Myocardial preconditioning (PC) has been the subject of intense laboratory and clinical research and is definitely one of the most important developments in the field of ischemic biology in the past 20 years. The implications of PC transcend the field of cardiovascular perioperative medicine and should be of interest to any anesthesiologist. This lecture will focus particularly on the physiology and pharmacology of myocardial preconditioning and will discuss the aspects of volatile anesthetics and preconditioning as well as focus on several other drugs and biological agents which may have cardioprotective properties.

First, it is important to establish the definition of ischemic PC. This is the phenomenon whereby brief episodes of sublethal ischemia render the heart more resistant to subsequent prolonged ischemic injury. The phenomenon of PC was initially described in 1986 by Murry et-al(1). In this study, the authors made what at that time appeared to be a paradoxical observation: they exposed a group of open-chest dogs to a sequence of four brief ischemic episodes (5-min coronary occlusions interspersed with 5-min reperfusion periods) and then subjected them to a prolonged, more severe ischemic insult (a 40-min coronary occlusion followed by 4 days of reperfusion). Theoretically, one would have expected that the dogs that received the four brief coronary occlusions would exhibit greater infarct size, because they had been exposed to an additional 20 min of ischemia. Surprisingly, it was found that actually infarct size was much smaller in the dogs that were exposed to the short periods of ischemia than in the controls, and that this effect was independent of differences in coronary collateral blood flow. They coined the term "ischemic preconditioning" to describe this phenomenon, opening the gates for what has become one of the major themes of research in cardiovascular medicine.

Ischemic preconditioning exerts robust and reproducible protection, and appears to be a ubiquitous endogenous protective mechanism at the cellular level that has been observed in the heart of every species tested. This protection is also seen in other organs such as the liver, kidney, gut and brain(2). The reduction in infarct size mediated by ischemic preconditioning disappears if the interval between the preconditioning protocol and the index ischemic period is longer than 3–4 h(2). This loss of effect suggests that there is an associated 'memory effect' and that protection is transient.

After the initial description of PC in 1986, the next major discovery came in 1993, when it was found that PC consists of two distinct phases: an early phase, which develops very quickly (within a few minutes from the exposure to the stimulus) but is rather short, lasting up to 2-4 h and a late phase, which develops more slowly (requiring 12-24 h) but lasts much longer (3–4 days)(3). The mechanisms for these two phases are completely different. The early phase is caused by rapid posttranslational modification of preexisting proteins, whereas the late phase is caused by the synthesis of new cardioprotective proteins (which explains the time course of this phenomenon). The range of protection is also different. The early phase is very effective in limiting lethal ischemia-reperfusion injury (i.e., infarction) but does not protect against reversible postischemic contractile dysfunction (myocardial "stunning"). The late phase protects against both infarction and stunning, although it is less powerful than the early phase in limiting infarct size.

Mechanisms of cardioprotection by ischemic preconditioning

The current paradigm suggests that the short ischemic episodes of preconditioning lead to the release of substances, such as adenosine and bradykinin. These substances bind to their G-protein-coupled receptors on the surface of myocytes and activate signal transduction cascades, which include phosphatidylinositol-3-kinase (PI3K)–Akt(4), extracellular signal-regulated kinase (Erk1/2)(2) and transcription factors such as the Hypoxia Inducible Factor (HIF) 1(5). Activation of these pro-survival mediators converge on the mitochondria, resulting in the opening of the ATP-dependent mitochondrial potassium channel(6,7). Reactive oxygen species are then released(8). Further signaling kinases are activated, such as protein kinase C, which is responsible for conveying the 'memory effect' of ischemic preconditioning(2). It must be appreciated, however, that alternative protective mechanisms of ischemic preconditioning might exist that are independent of signal transduction pathways, such as those mediated by antioxidant and anti-inflammatory mechanisms.
During the second window of protection, signaling kinases mediate the transcription of distal mediators and effectors, such as inducible nitric oxide synthase (iNOS), manganese superoxide dismutase, heat-stress proteins and cyclo-oxygenase 2 (COX-2), 24–72 h after infarction, which manifest the late protection(2). How these signaling transduction pathways mediate protection and ultimately reduce infarct size is currently unknown. Suggested mechanisms include maintenance of mitochondrial ATP generation, reduced mitochondrial calcium accumulation, reduced generation of oxidative stress, inhibition of apoptosis and prevention of mitochondrial permeability transition-pore (mPTP) opening(2,9).

Anesthetic-Induced Cardiac Protection

A rapidly growing body of evidence indicates that volatile anesthetics protect myocardium against ischemic injury. Initially, several studies have suggested that isoflurane and other volatile agents may actually cause myocardial ischemia through “coronary steal”(10,11). Later, The implication that isoflurane might produce myocardial ischemia through such a steal mechanism was dispelled by several investigations conducted in animal models(12) and humans with coronary artery disease(13,14). Many laboratory and clinical investigations conducted since the resolution of the coronary steal controversy have convincingly shown that volatile anesthetics protect the heart against ischemia and reperfusion injury(15). Isoflurane, for instance, reduced myocardial infarct size in dogs, and this beneficial action was found to persist despite discontinuation of the volatile anesthetic before coronary artery occlusion(16). This phenomenon was termed anesthetic-induced preconditioning (APC) and was characterized by a short-term memory phase similar to that observed during ischemic preconditioning.

Anesthetic-induced preconditioning has also been described in other animal species, including rats(17) and rabbits(18). The efficacy of APC conferred by isoflurane to reduce infarct size has been shown to be dose dependent in rats(17), an animal model with minimal coronary collateral flow(19). Similarly, isoflurane and sevoflurane dose-dependently preserved the viability of isolated cardiac myocytes during ischemia(20).

Interestingly, recent findings showed that isoflurane reduced myocardial damage when administered 24 h before coronary artery occlusion and reperfusion in rabbit hearts in vivo(21). Pretreatment with isoflurane also preserved endothelial and vascular smooth muscle cell viability 12–48 h after cytokine-induced injury(22). Therefore, volatile anesthetics also produce a late phase (i.e., a second window) of myocardial protection similar to IPC. In addition, sevoflurane reduced the duration of a brief ischemic episode required to protect against infarction during IPC(23). Sevoflurane also enhanced cardioprotection when administered 24 h after an initial IPC stimulus(24). These findings showed that administration of a volatile anesthetic combined with a brief ischemic event synergistically protects myocardium against subsequent damage as well.

Volatile anesthetics have been shown to produce coronary vasodilation by activating K\textsubscript{ATP} channels(25) or by favorably affecting intracellular Ca\textsuperscript{2+} homeostasis in vascular smooth muscle. Sevoflurane increased collateral blood flow to ischemic myocardium when perfusion pressure was maintained(26) Sevoflurane also improved the functional recovery of coronary vascular reactivity and nitric oxide release in isolated hearts after global ischemia(27). Volatile anesthetics attenuated neutrophil and platelet aggregation(28) and also inhibited cytokine-induced cell death(22,29) after ischemia-reperfusion injury in vitro. Lastly, studies also show that volatile anesthetics attenuate apoptosis as well as necrosis after ischemia and reperfusion and shift the myocardium into an “anti-apoptotic” state by modulation of proteins of the BCL-2 family (30,31)

The signal transduction pathways involved in APC bear striking similarity to those responsible for IPC. It is hypothesized that volatile anesthetics stimulate a trigger that initiates a cascade of events leading to activation of an end-effector that is responsible for resistance to injury. To date, adenosine type 1 (A\textsubscript{1}) receptors(32,33) protein kinase C (PKC)(34), inhibitory guanine nucleotide binding (G\textsubscript{i}) proteins(35), ROS(36,37), and mitochondrial and sarcolemmal K\textsubscript{ATP} channels(16,38)(39) have been shown to mediate APC. Recently several investigations have also demonstrated important roles for pro-survival kinases such as PI3K/Akt(40) and the transcription factor HIF-1(41).

The clinical potential of preconditioning

In vitro studies(42) suggest that the human myocardium can be preconditioned. The existence of this phenomenon in vivo has been suggested by several surrogate models of preconditioning in humans. In preinfarction angina, for example, antecedent angina improves clinical outcome after myocardial infarction(43). Furthermore, intermittent aortic cross-clamping during cardiac surgery before the sustained period of global ischemia required for cardiopulmonary bypass seem to provide cardioprotection(44).
Several preconditioning mimetic agents have been investigated in clinical studies of myocardial ischemia reperfusion, but with limited results. Only nicorandil has been investigated as a true preconditioning agent. This drug is believed to open ATP-dependent mitochondrial potassium channels, as well as cause coronary vasodilatation. The Impact Of Nicorandil on Angina (IONA) study(45) examined nicorandil in patients with chronic stable coronary artery disease and demonstrated a small but significant reduction in major coronary events. Nicorandil also has cardioprotective effects when given as adjunctive therapy at the time of reperfusion after MI by primary percutaneous coronary intervention (PCI)(46). Other agents, such as adenosine and sodium–hydrogen exchanger inhibitors, have been investigated when given as adjuncts to reperfusion, as opposed to being investigated as true preconditioning mimetics, which necessitates giving the agent before the index ischemic period. Preclinical studies demonstrated that pharmacologic inhibition of the sodium–hydrogen exchanger before myocardial ischemia could reduce infarct size, through a reduction in myocardial calcium accumulation, to a level comparable to ischemic preconditioning(47). Unfortunately, the findings from subsequent clinical studies were not so clear.

Many other drugs and pharmacological agents are under research for their preconditioning mimetic effects. Among those are found opioid receptor agonists (morphine, remifentanil)(17,48,49) that were found to provide cardioprotection by themselves or enhance the protection achieved by ischemic or anesthetic preconditioning, the phosphodiesterase-5 inhibitor sildenafil (viagra)(50,51) and statins(52,53), however, large randomized controlled clinical trials are yet to be done.

Several studies have shown a preconditioning effect for volatile anesthetics in cardiac surgery, when administered prior to aortic cross clamping(54-56), however they consistent of small experimental groups and had to focus on surrogate outcome markers such as post-ischemic ventricular dysfunction and markers of cellular myocardial injury (troponin). In 2002 De Hert and colleagues(57) have published a different protective approach: they have administered sevoflurane throughout the entire operation (thus combining preconditioning and postconditioning), comparing it to propofol-based intravenous anesthesia. Although only 20 patients were enrolled in this study there was a clear difference between the study groups: the patients in the sevoflurane group had a better LV function post CPB and lower levels of troponin (i.e. reduced myocardial injury) for 26 hours following surgery. Similar results were also confirmed in older patients with poor ventricular function(58). A recent study investigated different administration modalities of sevoflurane – before (preconditioning), during and after (postconditioning) cardiopulmonary bypass(59). The results indicated that only the administration of sevoflurane throughout the entire operation resulted in a decrease in troponin I release as well as decreased duration of in-hospital stay. Furthermore, similar results were also found in a recent randomized controlled multicenter study comparing desflurane anesthesia to propofol-based intravenous anesthesia in off pump coronary bypass(60). The patients in the desflurane group demonstrated decreased postoperative myocardial damage, resulting in a decreased need for ionotropic support, eventually leading to a significant reduction in hospital stay. Taken together, there is data supporting a cardioprotective effect for volatile anesthetics administered during coronary surgery. However, the optimal dosing and timing for administration have not been determined yet. It seems that for maximal protection administration of volatile agents is required throughout the entire duration of surgery. Larger randomized controlled trials are required for better understanding of the mechanisms of volatile anesthetics-induced protection in the clinical arena.

Myocardial postconditioning

In order to harness the cardioprotective potential of preconditioning, the intervention needs to be implemented before the onset of myocardial ischemia. In the settings of an acute myocardia infarction this timing is difficult to achieve. The approach might be possible, however, during elective coronary catheterization and cardiac surgery, in which the onset of myocardial ischemia is predictable. Given the prerequisite for a preconditioning agent to be present before the onset of myocardial ischemia, attention in the field of cardioprotection has focused on modifying events occurring at the time of myocardial reperfusion (i.e. postconditioning).

Postconditioning describes the reduction in infarct size induced by the application of alternating episodes of myocardial ischemia and reperfusion or cardioprotective pharmacological agents at the end of the index ischemic period. This concept was first introduced in 2003 by Zhao et al(61). They demonstrated that the in vivo application of three 30 s episodes of alternating left anterior descending artery reocclusion and reperfusion, immediately following a 1 h period of sustained occlusion, produced a significant reduction in infarct size. This effect is comparable to that of ischemic preconditioning. Since its introduction, ischemic postconditioning has been demonstrated in vivo in several different species, as well as ex vivo in the rat heart and rat myocytes. In addition to ischemia and similarly to preconditioning volatile anesthetics have also been found to be cardioprotective when administered at the end of the index ischemia and early reperfusion (i.e. anesthetic postconditioning)(62).

Mechanisms of cardioprotection by ischemic postconditioning
As with ischemic preconditioning, the exact mechanism by which ischemic postconditioning reduces infarct size is unknown. Study findings suggest that protection is dependent on adenosine-receptor stimulation, activation of the survival kinases (PI3K–Akt(63), Erk1/2(64)) and inhibition of mPTP opening(65). Ischemic postconditioning is also accompanied by a reduction in factors known to mediate myocardial reperfusion injury, such as oxidative stress, apoptotic factors and neutrophil accumulation(61). Interestingly, although both preconditioning and postconditioning activate very similar protective mechanisms in the heart, a recent study by Lucchinetti et-al(66) has shown evidence of opposing genomic responses in cardioprotection by pre- and postconditioning.

**The clinical potential of myocardial postconditioning**

Dependent on the clinical scenario of myocardial ischemia and reperfusion, the application of intermittent myocardial ischemia and reperfusion might be difficult to implement and justify. For example, the use of ischemic postconditioning would not be possible in an AMI patient referred for thrombolysis, in cases of unstable angina, in patients presenting with non-ST-segment elevation myocardial infarction or in the event of a cardiac arrest. Such a protocol might be possible to apply in a patient with myocardial infarction referred for PCI, elective PCI or at the time of cardiac surgery. Justification for applying intermittent episodes of balloon inflation or cross-clamping of the aorta at the time of myocardial reperfusion might, however, be difficult.

Taken together, and considering the fact that the survival kinases (PI3K–Akt, ERK1 and ERK2) mediate the protection induced by ischemic postconditioning, a more practical approach would be to pharmacologically activate these kinases at the time of reperfusion to harness the powerful cardioprotective potential of ischemic postconditioning. Importantly, this approach can be readily applied to all clinical scenarios of myocardial ischemia and reperfusion(67).

As with preconditioning, volatile anesthetic agents have been found to protect the heart against ischemia and reperfusion also when administered during reperfusion. Several animal studies have demonstrated this cardioprotective effect and suggested that it is mediated by similar mechanisms that are activated in ischemic postconditioning (62,68-70). Several studies in coronary bypass patients suggest that it may also have clinical implications (59).

**Conclusions**

The field of myocardial protection has had several major implications in cardiovascular and peri-operative medicine. First, it has revealed that the heart possesses a remarkable phenotypic plasticity that enables it to overcome ischemia-reperfusion induced injury. Second, myocardial protection can be achieved not only by ischemia but also using cardioprotective agents such as volatile anesthetics, opioids and statins.

Although the cardioprotective potential of preconditioning is hindered by the requirement to intervene before onset of ischemia—which is unpredictable in the setting of an acute myocardial infarction, postconditioning might allow a clinical intervention at the time of myocardial reperfusion to reduce infarct size after infarction. The recruitment of a common signaling pathway at the time of myocardial reperfusion in preconditioning and postconditioning provides a potential target for cardioprotection through the use of pharmacologic agents to activate survival kinases (PI3K–AKT and ERK 1 and 2), directly inhibit mPTP opening or both. Future trials will be required to validate this novel approach to cardioprotection in clinical practice and identify the most effective pharmacologic agents.

**References**


