilation.

It should be noted that a number of studies indicate that volatile anesthetics may also provide protection against reperfusion injury, but only when administered during the early reperfusion period. The underlying mechanisms for this effect are poorly understood, but one that has been suggested involves the prevention of reoxygenation-induced cellular contraction. Other possible effects include actions on activated leucocytes and ROS. Indeed, neutrophil activation, adherence, and release of oxygen-free radicals are known to play a major role in reperfusion injury. An experimental study on isolated rabbit hearts demonstrated that isoflurane and sevoflurane have the ability to suppress neutrophil activation and neutrophil-endothelium interactions that cause cardiac dysfunction.

Post-ischemic reperfusion injury results, in large part, from mitochondrial and myoplasmic Ca^{2+} overloading. In a study on isolated guinea pig hearts, it was observed that sevoflurane improved post-ischemic cardiac function when administered before or after ischemia. However, protection appeared

better when sevoflurane was administered before ischemia. The major effector of both preischemic and postischemic sevoflurane was reduced Ca^{2+} loading, which was similar with the 2 administration protocols. However, it appeared that when sevoflurane was administered before ischemia, there was a small metabolic sparing effect that triggered mechanisms leading to cardioprotection (*anesthetic preconditioning*), whereas postischemic sevoflurane treatment did not seem to have this effect.

Further studies will determine if the improved function and Ca^{2+} homeostasis observed after anesthetic postischemic treatment involves similar pathways as anesthetic preconditioning or if other mechanisms are involved. Finally, it remains to be elucidated whether the cardioprotective effects of anesthetic agents are comparable and whether this phenomenon is dose-dependent.

DIRECT CARDIOPROTECTIVE EFFECTS OF ANESTHETIC AGENTS

Direct cardioprotective effects related to a preconditioning action and/or an effect when administered only during the reperfusion period have been demonstrated primarily for the volatile anesthetics. In addition, several studies have indicated that activation of opioid-receptors by morphine also elicits a cardioprotective effect that acts via the K_{ATP} channels. The combined administration of isoflurane and morphine enhances protection against myocardial damage to a greater extent than either drug alone. It appears that opioid receptor activation mediates both isoflurane- and the morphine-induced preconditioning.

The effects of other intravenous (IV) anesthetic drugs are less straightforward. In isolated adult rat ventricular myocytes, anesthetics exhibit a differential effect on mitochondrial K_{ATP} channel activity and cardiomyocyte protection. Fentanyl increases protection, whereas etomidate, propofol, and midazolam appear to have no effect. Several studies have shown that propofol has an antioxidant capacity and there are claims that this property protects the myocardium; however, the possible implications of increased antioxidant capacity in preserving tissue function remain to be demonstrated.⁸

CLINICAL IMPLICATIONS

The implementation of cardioprotective effects via anesthetic agents during clinical anesthesia may provide an additional tool in the treatment and/or prevention of cardiac dysfunction

during the perioperative period. In clinical practice, these effects should be associated with improved cardiac function, ultimately resulting in a better outcome for patients with coronary artery disease. However, thus far, the clinical benefits have been related mainly to a lower release of biochemical markers for myocardial damage. Initial studies have been encouraging, but were hampered by the limited number of patients and a primarily unblinded design.

In contrast to experimental studies, the results from clinical studies on the cardioprotective effects of anesthetic agents are less straightforward. Indeed, these effects appear to be more important in protocols where the volatile anesthetic was administered throughout the *entire* operative period. There were more variable results when it was administered only *before* aortic clamping (“preconditioning” protocols).

- In a study by Belhomme et al, isoflurane 2.5 MAC was administered for 5 min via the oxygenator of the cardiopulmonary bypass (CPB) circuit, followed by a 10 min washout period before aortic cross clamping.⁹ Isoflurane preconditioning (n = 10) resulted in increased ectosolic activity of 5'-nucleotidase (a surrogate marker for the activation of protein kinase C), but postoperative release of creatine kinase (CK)-MB, and troponin I was not different from the control group (n = 10).

- In a study on 22 patients (6 dropped out for different reasons), Penta de Peppo et al evaluated the effects of enflurane 1.3% (range: 0.5 - 2%) administered through the respirator for 5 min immediately before CPB.¹⁰ Enflurane enhanced postoperative left ventricular function in the study group, but there were no differences in postoperative CK -MB and troponin I release between the study and control groups.

- In a study on 40 patients, Tomai et al administered isoflurane 1.5% for 15 min through the respirator, followed by a washout period of 10 min before the start of CPB.¹¹ No differences were observed between the treatment and control groups in postoperative cardiac function and peak troponin I values. In the subgroup of patients with a left ventricular ejection fraction <50%, however, troponin I levels 24 hours postoperatively were lower in the isoflurane group (n=9) than in the control group (n=11).

- In another study on 49 patients, Haroun-Bizri et al administered isoflurane 0.5 to 2% until the start of CPB and observed a higher postoperative cardiac index in the isoflurane group than in the control group.¹²

- In the largest study of this kind (72 patients), performed by Julier et al,¹³ sevoflurane 4% was administered during the first 10 min of CPB, just before aortic crossclamping. Compared to the control group, a significantly lower postoperative release of brain natriuretic peptide – a sensitive biochemical marker for myocardial contractile dysfunction – was observed. In addition, this study was the first to demonstrate that in response to sevoflurane, translocation of protein kinase C δ and ϵ isoforms, one of the mechanisms implicated as a pivotal step in anesthetic preconditioning, also occurred in the human myocardium. However, no differences were observed between groups for perioperative ST-segment changes, arrhythmias, CK-MB, and cardiac troponin T release.

To date, there are no published clinical reports on the potential cardioprotective effects of volatile anesthetic agents administered only during the reperfusion period. The absence of an unequivocal and reproducible clinical protective effect with clinical preconditioning protocols has prompted a number of researchers to study whether the choice of anesthetic regimen might influence clinical variables of outcome or postoperative function. Two recent studies on 20 and on 45 patients undergoing CPB surgery evaluated the effects of an inhalational anesthetic regimen administered throughout the entire operative period. A significantly lower troponin I release was observed with this anesthetic regimen than with an IV anesthetic regimen.^{14,15} In addition, patients administered the volatile anesthetic regimen had preserved cardiac performance, as was evident from preserved stroke volume, dp/dt_{max} , and length-dependent regulation of myocardial function. The need for inotropic support in the early postoperative period was also significantly less with the volatile anesthetic regimen compared to the total IV anesthetic regimen. These data, therefore, suggest that volatile anesthetics provide a cardioprotective effect that is not observed with an IV anesthetic regimen. A retrospective analysis of data, performed at another centre, before and after the implementation of a volatile anaesthetic regimen, support these initial findings regarding the cardioprotective effects of a volatile anesthetic regimen.¹⁶ The addition of sevoflurane to an IV anesthesia regimen for cardiac surgery consistently lowered troponin T levels, with less need for inotropic support when weaning from CPB, and a lower incidence of low cardiac output.

The cardioprotective effects of a volatile anesthetic regimen were also observed in off-pump coronary surgery. Conzen et al found significantly better cardiac function in patients who received sevoflurane for maintenance of anesthesia during surgery compared with patients who received propofol anesthesia.¹⁷ In addition, serum troponin I levels were significantly less in the sevoflurane group, although no significant effect on CK-MB was demonstrated between the treatment groups.

Although all these clinical observations clearly indicate that volatile anesthetics protect the myocardium during coronary surgery, the impact of this phenomenon on postoperative morbidity and clinical recovery remains to be established. Thus far, only one small study in 20 coronary surgery patients has shown that sevoflurane anesthesia is associated with a decrease in plasma tumour necrosis factor α levels compared to an IV anesthetic regimen with midazolam.¹⁸ This regimen also appeared to be associated with a shorter length of stay in the intensive care unit (ICU). The potential effect of the choice of the primary anesthetic regimen on length of ICU stay as a primary outcome variable was addressed in a very recent study.¹⁹ Data from this study indicated that the length of stay in the ICU appeared to be related to the choice of the anesthetic regimen. The use of a volatile anesthetic regimen during coronary surgery was associated with a lower incidence of a prolonged ICU stay (>48 hours) than a total IV anesthetic regimen. The individual variables responsible for a prolonged length of stay were occurrence of atrial fibrillation, increase in postoperative troponin I levels >4 ng/mL, and the need for prolonged inotropic support (>12 hours). While the incidence of atrial fibrillation was similar with all the agents studied, the number of patients having increased troponin I levels >4 ng/ml and those necessitating prolonged inotropic support were significantly less with volatile anesthetic regimens than with total IV anesthetic regimens.

CONCLUSIONS

Over the past few years, increasing experimental evidence has indicated that volatile anesthetic agents may have direct cardioprotective effects. Although part of the underlying pathways has been identified, the exact mechanisms for this phenomenon have not been definitively elucidated. Only recently, has research focused on the possible implementation of this experimentally observed cardioprotection

in clinical patient care. Initial observations are encouraging, indicating that in the clinical setting, anesthetic agents may exhibit direct cardioprotective effects. These data were obtained in the specific setting of cardiac surgery and are primarily related to better early postoperative cardiac function and less release of biochemical markers of myocardial damage. The possible impact on real clinical outcome data, however, remains to be demonstrated. This will be an extremely difficult task because of the number of interfering factors (skills of the surgeon, use of intentional or the presence of unintentional ischemic preconditioning, the array of cardioprotective measures used, and others). In addition, it should be remembered that the majority of patients with ischemic heart disease are scheduled for noncardiac surgery (abdominal, vascular) and represent, as such, a high-risk population. Ultimately, it is this population that should benefit most from the effects of a cardioprotective anesthetic regimen.

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