General Anesthesia

Myocardial protection by anesthetic agents against ischemia-reperfusion injury: an update for anesthesiologists

[La protection myocardique contre les lésions d'ischémie-reperfusion par des anesthésiques : une mise à jour pour les anesthésiologistes]

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Purpose: The aim of this review of the literature was to evaluate the effectiveness of anesthetics in protecting the heart against myocardial ischemia-reperfusion injury.

Source: Articles were obtained from the Medline database (1980-, search terms included heart, myocardium, coronary, ischemia, reperfusion injury, infarction, stunning, halothane, enflurane, desflurane, isoflurane, sevoflurane, opioid, morphine, fentanyl, alfentanil sufentanil, pentazocine, buprenorphine, barbiturate, thiopental, ketamine, propofol, preconditioning, neutrophil adhesion, free radical, antioxidant and calcium).

Principal findings: Protection by volatile anesthetics, morphine and propofol is relatively well investigated. It is generally agreed that these agents reduce the myocardial damage caused by ischemia and reperfusion. Other anesthetics which are often used in clinical practice, such as fentanyl, ketamine, barbiturates and benzodiazepines have been much less studied, and their potential as cardioprotectors is currently unknown. There are some proposed mechanisms for protection by anesthetic agents: ischemic preconditioning-like effect, interference in the neutrophil/platelet-endothelium interaction, blockade of Ca^{2+} overload to the cytosolic space and antioxidant-like effect. Different anesthetics appear to have different mechanisms by which protection is exerted. Clinical applicability of anesthetic agent-induced protection has yet to be explored.

Conclusion: There is increasing evidence of anesthetic agent-induced protection. At present, isoflurane, sevoflurane and morphine appear to be most promising as preconditioning-inducing agents. After the onset of ischemia, propofol could be selected to reduce ischemia-reperfusion injury. Future clinical application depends on the full elucidation of the underlying mechanisms and on clinical outcome trials.

Objectif : Évaluer l'efficacité des anesthésiques dans la protection du cœur contre les lésions myocardiques d'ischémie-reperfusion.

Source : Des articles ont été obtenus de la base de données Medline (1980-, les mots clefs étant heart, myocardium, coronary, ischemia, reperfusion injury, infarction, stunning, halothane, enflurane, desflurane, isoflurane, sevoflurane, opioïd, morphine, fentanyl, alfentanil sufentanil, pentazocine, buprenorphine, barbiturate, thiopental, ketamine, propofol, preconditioning, neutrophil adhesion, free radical, antioxidant et calcium).

Constatations principales : La protection par des anesthésiques volatils, morphine et propofol, est relativement bien explorée. On s'accorde généralement pour dire que ces agents réduisent les lésions myocardiques causées par l'ischémie et la reperfusion. D'autres anesthésiques utilisés souvent en clinique, comme le fentanyl, la kétamine, les barbituriques et les benzodiazépines, ont été moins étudiés et leur potentiel cardioprotecteur est actuellement inconnu. On propose certains mécanismes de protection par les anesthésiques : un effet qui s'apparente à un préconditionnement, une interférence dans l'interaction entre polynucléaires neutrophiles/plaquettes-endothélium, un blocage de la surcharge de Ca^{2+} à l'espace cytosolique et un effet du genre antioxydant. Différents anesthésiques semblent présenter des mécanismes différents par lesquels la protection s'exerce. L'applicabilité de la protection induite par les agents anesthésiques est encore à étudier.

Conclusion : Il y a de plus en plus d'évidence de la protection induite par les anesthésiques. Présentement, l'isoflurane, le sévoflurane et la morphine semblent les agents inducteurs de préconditionnement les plus prometteurs. Après le début de l'ischémie, le propofol peut être choisi pour réduire les lésions d'ischémie-reperfusion. L'application clinique future repose sur la mise en lumière complète des mécanismes sous-jacents et sur des essais relatifs aux avantages cliniques.

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1. Introduction

Anesthesiologists frequently treat patients with ischemic heart disease, as the number of such patients presenting for surgery is increasing. Accordingly, anesthesiologists witness the frequent occurrence of perioperative myocardial ischemia. Because myocardial ischemia-reperfusion injury can lead to severe complications, measures to minimize myocardial damage have been an important target of research. Anesthetics may provide protection so, consequently, a better understanding of the role of anesthetics in the prevention of myocardial injury may provide anesthesiologists with strategies to improve outcome.

Since Freedman reported that enflurane improved postischemic functional recovery in 1985,¹ the protective effect of halogenated anesthetics against myocardial ischemia-reperfusion injury has been investigated in various animal models. There is accumulating evidence that halothane, isoflurane and sevoflurane possess such properties. The search for protection by opioids started only recently, when Schultz *et al.*² found that ischemic preconditioning, a powerful intervention to reduce ischemia-reperfusion injury, is mediated by opioid receptors. This study led to the discovery that exogenous morphine protects the heart

against infarction.³ Propofol is known to be a free radical scavenger^{4,5} and has recently been shown to be protective.⁶⁻¹⁰

This review summarizes our current understanding of cardioprotection to evaluate possible protective effects in patients who are at risk of myocardial ischemia.

2. Methods

Articles examining whether an anesthetic agent provides myocardial protection against ischemia-reperfusion injury were obtained from the Medline database (1980-). Search terms included heart, myocardium, coronary, ischemia, reperfusion injury, infarction, stunning, halothane, enflurane, desflurane, isoflurane, sevoflurane, opioid, morphine, fentanyl, alfentanil, sufentanil, pentazocine, buprenorphine, barbiturate, thiopental, ketamine, propofol, midazolam, diazepam, preconditioning, neutrophil adhesion, free radical, antioxidant and calcium. The language of articles was limited to English. All articles of investigation obtained using the above-mentioned search strategy were included in this review article, except those already reviewed elsewhere.¹¹ Articles investigating the mechanisms of anesthetic-induced protection were searched using the same method. Recent and representative studies are cited in this narrative review.

The limitations of our search method include: 1) the article list may not be complete because: a) only one database, Medline, was used; b) the language of the articles was limited to English; and c) relevant articles written in English may have been missed in Medline;¹² 2) we did not take publication bias (negative results are less likely to be published) into consideration; 3) the process by which articles were selected was not strictly objective; and 4) the interpretation of previous findings and our conclusions remain subjective.

3. Ischemia-reperfusion injury

Myocardial ischemia initiates a range of cellular events, which are initially mild and become progressively damaging with increasing duration of ischemia. The damage caused during ischemia is called "ischemic injury". Although reperfusion means a termination of ischemia and is essential for the cell to survive and to restore normal function, it paradoxically causes damage to the cell; this injury is called "reperfusion injury". The term "ischemia-reperfusion injury" is also used to represent both types of damage together, as 1) it is not always easy to distinguish one from the other, and 2) ischemia is often accompanied by reperfusion and reperfusion cannot occur without prior ischemia.

We briefly address the mechanisms of ischemia-reperfusion injury. Further information is found elsewhere.^{13–17} Ischemia precludes adequate oxygen supply, which rapidly results in depletion of adenosine triphosphate (ATP). This inhibits ATP-driven $\text{Na}^+\text{-K}^+$ pumps, increasing $[\text{Na}^+]_i$. $[\text{H}^+]_i$ is increased because of poor washout of metabolites and inhibition of mitochondrial oxidation of NADH_2 . Increased $[\text{H}^+]_i$ enhances $\text{Na}^+\text{-H}^+$ exchange to retain normal pH_i , leading to increased $[\text{Na}^+]_i$, hence $[\text{Ca}^{2+}]_i$ is augmented via $\text{Na}^+\text{-Ca}^{2+}$ exchange.^{13,15} High $[\text{Ca}^{2+}]_i$ degrades proteins and phospholipids.^{14,16} The production of free radicals is also enhanced after the onset of ischemia. They are known to be derived mainly from neutrophils and mitochondria.^{13,16} The target components of free radicals involve lipids and proteins,¹⁶ which constitutes the structure of the cell and enzymes.

Injury after the onset of ischemia is further worsened when coronary vessels are damaged. Swollen endothelial cells prevent swift gas exchange. Malfunctioning endothelium and smooth muscle cannot provide vasodilatation when necessary. Neutrophils/platelets aggregating in the lumen hamper adequate coronary flow.^{14,16} Neutrophils play a central role in the propagation of damage. They are attracted towards endothelial cells and subsequently migrate across the endothelium. They also release oxygen free radicals, cytokines and other proinflammatory substances. These substances harm the endothelium, vascular smooth muscle and myocardium.¹⁷ A pathway for neutrophil sequestration is the specific interaction of adhesion molecules whose expression is promoted by ischemia-reperfusion. They are expressed on neutrophils and endothelial cells. Intercellular adhesion molecule-1 (ICAM-1), L-selectin and CD11b/CD18 are examples of these molecules. Treatment with monoclonal antibodies against adhesion molecules results in a significant reduction of ischemia-reperfusion injury.¹⁷

On reperfusion, $[\text{H}^+]$ outside the cell is abruptly reduced to normal levels because it is washed out. This results in an increase in $[\text{Ca}^{2+}]_i$ due to enhanced $\text{Na}^+\text{-H}^+$ and $\text{Na}^+\text{-Ca}^{2+}$ exchange.^{14,15} Reperfusion also results in a burst of free radical generation because oxygen is abundantly supplied.^{14,16} Ca^{2+} and free radicals injure the heart further at reperfusion.^{14,16} Damage of the vascular system is more prominent during reperfusion than ischemia.^{16,17}

Ischemia-reperfusion injury has various clinical consequences. Infarction is one of the major events which we witness in clinical practice. Another consequence of ischemia-reperfusion injury is myocardial stunning. This phenomenon is defined as reversible myocardial dysfunction that persists after reperfusion.^{14,18,19}

4. Ischemic preconditioning

There have been many reviews on ischemic preconditioning.^{20–22} In brief, Murry *et al.* introduced this concept when they found, in a canine model, that four cycles of five-minute left circumflex coronary artery (Lcx) occlusion, in advance of 40-min Lcx occlusion, reduced infarct size by 75%. They named this protective effect ischemic preconditioning,²³ a phenomenon that has been extensively investigated because of its potency. Ischemic preconditioning can be observed in a wide range of preparations: from isolated cardiomyocytes and vascular endothelial cells to hearts *in situ* in various species.^{20–22,24} Although ischemic preconditioning initially referred to the ability to mitigate infarction, the definition has been extended to employ other endpoints, such as stunning¹⁸ and coronary abnormalities.²² In humans, ischemic preconditioning enhanced postischemic contraction in ventricular trabeculae muscle, and survival rate of isolated cardiomyocytes.²⁴ Ischemic preconditioning elicited by two periods of three-minute aortic cross clamping prior to cardiopulmonary bypass for valve replacement reduced myocardial enzyme leakage, free radical formation and histological degeneration and enhanced contractility after weaning from cardiopulmonary bypass.^{25,26} Szmaga *et al.* applied four-minute aortic cross clamping and six-minute reperfusion before coronary artery bypass grafting; troponin (T) from blood samples was reduced.²⁷

Many investigators have investigated the mechanisms of ischemic preconditioning. The current understanding of the mechanisms as they relate to myocardial protection by anesthetic agents are reviewed. Further descriptions may be found elsewhere.^{20–22} Preconditioning is a treatment “prior” to an ischemic event while ischemia-reperfusion injury is formed “during” and “after” an ischemic period. In principle, the signals generated by brief periods of ischemia in ischemic preconditioning must be passed to, and preserved in, intracellular component(s). This memory should be retrieved, at the time of ischemia, resulting in the forwarding of signals to the effector(s) that can mitigate ischemia-reperfusion damage. This basic hypothesis was used to elucidate the mechanisms of ischemic preconditioning; the search for cellular contributors has continued since then. Previous studies, by and large, led to identify the constituents of a series of cellular events in the heart (Figure). Ischemic stimuli cause the release of stress mediators from the heart, including adenosine, bradykinin, opioids, norepinephrine and free radicals.^{20–22} They contribute as initiators, which pass signals to intracellular components, such as inhibitory guanine nucleotide binding proteins (G_i proteins) and protein kinase C (PKC).^{20–22} Eventually,

ATP-sensitive K^+ channels (K_{ATP} channels) on the sarcolemma and mitochondria are activated.²⁰⁻²² Recent studies support the view that mitochondrial K_{ATP} channels play a greater role than sarcolemmal K_{ATP} channels.^{21,22} It also seems certain that ischemic preconditioning depends upon stimulation of mitogen-activated protein kinases. Yet, it is still not clear where these kinases lie in the cascade of the signal transduction; it may be downstream of PKC.²⁰⁻²² The biggest concern of this signal transduction theory is that the events which link K_{ATP} channel opening and protection remain unknown. Blockade of the identified mediators involved in ischemic preconditioning reverses the protective effect. Conversely, treatments with chemicals that stimulate these mediators salvage the heart from the insult of ischemia-reperfusion.

5. Halogenated anesthetics

5.1 Evidence of protection by halogenated anesthetics

5.1.1 Summary of evidence before 1997

Halogenated anesthetics have been studied more extensively than any other anesthetics. In 1988, Warltier and colleagues demonstrated that pretreatment with halothane or isoflurane improved left ventricular systolic function after left anterior descending coronary artery (LAD) occlusion lasting 15 min. Segmental shortening of the myocardial wall in the LAD area recovered completely over five hours following reperfusion in anesthetic-pretreated dogs, while untreated dogs showed only 50% recovery.²⁸ This study triggered a dramatic proliferation of investigations regarding protection by anesthetics. The progress made by mid-1997 was reviewed by Ross and Foëx.¹¹ Briefly, a growing number of investigations have shown that halothane, enflurane and isoflurane enhance postischemic mechanical function at equianesthetic concentrations in various animal species, with only a few exceptions in isolated heart models. A few studies have reported an infarct-reducing effect of halogenated anesthetics.

5.1.2 Sevoflurane and desflurane

Further evidence for the protective properties of halogenated anesthetics was collected for halothane and isoflurane after 1997.²⁹⁻⁴⁵ A new agent whose protection was demonstrated recently is sevoflurane. This anesthetic improves postischemic mechanical and coronary function, and reduces infarct size.^{32,34,37,45-50} A beneficial effect of desflurane was suggested by a few groups.^{34,49,51} Further investigations are needed to determine the effect of desflurane in other experimental settings.

5.1.3 Different approaches to assess myocardial injury

Several indices other than postischemic ventricular mechanical function have been examined to assess the degree of myocardial injury in the past few years. Reduction in infarct size has been well demonstrated with volatile anesthetics.^{29-31,34,38,39,41,50} Results of infarction studies are more consistent than those of postischemic contractility. Kersten and coworkers administered isoflurane to dogs for one hour before 60-min LAD occlusion. The extent of infarction was reduced from 25% to 12%.³¹ According to Cope *et al.*, preconditioning with halothane, enflurane or isoflurane diminished infarct size to less than one third in rabbits.³⁰

There were a few infarction studies performed in the 1980s.⁵²⁻⁵⁴ The infarct-reducing effect of halothane or isoflurane was inconclusive. These studies should be distinguished from those reported after 1995 because they differ largely in their experimental protocols. Previous studies employed longer duration of ischemia (6-48 hr) without reperfusion,^{52,53} whereas the ischemic period was less than one hour followed by a reperfusion period in recent studies.^{29-31,34,38,39,41,50}

Another approach to evaluate postischemic injury of the heart is to examine the coronary vasculature. Halothane, isoflurane and sevoflurane reduced the number of neutrophils sequestered in the coronary vasculature after ischemia.^{32,37} A similar effect was also shown for platelets.^{45,47} Reduced neutrophil/platelet entrapment by anesthetics was accompanied by enhancement of postischemic mechanical function.^{37,47} However, the effects of halogenated anesthetics on neutrophil/platelet sequestration have been studied by a limited number of research groups.^{32,37,45,47}

Novalija and coworkers measured coronary flow changes in response to endothelial-dependent and independent vasodilators. Sevoflurane preserved the reaction provoked by both types of vasodilators during the reperfusion period better than no treatment.⁴⁸

5.2 Mechanisms of protection by halogenated anesthetics

Before 1997, mechanisms underlying the protection were suggested to be preservation of ATP, reduction in Ca^{2+} influx to the cell, inhibition of free radical formation, and activation of K_{ATP} channels.¹¹ Recently, progress in elucidating the mechanisms responsible for protection was achieved when investigators: 1) related ischemic preconditioning and anesthetic-induced protection and 2) examined the coronary system.

5.2.1 Preconditioning

Phenomena similar to ischemic preconditioning have been observed with halogenated anesthetic agents;

myocardial protection persists even though anesthetics were allowed to wash out. Because evidence indicated that halogenated anesthetics dilated the coronary arteries *via* K_{ATP} channels, known as a key constituent of the ischemic preconditioning pathway, Cason *et al.* hypothesized that halogenated anesthetics induced an ischemic preconditioning-like effect. They studied rabbit hearts *in situ* treated with five-minute coronary occlusion followed by reperfusion or 15-min isoflurane followed by washout before 30-min coronary occlusion. In the ischemic preconditioning group infarction was reduced by 74% compared to the non-pretreated group, and by 30% in the isoflurane group. Although less effective than ischemic preconditioning, isoflurane limited ischemic injury even though isoflurane was washed out, i.e., isoflurane had an ischemic preconditioning-like effect.²⁹ Cope *et al.* perfused isolated rabbit hearts with halothane, enflurane or isoflurane for five minutes and washed out the anesthetic for ten minutes before the onset of coronary occlusion. This treatment reduced infarction to the same extent as a single five-minute coronary occlusion.³⁰ One might doubt that anesthetics were eliminated completely from the heart tissue by washing for ten to 15 min, and suspect that the protection may not have been solely due to preconditioning. Kersten *et al.* used a longer washout period. Canine hearts *in situ* were protected to a similar degree when isoflurane was washed out for five or 30 min.³¹ As studies to date unanimously conclude that halogenated anesthetics alleviate myocardial ischemic damage even when washed out,^{29–31,38–40,44,46,48} it is generally considered that volatile anesthetics can “precondition” the heart.

These findings indicate that the signals for halogenated anesthetics, like for brief ischemia in ischemic preconditioning, are preserved in intracellular components that can mediate protection against forthcoming ischemia. The protection by halogenated anesthetics has been reversed by a selective adenosine A_1 receptor antagonist,⁴⁴ a G_i protein inhibitor,⁴¹ PKC inhibitors,^{30,42} and K_{ATP} channel blockers.^{31,39,40,43,44,50,51} Contribution of the mitochondrial K_{ATP} channel appears certain,^{39,40,51} but not the sarcolemmal K_{ATP} channel.⁵¹ These observations strongly suggest that halogenated anesthetic agents provide protection *via* a mechanism similar to that of ischemic preconditioning. Hence, it can be assumed that the halogenated anesthetics stimulate adenosine receptors, followed by G_i proteins, PKC and K_{ATP} channels as shown in the Figure. As the protection by halogenated anesthetics is not accompanied by augmented release of adenosine,³⁰ it could be assumed that they stimulate adenosine receptors *via* a non-adenosine mechanism, or upregulate the adenosine receptor-G protein complex to

promote the signal transduction downstream. However, there is no evidence to support this hypothesis.

A mechanism similar to that of ischemic preconditioning is very plausible. Nonetheless, there have been reports that suggest other mechanism(s). According to Schlack and coworkers, halogenated anesthetics have shown protection when they were administered only during ischemia⁵⁵ or reperfusion.^{34,35,49} Protection was also observed with administration of these agents in a cardioplegic solution.³³ In addition, Yao *et al.* showed that isoflurane reduced stunning by a mechanism which is independent of the adenosine A_1 receptor.⁵⁶

5.2.2 Coronary vasculature

According to recent reports, halothane, isoflurane and sevoflurane reduced the number of trapped neutrophils in the heart during reperfusion.^{32,37} The postischemic expression of CD11b, which forms an integrin with CD18, was also suppressed by volatile anesthetics.³⁷ Kowalski *et al.* showed that neutrophil adhesion was attenuated even when sevoflurane was administered only during reperfusion.³² Mobert *et al.* treated neutrophils and endothelial cells with volatile anesthetics, and measured the extent of activation in both cell types when they were pharmacologically stimulated. The anesthetic treatment decreased neutrophil adhesion on the endothelium and expression of CD11b, while the anesthetics did not affect endothelial cell activation *vis-à-vis* neutrophils.⁵⁷ These studies imply that halogenated anesthetics can act directly on neutrophils at the time of reperfusion. Volatile anesthetics also reduced platelet adhesion to the vascular wall after ischemia,^{45,47} but sevoflurane failed to reduce the expression of glycoprotein IIb/IIIa, a platelet adhesion molecule involved in the platelet-endothelium interaction.⁴⁷

Another possibility of coronary protection by halogenated anesthetics is *via* an ischemic preconditioning-like effect. Ischemic preconditioning is known to reduce ICAM-1 production and neutrophil entrapment, and to preserve the response to vasodilators.²²

When ischemia is regional, one way to slow the progression of ischemic injury is to increase coronary collateral flow. Kersten *et al.* showed that sevoflurane selectively increased collateral flow to the ischemic area in dogs with chronic LAD stenosis. This effect was not reversed by glibenclamide, a non-selective K_{ATP} channel blocker.⁵⁸

5.2.3 Energy metabolism

ATP is required by numerous ongoing chemical reactions and ion pumps to maintain cell integrity. The less

ATP consumed by contractile work, the less the myocardium suffers during ischemia. Because of their distinctive negative inotropic and vasodilative effect, it has long been thought that halogenated anesthetics might lessen myocardial injury by reducing ATP consumption during ischemia.¹¹ However, it is unlikely that protection derives solely from this negative inotropic effect, since the extent of protection has been shown to be independent of mechanical function during ischemia.^{30,43,48}

6. Opioids

6.1 Evidence of protection by opioids

Protection by opioid receptor agonists against ischemia-reperfusion injury has been demonstrated during the last several years. Contribution of endogenous opioid peptides to adaptation to hypoxia had been suggested⁵⁹ when Mayfield and D'Alecy, in 1994, examined whether exogenous opioid receptor agonists can increase tolerance to hypoxia. They found that D-Pen2-D-Pen5-enkephalin (DPDPE), a δ -opioid agonist, can extend survival time of mice under severe hypoxia.⁶⁰ Meanwhile the δ -agonist D-Ala2-D-Leu5-enkephalin (DADLE), which had been identified as a hibernation-inducing trigger in nature, showed protective effects in multi-organ preparations, including the heart, preserved for transplant.⁶¹

In 1996, Schultz and colleagues were the first to demonstrate that an opioid could attenuate ischemia-reperfusion damage in the heart. Morphine at the dose of 300 $\mu\text{g}\cdot\text{kg}^{-1}$ was given before LAD occlusion for 30 min in rats *in vivo*. Infarct area/area at risk was diminished from 54 to 12% by this treatment.³ The infarct-reducing effect of morphine has been shown in hearts *in situ*, isolated hearts and cardiomyocytes.^{62–64} Morphine also improved postischemic contractility.⁶⁵ Consequently, it is now well accepted that morphine provides protection against ischemia-reperfusion injury. Kato *et al.* demonstrated that fentanyl enhances postischemic mechanical function in isolated rat hearts.^{66,67} However, this opioid did not show protection in isolated rabbit hearts according to Benedict *et al.*⁶⁵ The discrepancy might be due to differences in species and/or fentanyl concentrations. Pentazocine and buprenorphine improved postischemic contractility in rabbits *in vitro*.^{65,68} Overall, the effects of opioids other than morphine have not been sufficiently investigated to allow conclusions to be drawn.

The concomitant use of opioids, cardioplegia and hypothermia has been investigated. Morphine, pentazocine and buprenorphine improved mechanical function after global total ischemia for two hours at

34°C.^{65,68} Opioids also elicited a protective effect in heart preservation at 4 or 10°C for four to 18 hr,^{68–70} this might be an indication of the usefulness of opioids in heart transplantation.

6.2 Mechanisms behind the protection by opioids

6.2.1 Preconditioning

The involvement of opioid receptors in ischemic preconditioning has been demonstrated in various animal species and humans.^{2,62,63,71–77} Among opioid receptor subtypes, there is evidence that δ -opioid receptors are responsible for ischemic preconditioning in rats^{71,75,78,79} and humans.⁷⁶ Although opioid receptors are more abundant in the central nervous system, they are also present in the heart.^{74,76} Opioid receptor subtype distribution in the heart appears to differ between species. δ - and κ -, but not μ -opioid receptors are expressed in the rat heart.⁷⁴ In human atrium, δ - and μ - have been shown to be dominant compared to κ -receptors.⁷⁶ Naloxone blocked the effect of ischemic preconditioning in isolated hearts,⁷³ and cardiac myocytes.⁶³ Quaternary naloxone, which does not cross the blood-brain barrier, eliminated the protection by ischemic preconditioning in *in vivo* models.^{72,73} Therefore it is suggested that it is in the heart itself that opioid receptors play a role in protection by ischemic preconditioning.

There is evidence that exogenous opioids precondition the heart. In the study by Liang *et al.* cardiac myocytes were treated with morphine followed by incubation in drug-free media, before ischemia was induced. The survival rate of morphine-treated cells was higher.⁶³ Yellon and colleagues treated isolated hearts with DADLE for two five-minute cycles, each of which was followed by five-minute drug-free perfusion. This treatment diminished infarct size.⁷⁵ A similar effect was observed in human trabeculae.⁷⁶

Morphine and fentanyl are capable of binding to δ - and κ -receptors although they are preferentially μ -agonists.⁸⁰ It appears that the δ -opioid receptor subtype is responsible for opioid-induced protection.^{64,67,75,76,78,81–86} Selective δ -^{64,75,76,83,84} and δ_1 -^{81,82,85–87} agonists have shown protection. Conversely protection by morphine and fentanyl is abolished by δ -antagonists.^{64,67,78,83} The role of κ -receptors remains controversial.^{75,86,88,89} Whether μ -receptors contribute to cardioprotection in humans is not known. Other cellular mediators which pass signals in ischemic preconditioning (Figure) are also involved in the protection conferred by opioid agonists. The beneficial effects were eliminated by a G_i protein inhibitor,⁸¹ a PKC inhibitor,^{62,67,85,86} and a selective mitochondrial K_{ATP} channel blocker.^{63,66,70,76,82,83,85,86}

The effect of "classic" or "early" ischemic preconditioning is transient and lost within 0.5–2 hr after brief

FIGURE Cellular mechanism of ischemic preconditioning. Activation of adenosine A₁ and A₃ (A_{1/3}), bradykinin₂ (B₂), δ₁-opioid (δ₁) and α₁-adrenergic (α₁) receptors stimulates phospholipase C (PLC) through inhibitory guanine nucleotide-binding proteins (G_i proteins). PLC produces diacylglycerol (DAG) and inositol 1,4,5-triphosphate (IP₃). Both DAG and IP₃ activate protein kinase C (PKC). PKC enhances opening of ATP-sensitive K⁺ channels (K_{ATP} channels), probably via mitogen-activated protein kinases (MAPK). The K_{ATP} channel seems to be the end-effector for inducing protection, though the downstream process is still unknown. Recently mitochondrial K_{ATP} channels have been considered more important than sarcolemmal K_{ATP} channels. PIP₂ = phosphatidylinositol; SR = sarcoplasmic reticulum.

ischemic episodes, but the protection exhibits a biphasic time course and returns after 24 hr.^{20,22} This late protection is called “late”, “delayed” or “second window” preconditioning. TAN-67, a selective δ₁-agonist, also provoked “late” preconditioning. The opioid showed protection one hour after its *iv* administration, but not after 12 hr. Then, the protective effect resumed after 24 hr and was not observed after 72 hr.⁸² A κ-agonist also showed late preconditioning-like effect.⁸⁹

6.2.2 Neutrophil adhesion and migration

The neutrophil hypothesis is much less convincing than the preconditioning hypothesis due to the lack of supporting evidence. There have been reports that morphine reduced plasma levels of ICAM-1, L-selectin and gp100^{MEL14} (equivalent to L-selectin in rats) during ischemia and reperfusion.^{90,91} This observation was obtained when hearts were pretreated with morphine and also when morphine was administered only during reperfusion.⁹⁰ Morphine reduced adhesion molecules in a PKC and K_{ATP} channel-independent manner.⁹¹ In this model it seems likely that morphine exerted a direct

effect on reperfusion injury rather than mimicking ischemic preconditioning. Hofbauer *et al.* reported that remifentanyl decreased neutrophil adhesion and transmigration, and ICAM-1 expression in a dose-dependent manner. Fentanyl also reduced migration of neutrophils.⁹² By contrast, Szekely *et al.* reported that fentanyl, at higher concentration than that used by Hofbauer *et al.*, did not reduce postischemic neutrophil adhesion in the guinea pig heart.⁹³

7. Propofol, ketamine, barbiturates and benzodiazepines

It has been shown that propofol decreases postischemic myocardial mechanical dysfunction, infarct size and histological degeneration.^{6–10} This anesthetic has a chemical structure similar to that of phenol-based free radical scavengers such as vitamin E, and reduces free radicals.^{4,5} Propofol attenuates [Ca²⁺]_i.^{94,95} Propofol also suppresses the activity of neutrophils.^{96,97} These features suggest that propofol may directly intervene at the critical phase of reperfusion injury by reducing free radicals, Ca²⁺ influx and neutrophil activity, but does not act as a preconditioning-inducing agent. Indeed, protection was observed when the heart was treated with propofol solely during reperfusion.⁷ Addition of glibenclamide, a K_{ATP} channel blocker, did not abolish the protection by propofol.⁸

Whether barbiturates protect the heart is still controversial, although these drugs were studied in the 1980s (Table I). Ketamine and benzodiazepines have hardly been investigated for myocardial protection (Table I). Whether these *iv* anesthetics interfere with neutrophil-endothelium interaction, Ca²⁺ influx and free radical production still needs to be elucidated (Table II). It seems unlikely ketamine has an ischemic preconditioning-like effect. This anesthetic blocked ischemic preconditioning,⁹⁸ reduced the production of inositol 1,4,5-triphosphate⁹⁹ and deactivated sarcolemmal K_{ATP} channels.¹⁰⁰ Thiamylal also inhibited sarcolemmal K_{ATP} channel activity.¹⁰¹

8. Comparisons between anesthetics

Several halogenated anesthetics, administered at the same minimum alveolar concentration (MAC) and in the same preparation, have been assessed for their protective effect in a number of investigations. Overall, there is little difference in the *extent* of protection among halogenated anesthetics. However, some studies have reported different protective properties between halogenated anesthetics. The results are not consistent with respect to which anesthetic agents are more protective than others. In addition, an explanation for the discrepancies between anesthetics is not readily available.^{34,35,44,102}

There has been no evidence to suggest significant differences among *iv* anesthetics, such as propofol, ketamine and barbiturates.^{30,103,104} Benedict *et al.* examined the effect of several opioids of equal potency on postischemic myocardial contractility. Morphine, buprenorphine and pentazocine improved postischemic function to a similar degree, while fentanyl did not.⁶⁵ According to Ross *et al.* postischemic contractility recovered to a similar degree in fentanyl- and propofol-anesthetized dogs.¹⁰⁵

Cope *et al.* reported that infarct size was smaller when rabbits were anesthetized with halothane, enflurane or isoflurane compared to pentobarbital, ketamine/xylazine or propofol.³⁰ Because the volatile anesthetics caused blood pressure to be lower than the *iv* anesthetics, the question was raised whether the difference in blood pressure was a determinant of infarct size, but there was no correlation between the two parameters within the halothane-anesthetized group.³⁰ Haessler *et al.* reported that there was no significant difference in the extent of infarction between isoflurane, ketamine/xylazine and pentobarbital in rabbits *in vivo*. Yet, isoflurane showed a tendency toward smaller infarction.¹⁰³ Similarly, significant differences were not found between sevoflurane and propofol assessed by postischemic ventricular function.⁸ However, it is not easy to establish the equipotency of doses for different types of anesthetics and, no clear justifications for choosing the dosage of anesthetics were presented in most studies. Hence the comparisons between anesthetics might not have been strictly valid. Meissner *et al.* compared desflurane and propofol at the concentrations that prevented movement at skin incision. The recovery from stunning was faster with desflurane.¹⁰⁶ However, in this study, the extent of ventricular wall dyskinesia seemed worse (although not statistically different) in the propofol-anesthetized group during the ischemic period; it is possible that the intensity of ischemic insult differed between the anesthetic groups.

9. Studies in humans

Because of obvious limitations, it has been difficult to provide evidence for anesthetic preconditioning in humans. In the study by Roscoe *et al.*, the protective effect of halothane and isoflurane was investigated in right atrial trabecular muscles obtained from patients undergoing coronary bypass grafting surgery. When the trabeculae were pretreated with isoflurane, the contractile force after the ischemic insult was improved. However, halothane did not show significant improvement.⁴⁴ The only study of opioids in humans is by Bell *et al.* DADLE administered to atrial trabeculae improved contraction.

Clinical studies have been conducted in patients undergoing coronary artery bypass graft surgery. Belhomme *et al.* assessed the effect of isoflurane on T I release. Preconditioning by isoflurane reduced T I release, but not to a statistically significant degree.¹⁰⁷ According to Tomai and coworkers, isoflurane suppressed the release of this enzyme in patients with compromised left ventricular function.¹⁰⁸ The same group employed postischemic mechanical function as another endpoint. Enflurane was administered immediately before starting cardiopulmonary bypass in coronary artery bypass graft surgery. Peak-systolic pressure in the ascending aorta was plotted against the end-diastolic area of the left ventricle. The postischemic change in the slope of this relationship was less pronounced in the enflurane group.¹⁰⁹ A limitation of these clinical studies is that the number of subjects was small. Taking into account patient variability, the number of subjects would have to be large for valid conclusions to be drawn.

10. Limitations of currently available data

All investigations of halogenated anesthetics cited in this review have demonstrated protection using anesthetic concentrations relevant to clinical practice, i.e., 0.5–2 MAC. Morphine diminished infarct area at a dose of 0.3 mg·kg⁻¹ in rats *in vivo*;^{3,78,91} this concentration is clinically relevant. Total plasma concentrations of morphine can reach 0.7 µmol·L⁻¹ after 0.2 mg·kg⁻¹ *iv* bolus injection for peripheral surgery.¹¹⁰ When *iv* morphine was used for analgesia after breast reconstruction or operation on the spine, the plasma concentration was about 0.1 µmol·L⁻¹.¹¹¹ Assuming morphine's protein binding to be 40%,¹¹² the concentrations used in some *in vitro* studies (0.3 µmol·L⁻¹,⁶² 0.1 µmol·L⁻¹)⁶³ are close to the clinical range, but not others (100 µmol·L⁻¹⁶⁴, 1 µmol·L⁻¹).⁸³ Fentanyl reached 0.07 µmol·L⁻¹ and remained 0.03–0.04 µmol·L⁻¹ after bolus dosage of 30 µg·kg⁻¹ followed by 0.3 µg·kg⁻¹·min⁻¹ for cardiac surgery.¹¹³ As fentanyl binds to plasma protein at the rate of 82%,¹¹² 0.47 µmol·L⁻¹,^{66,67} the concentration used in experimental studies is outside the clinical range. Propofol provides protection at 18–100 µmol·L⁻¹ in rats,^{6–9} while free plasma concentration during surgery is estimated to be less than 1 µmol·L⁻¹.^{112,114} Propofol failed to protect against reperfusion injury at a concentration of 4.5 µmol·L⁻¹ in rats.¹¹⁵ In the case of ketamine, neutrophil adhesion during reperfusion was inhibited at clinically relevant concentrations.^{116,117} In summary, concentrations of *iv* anesthetics which protect the heart were not always within the therapeutic range for humans. However, it should be noted that pharmaco-

TABLE I Protection by different anesthetics

	<i>Timing of administration</i>		
	<i>Preconditioning</i>	<i>Preischemia/ Pre-, during ischemia</i>	<i>During and/or postischemia</i>
Halogenated	++ (5.2.1)	++ ^{41,43,109,118}	± (5.2.1)
Opioids	++ (5.2.1)	++ ^{3,62,64,70}	(10)
Propofol		++ (7)	(7)
Ketamine		⁹³ *1	
Barbiturates		± ⁹³ *1 ¹¹⁹⁻¹²¹	+ ^{120,122}
Benzodiazepines		⁹³ *1	

The effect is sorted according to the timing of anesthetic administration. + = supported by published studies; ++ = supported by published studies by multiple institutes; ± = published studies are conflicting; - = negated by published studies. Numbers in () indicate sections in the text where these issues are discussed. *1 = the anesthetic was given pre-, during and postischemia.

TABLE II Possible mechanisms by which an anesthetic agent confers protection

	<i>Mechanisms</i>			
	<i>Preconditioning</i>	<i>Neutrophil</i>	<i>Ca²⁺</i>	<i>Free radicals</i>
Halogenated	++ (5.2.1)	+ (5.2.2)	++ ¹¹	+ ¹¹
Opioids	++ (6.2.1)	± (6.2.2)	± ^{123,124}	+ ^{125,126}
Propofol		++ (7)	++ (7)	++ (7)
Ketamine	- (7)	+ ^{93,127}	+ ^{128,129}	
Barbiturates		+ ^{93,96,130}	± ^{131,132}	+ ^{126,133}
Benzodiazepines		± ^{93,97,130}	+ ^{95,134}	

Different agents might have different mechanisms. Preconditioning = preconditioning-like effect in the heart; neutrophil = interference in neutrophil function; Ca²⁺ = blockade of Ca²⁺ overload in the myocyte; free radicals = antioxidant-like effect; + = supported by published studies; ++ = supported by published studies by multiple institutes; ± = published studies are conflicting; - = negated by published studies. Numbers in () indicate sections in the text where these issues are discussed.

dynamics are largely species-dependent. It is, therefore, difficult to determine whether these *in* anesthetics could be cardioprotective at the concentrations used in humans.

It is well demonstrated that anesthetics are protective when administered before ischemia. However, unlike cardiopulmonary bypass and transplantation, myocardial ischemia is not usually planned or expected in clinical practice, and in many cases patients can be treated only after myocardial ischemia is established. Are anesthetics effective when they are given during and/or after ischemia? As summarized in Table II, anesthetics have attributes which may contribute to protection when administered after the onset of ischemia, such as mitigation of Ca²⁺ overload, free rad-

ical production and neutrophil adhesion. Indeed, postischemic treatment with halogenated anesthetics^{34,35,49,55} and propofol⁷ had favourable effects in animals. Morphine has been tested for adhesion molecule levels in blood from patients with acute myocardial infarction. Intravenous administration of 3 mg morphine after the onset of myocardial infarction reduced the serum ICAM-1 level.⁹⁰ However it is of note that there have been reports which showed that halogenated anesthetics⁴³ and opioids⁸³ were not protective when administered after the onset of ischemia. Overall, it is still controversial whether anesthetics protect the heart when administered after the onset of ischemia.

11. Conclusion

An increasing number of investigations demonstrate that halogenated anesthetics, opioids and propofol protect against myocardial ischemia-reperfusion injury. The protective effect of ketamine, barbiturates and benzodiazepines remains to be elucidated. The mechanisms by which the protection is afforded may include an ischemic preconditioning-like effect, blockade of Ca²⁺ overflow to the cytosolic space, an antioxidant-like effect, and/or interference in the neutrophil/platelet-endothelium interaction. Halogenated anesthetics and opioids seem to be potent preconditioning-inducing agents. By contrast, propofol might provide protection via different mechanisms. Comparative investigations suggested that halogenated anesthetics might be more potent cardioprotectors than *in* anesthetics. Isoflurane and a δ -opioid agonist showed protection in human hearts.

Currently halogenated anesthetics are arguably the most promising agents as cardioprotectors among anesthetics. Their beneficial effects against ischemia-reperfusion injury have been demonstrated better than for any other anesthetic. In addition halogenated anesthetics confer protection at clinically relevant concentrations and comparative studies support their use. Although the evidence is less supportive, morphine has also been shown to be protective at clinical concentrations. Hence, halogenated anesthetics and morphine might be good choices in anesthetizing patients at risk of myocardial ischemia. This does not necessarily indicate that other opioids and propofol are not effective, but that they have not been fully examined yet. The effect of halogenated anesthetics and morphine, when they are administered after the onset of ischemia, remains questionable. Being a distinct free radical scavenger, propofol might be able to mitigate injury during and/or after ischemia.

Further studies are needed to draw clear conclusions as to which anesthetic is most useful in protecting the myocardium. It is time for interested clinicians

to evaluate the effectiveness of anesthetics in the clinical setting.

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