Ischemic preconditioning of myocardium -effects of inhalation anesthetics
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By the end of this lecture you should be able to answer the following questions:

1- Enumerate the ionic changes that occur with ischemia and reperfusion of the heart?
2- What is the definition of ischemic preconditioning of myocardium?
3- What is the mechanism of ischemic preconditioning of myocardium?
4- What are K_{ATP} channels and K_{Ca+2} channels?
5- Describe pharmacological preconditioning of inhalational anesthetics?

Ischemia precludes adequate oxygen supply, which rapidly results in depletion of ATP. This inhibits ATP-driven Na^{+}-k^{+} pumps, increasing intracellular sodium [Na^{+}]i. Intracellular hydrogen [H^{+}]i is increased due to poor washout of metabolites. Increased [H^{+}]i enhances Na^{+}-H^{+} exchange to retain normal intracellular pH [pHi], leading to increased [Na^{+}]i. Accordingly, [Ca^{2+}]i is augmented via Na^{+}-Ca^{2+} exchange. High [Ca^{2+}]i degrades proteins and phospholipids.

On reperfusion, [H^{+}] outside the cell is rapidly decreased to normal levels because of washout. This results in an increase in [Ca^{2+}]i due to enhanced Na^{+}-H^{+} and Na^{+}-Ca^{2+} exchange. (1)

In 1986 Reimer et al. reported a series of experiments in the dog heart designed to dissect the contributions of ATP depletion from catabolite accumulation in the genesis of lethal ischemic injury. Their experimental model involved repetitive brief ischemic episodes, working on the premise that each ischemic episode would cause cumulative ATP depletion while the intermittent
reperfusion would wash out ischemic catabolites. To their surprise they found that, following the initial ischemic period, ATP levels were not depleted further by subsequent similar ischemic challenges. (2)

**Definition of preconditioning:**
Ischemic preconditioning was originally described as a decrease in high energy catabolism during brief periods of ischemia that limit myocardial infarct size after subsequent prolonged ischemic challenge.

Now the definition is extended to all contractile dysfunction, arrhythmia, and intra cellular acidosis. (3)

Ischemic preconditioning (IP) is a powerful protective endogenous adaptive response of the heart against a prolonged ischemic insult. However, the application of IP requires a physical cut of the blood supply which can be difficult or impractical in many clinical situations. To overcome this we may use pharmacological means i.e. pharmacological preconditioning (pp).

A number of membrane receptors are involved in the phenomenon of IP including $\alpha_1$ and $\beta$-adrenoceptors, opioid and adenosine A1 and A3 receptors. Other factors such as heat shock proteins, bradykinin, calcium and nitric oxide synthase activity have also been shown to participate in the protection of IP; however, whether the various forms of PP share the same molecular mechanism with IP is not fully elucidated. Recent evidence from several investigators has shown that the mitochondrial and not the sarcolemmal $K_{ATP}$ channels are involved. The order of involvement of the above mediators remains controversial although recently it has been suggested that mitochondrial $K_{ATP}$ channels are the triggers in the signal transduction mechanism rather than the end effectors. (4)

PP and IP of the human myocardium share identical signal transduction cascade that involves mito$K_{ATP}$ channels, protein kinase C (PKC).
An important finding is that hypertrophied myocardium can be protected from I/R-induced contractile dysfunction by preconditioning with transient ischemia, and this protection can be further enhanced by treatment with losartan, an AT$_1$-receptor blocker. (4)

**Mechanism of preconditioning:**

Both an early and a late phase of preconditioning have been described. Ischemic preconditioning is associated with two forms of protection: a classical form or first window of protection lasting approximately 2-3 h after the preconditioning ischemia, followed a day later by a second window of protection (SWOP), lasting approximately 3 days. The mechanism of ischemic preconditioning involves both triggers and mediators and involves complex second messenger pathways that appear to involve such components as adenosine, adenosine receptors, nitric oxide (NO), heat shock proteins (HSP), the epsilon isoform of protein kinase C (PKC), mitogen-activated protein kinases (MAPK), the mitochondrial ATP-dependent potassium ($K_{ATP}$) channels, as well as others, including a paradoxical protective role of oxygen free radicals. (5)

An increase in the release of endogenous agents such as nitric oxide (NO) and adenosine may be responsible for both windows of protection, probably via different mechanisms. Nitric oxide acts as a trigger in the first window of protection via activation of a constitutive Nitric Oxide Synthase (NOS) isoform and cGMP pathway. Nitric oxide is also involved in the second window of protection (SWOP), however, via a different mechanism, through the activation of a protein kinase C (PKC), which in turn activates ATP sensitive potassium $K_{ATP}$ channels. In the second window of protection (SWOP), the origin of nitric oxide is attributed to the activity of an endothelial Nitric Oxide Synthase (eNOS). Adenosine-induced preconditioning involves p38 MAP kinase, and mitochondrial $K_{ATP}$ channels. Recently, it has been suggested that
the $K_{ATP}$ channels involved in the protection are mitochondrial rather than sarcolemmal.

Reactive Oxygen Species (ROS) can trigger preconditioning by causing activation of the mitochondrial $K_{ATP}$ channel, which then induces generation of ROS and NO, which are essential for preconditioning protection. Activated PKC, by phosphorylation, stabilizes the open state of the mitochondrial $K_{ATP}$ channel, which is believed to be the main end-effector in ischemic preconditioning. The opening of $K_{ATP}$ channels ultimately confers cytoprotection by decreasing cytosolic and mitochondrial Ca$^{+2}$ overload.

The response of $[Na^+]$i in the PC hearts was an increase in $[Na^+]$i at the end of preconditioning and an accelerated decrease during the first few minutes of post-ischemic reperfusio. These data suggest that PC stimulated preliminary activation of ion transport processes involving Na$^+$ may protect the heart from intracellular acidosis during prolonged ischemia, promote rapid recovery of pH$_i$ during reperfusion, and thus result in better recovery of mechanical function (LVDP and heart rate) during post-ischemic reperfusion.

Experiments with the $Kir6.2^{(-/-)}$ mouse [deficient in $K_{ATP}$ channels] have shown that functional sarc$K_{ATP}$ channels (Kir6.2/SUR2A) are required for adaptation of the heart to stress. In severe ischemia and hypoxia, the decrease in the ratio of ATP to ADP and the increase in oleoyl-coenzyme A ester levels lead to a massive opening of sarc$K_{ATP}$ channels. Simultaneously, a variety of tissue hormones (among them adenosine) are released, which triggers the process of ischemic preconditioning. This mechanism was first linked to the opening of the sarc$K_{ATP}$ channel, later to the opening of the mito$K_{ATP}$ channel, and then to the opening of both channels.

Until recently, it was thought that under physiological conditions,
sarcK$_{ATP}$ channels had no function since the high ATP concentrations in the healthy cardiomyocyte kept them locked in the closed state. This notion changed dramatically when it was found that Kir6.2$^{(-/-)}$ mice were much less tolerant to physical and sympathetic stress than wild-type mice. The sarcK$_{ATP}$ channel–deficient mice performed poorly in the treadmill exercise test. Under vigorous β-adrenergic stimulation, these animals died from arrhythmia; cardiomyocytes showed a diminished reduction in action potential duration, Ca$^{2+}$ overload, and myocardial contraction bands. In humans, defective regulation of channel activity due to mutations in SUR2A has been linked to the occurrence of dilated cardiomyopathy. (9)

The opening of sarcK$_{ATP}$ channels in cardiac hypoxia and ischemia reduces action potential duration and clamps the cardiomyocyte at the potassium equilibrium potential, rendering the cell unexcitable. Whereas this may salvage ATP and preserve the structural integrity of the cell, it also increases the electrical heterogeneity of the heart and promotes reentry arrhythmias. In addition, a prolonged opening of sarcK$_{ATP}$ channels leads to the accumulation of extracellular K$^+$ in the ischemic zone, depolarizes the cell, and induces cytotoxic Ca$^{2+}$ entry. Along these lines, prevention of the opening of these channels in ischemia was shown to protect against ischemia-induced ventricular fibrillation. Using the selective block of sarcK$_{ATP}$ channels as an antiarrhythmic strategy in cardiac ischemia, however, raises two points of concern. First, the opening of sarcK$_{ATP}$ channels in cardiac ischemia leads to heterogeneity of the plateau phase of myocardial action potentials and induces the deviation (elevation or depression) of the ST-segment of the electrocardiogram observed in cardiac ischemia. Accordingly, in animals with experimental cardiac ischemia, pretreatment with sulfonylureas or HMR 1883 blunted the deviation. In a recent retrospective study, the electrocardiogram (ECG) charts from 88 patients with type 2 diabetes and myocardial infarction were
analyzed. In patients treated with "sulfonylureas of all kinds," the ischemia-induced ST elevation was reduced and these patients were significantly less likely to meet the standard ECG criteria for admission to thrombolytic therapy. In the light of this new evidence, however, they recommended to discontinue sulfonylurea treatment in type 2 diabetic patients with suspected acute coronary syndrome and to infuse insulin instead, if necessary, until myocardial ischemia was ruled out.

The second point of concern is that functional sarcK\textsubscript{ATP} channels are required for the adaptation of the heart to stress. In addition, opening of the sarcK\textsubscript{ATP} channel plays a central role in ischemic preconditioning.

There is, however, overwhelming pharmacological evidence also for a mitochondrial pathway of ischemic preconditioning. This is mainly based on the differential effects of the "mitoK\textsubscript{ATP} channel–selective" blocker 5-hydroxydecanoate versus the sarcK\textsubscript{ATP} channel–selective blocker HMR 1883 or on the effects of the "mitoK\textsubscript{ATP} channel–selective" opener diazoxide. Experiments in human ventricular myocytes and atrial trabeculae have provided evidence for both the early and delayed phases of ischemic preconditioning in the human heart and for the involvement of the mitochondrial pathway in these phenomena. As an example, recovery of contractile force of atrial trabeculae obtained from nondiabetic patients or from diabetic patients taking insulin was augmented by ischemic preconditioning; however, ischemic preconditioning was ineffective when applied to trabeculae from type 2 diabetic patients taking glibenclamide (2x5 mg/day) or glipizide (10 mg/day). This suggests that chronic treatment with these sulfonylureas abolishes ischemic preconditioning.
Basic scientific experiments and preliminary clinical trials in humans suggest that remote ischemic preconditioning (RIPC), where brief ischemia in one tissue confers resistance to subsequent sustained ischemic insults in another tissue, may provide a simple, cost-effective means of reducing the risk of perioperative myocardial ischemia. Less is known about the mechanisms underlying RIPC. In general, signaling from one tissue to another may be achieved by humeral or neural pathways. Gho and colleagues found that reperfusion was an essential requirement for obtaining a preconditioning effect, implying that ischemic tissue releases some mediator which triggers preconditioning in distant tissues if it enters the general circulation, that is, a humoral pathway. Dickson and colleagues demonstrated that the
preconditioning effect can be transferred between isolated hearts. One group of isolated rabbit hearts was preconditioned. Fluid washed through the coronary vasculature was then collected and infused into separate isolated receptor hearts. Receptor hearts which received effluent from preconditioned donor hearts demonstrated reduced infarction size when subsequently subjected to prolonged ischemia compared with hearts which received effluent from control, non-preconditioned donor hearts.

Adenosine, bradykinin, and opioid release from ischemic tissues do appear to be involved in the RIPC pathway, just as they play a role in direct preconditioning. The administration of a PKC blocker abolishes the cardioprotective effect of transient infra-renal aortic occlusion or mesenteric occlusion and the direct preconditioning effect of transient coronary occlusion, suggesting that PKC activation is an event common to both direct and remote pathways. Moreover, PKC activation is higher in remote preconditioned hearts compared with controls. This PKC activation in RIPC may be triggered by adenosine, bradykinin, or opioids. An adenosine-receptor antagonist abolishes the cardio-protective effect of both direct cardiac preconditioning and remote renal preconditioning. A bradykinin-receptor antagonist blocks the cardioprotective effect of mesenteric preconditioning, by inhibiting activation of PKC, whereas infusion of bradykinin into the mesenteric circulation mimics the cardioprotective effect. δ1-opioid receptor inhibition abolishes both direct and remote cardiac preconditioning. However, although inhibition of endogenous free radicals has little effect on infarct size in directly preconditioned myocardium, it reduces the protection provided by RIPC. (12)

There is also evidence of a potential neural pathway in RIPC. The gastroprotective effects of RIPC in a rat model are significantly reduced by capsaicin-denervation or truncal vagotomy. Ganglion blockade with hexamethonium prevents PKC activation in rats, impeding the RIPC effect when the stimulus is brief mesenteric
occlusion, although not when the stimulus is infra-aortic occlusion. In a pig model of heart transplantation, RIPC with transient limb ischemia in the recipient animals reduced the extent of myocardial infarctions in subsequently transplanted hearts. The effect was abolished by administration of glibenclamide, a $K_{\text{ATP}}$ channel blocker. Given that transplanted hearts have no innervation; these data appear to suggest that RIPC cannot be produced by a neural mechanism. On the other hand, a recent study in humans found that administration of a ganglion blocker attenuated the effect of RIPC on endothelial ischaemia–reperfusion injury assessed by flow-mediated vasodilatation.

There may be some overlap between potential humoral mediators and neural pathways. Experiments in a rabbit model of RIPC using renal ischaemia as the stimulus demonstrated that adenosine released by the ischemic kidney acted locally on the afferent renal nerves to trigger myocardial protection. A series of experiments using a rat model demonstrated that adenosine released locally during small intestinal ischaemia stimulates afferent nerves in the mesenteric bed during early reperfusion, triggering a neural pathway that activates myocardial adenosine receptors. (13)

To determine the role of the $K_{\text{Ca}}$ channel in cardioprotection of IPC, we first determined the effects of preconditioning with ischemic insults on injury induced by ischemia/reperfusion upon blockade of the high-conductance $K_{\text{Ca}}$ channel with a blocker of the channel, paxilline. To delineate the role of the mitochondrial permeability transition pore (mPTP) in the cardioprotection by activation of the $K_{\text{Ca}}$ channel, the effect of blockade of mPTP on cardioprotective effects of ischemic insults or activation of the $K_{\text{Ca}}$ channel in the isolated perfused rat heart and isolated ventricular myocyte was determined. The results showed that the $K_{\text{Ca}}$ channel triggers the cardioprotection of IPC, and the mPTP is involved. (14)
Activation of mitoK<sub>ATP</sub> channels also confers cardioprotection by inhibiting mitochondrial permeability transition pore (mPTP) opening. Therefore, both potassium channels located in mitochondria confer cardioprotection via the same machinery, the mPTP. (6)

One of the common features of these two channels is influx of K<sup>+</sup> into mitochondria upon activation. That opening of these channels results in cardioprotection suggests that K<sup>+</sup> influx may play a crucial role in cardioprotection. There is evidence that K<sup>+</sup> influx into mitochondria may be important for oxidative phosphorylation, regulation of mitochondrial functions such as reactive oxygen species production, and mitochondrial volume regulation. It is also interesting to note that the K<sub>Ca</sub> channel acts as a trigger, whereas mitochondrial K<sub>ATP</sub> channel acts as a trigger as well as a mediator. Therefore, although both channels share a common feature, namely increased K<sup>+</sup> influx into mitochondria upon activation, they may have unique properties other than influx of K<sup>+</sup>, which are responsible for different roles each of them plays. (6)

It was also observed that blockade of the K<sub>Ca</sub> channel abolished the protective effects of IPC accompanied by impairment of contraction, whereas activation of the channel conferred cardioprotection accompanied by improved contractile functions. Further study is needed to determine whether improved/impaired contractile function is secondary to cardioprotection/injury upon activation/inactivation of the channel. (13)
Figure 2. A suggestion for the cardioprotective mechanism in mitochondrion following mitK<sub>ATP</sub> opening in IPC. Light grey arrows represent the major steps in the chain of events. MitK<sub>ATP</sub> opening increases IF<sub>1</sub>-binding to F<sub>1</sub>F<sub>o</sub>-ATPase in an unknown manner during ischemia, which accelerates ischemic F<sub>1</sub>F<sub>o</sub>-ATPase inhibition. F<sub>1</sub>F<sub>o</sub>-ATPase inhibition attenuates mitochondrial ATP degradation, and accelerates the decline of the mitochondrial membrane potential (ΔΨ), which leads to the attenuation of voltage-dependent calcium accumulation in the mitochondrion. These factors decrease the appearance of the mitochondrial permeability transition (MPT). An increase in MPT is associated with cellular necrosis and apoptosis leading to irreversible myocardial damage. (15)
Anesthetics and Myocardial Preconditioning

Perioperative ischemia is common in patients at risk of or with known coronary artery disease undergoing noncardiac or cardiac surgery. The resultant ischemic injury that occurs during surgery can result in a significant morbidity and mortality. Some of the consequences of ischemic injury that occurs during surgery include a delay in extubation and hospital discharge, impaired quality of life after surgery, and a disproportionate consumption of health resources. The goal of anesthesiologists is to prevent this poor perioperative morbidity and mortality, which has led to a significant research in the field of anesthetic preconditioning. Experimental as well as clinical studies have shown that in addition to brief ischemia and pharmacological agents, volatile anesthetics used perioperatively also precondition the myocardium. Halothane, Desflurane, Isoflurane, and Sevoflurane have been extensively studied and these studies reveal promising results with potential clinical implications. (7)

Mechanisms Underlying Anesthetic Preconditioning

Anesthetic preconditioning and ischemic preconditioning have many fundamental steps in common, including formation of nitric oxide, protein kinase C (PKC), free radicals, activation of adenosine receptors and ATP-sensitive potassium (K\textsubscript{ATP}) channels. It is believed that many anesthetics and a significant number of perioperatively administered drugs ultimately affect the activity of cardiac sarcolemmal and mitochondrial K\textsubscript{ATP} channels, which are the end-effectors of cardiac preconditioning. Volatile anesthetics reduce the ischemia induced cell damage, infarct development and infarct size by causing activation of the sarcolemmal and mitochondrial K\textsubscript{ATP} channels, by stimulation of adenosine receptors and subsequent activation of protein kinase C (PKC) and by increased formation of nitric oxide and free oxygen radicals. Activated PKC then amplifies the preconditioning stimulus and by phosphorylation, stabilizes the open state of the mitochondrial
K$_{\text{ATP}}$ channel (which is believed to be the main end-effector in anesthetic preconditioning) and the sarcolemmal K$_{\text{ATP}}$ channel. The opening of K$_{\text{ATP}}$ channels ultimately confers cytoprotection by decreasing cytosolic and mitochondrial Ca$^{2+}$ overload. (11)

It has been demonstrated that ischemia and reperfusion cause increases in [Ca$^{2+}$]$_i$ and [Ca$^{2+}$]$_m$ resulting in further Ca-dependent events leading to cell damage. Several studies have shown that a brief exposure to inhaled anesthetics before ischemia results in improved myocardial function and decreased infarct size in a manner similar to ischemic preconditioning (IPC) in adult hearts. One of the proposed mechanisms of IPC is the opening of mitochondrial K$_{\text{ATP}}$ channels which results in K influx, expansion of the mitochondrial matrix volume, and a reduction of the inner mitochondrial membrane potential established by the proton pump. This change is expected to decrease the driving force for Ca$^{2+}$ influx, therefore attenuating [Ca$^{2+}$]$_m$ overload under conditions (such as I/R) in which cytosolic calcium is increased. (7)

FIGURE 3: Infarct size reduction by ischemic and isoflurane preconditioning. (11)
Preconditioning with sevoflurane (SPC) Decreases $[\text{Ca}^{2+}]_i$ and $[\text{Ca}^{2+}]_m$ During I/R

$[\text{Ca}^{2+}]_i$ overload during myocardial I/R comes largely from extracellular $\text{Ca}^{2+}$ via $\text{Na}^+\text{-Ca}^{2+}$ exchanger. However, mitochondria have distinct pathways for $\text{Ca}^{2+}$ influx and efflux. The mitochondrial membrane potential driven uniporter is the primary influx pathway for calcium, whereas the mitochondrial permeability transition pore and $\text{Na}^+\text{-Ca}^{2+}$ exchanger are the main efflux pathways in mitochondria. Studies in adult hearts have shown that $[\text{Ca}^{2+}]_i$ overload is closely correlated with myocardial damage and cell death. (8)

SPC Preserves High-Energy Phosphates and Contractile Function and Decreases Myocardial Injury During Reperfusion

Although the above-described alterations in ion homeostasis are vitally important, changes in energy metabolism may also have an important role in the development of irreversible myocyte injury during I/R. It is generally accepted that I/R injury profoundly disrupts mitochondrial energy metabolism, and numerous studies have shown that mitochondria isolated from I/R hearts manifest reduced function, decreased membrane potential, and respiratory impairment.

Inhibition of Mitochondrial $K_{\text{ATP}}$ Channels Blunts the Protective Effects of SPC on $[\text{Ca}^{2+}]_i/[\text{Ca}^{2+}]_m$ During I/R

It has been suggested that the activation of the mitochondrial $K_{\text{ATP}}$ channels has an important role in myocardial protection during IPC and SPC. One mechanism could be the opening of mitochondrial $K_{\text{ATP}}$ channels which reduces the driving force for $\text{Ca}^{2+}$ influx, thus attenuating $[\text{Ca}^{2+}]_m$ overload and preserving mitochondrial respiration and ATP synthesis. Studies in newborn hearts support the previous findings in adult hearts using either IPC or SPC, indicating that similar mechanisms are operative, independent of age. (8)
One interesting finding from these studies is that 5-HD had its greatest effect on mitochondrial \([\text{Ca}^{2+}]\) during ischemia, essentially abolishing the effect of SPC, whereas the effect on cytosolic \([\text{Ca}^{2+}]\) was only partial. The concurrence of the effect of 5-HD on mitochondrial \([\text{Ca}^{2+}]\) with changes in ATP, CK release, and function suggest that the accumulation of calcium by mitochondria, rather than in the cytosol, is a key event in determining cellular injury and survival. However, there is no proof of a causal role of higher \([\text{Ca}^{2+}]_m\) in mediating injury in this setting. (11)

Insulin secretagogues (sulfonylureas and glinides) increase insulin secretion by closing the ATP-sensitive K\(^+\) channel (K\(_{\text{ATP}}\) channel) in the pancreatic ß-cell membrane. K\(_{\text{ATP}}\) channels subserve important functions also in the heart. First, K\(_{\text{ATP}}\) channels in coronary myocytes contribute to the control of coronary blood flow at rest and in hypoxia. Second, K\(_{\text{ATP}}\) channels in the sarcolemma of cardiomyocytes (sarcK\(_{\text{ATP}}\) channels) are required for adaptation of the heart to stress. In addition, the opening of sarcK\(_{\text{ATP}}\). (9)

Volatile anesthetic-induced preconditioning in CABG surgery

Volatile anesthetics are well suited to preconditioning during the operative period as they can be administered via the ventilator or the cardiopulmonary bypass oxygenator. Only a few, small studies have investigated the preconditioning effects of volatile anesthetics in human myocardium. So far, three studies have evaluated the preconditioning effects of isoflurane and one the effects of enflurane on either post-ischemic cardiac dysfunction or the release of cardiac injury markers in patients undergoing CABG surgery under cardioplegic arrest. A small study compared sevoflurane with propofol anesthesia in CABG patients and found improved postoperative myocardial function in the sevoflurane patients. This study of only 20 patients further claimed that sevoflurane would decrease the release of cardiac troponin I, which is surprising
considering the marked variability between patients and the large number of surgical techniques. Nonetheless, pharmacological induction of preconditioning, in contrast to classic ischemic preconditioning, would be desirable, specifically in high-risk patients such as CABG surgery patients, in whom an ischemic-type of preconditioning may further jeopardize diseased myocardium. Tomai and colleagues gave isoflurane for 15 min at 1.5 vol/vol % through the ventilator followed by a washout period of 10 min before starting cardiopulmonary bypass. No differences in hemodynamic variables, such as cardiac index and left ventricular ejection fraction, were found between control and preconditioned groups. However, a decrease in postoperative phosphocreatine kinase MB and troponin I release could be detected in patients with a poor preoperative left ventricular ejection fraction (<50%). Conversely, when administering isoflurane 0.5–2 vol/vol % shortly before cardiopulmonary bypass through the ventilator, Haroun-Bizri and colleagues demonstrated improved hemodynamic recovery and decreased ST-segment changes, but no reduction in dysrhythmias in the immediate reperfusion period. Administration of isoflurane 2.7 vol/vol % for 5 min on established cardiopulmonary bypass followed by a 10-min washout period before aortic cross-clamping only showed a tendency to lower phosphocreatine kinase MB isoenzyme and troponin I release (not statistically significant). Penta de Peppo and colleagues applied enflurane 1.3 vol/vol % over 5 min immediately before cardiopulmonary bypass. Preconditioning afforded increased left ventricular contractility, but no decrease in perioperative phosphocreatine kinase MB isoenzyme or cardiac troponin T release was noted. As raised concentrations of myocardial enzymes after CABG surgery can occur from cannulation of the right atrium, cardioplegia, inadequate delivery of cardioplegia in the presence of stenosis or hypertrophy, vigorous manipulations of the heart, prolonged surgery and differences in surgical techniques, they may not properly reflect the protection afforded by preconditioning. (10)
Collectively, these data provide some evidence that volatile anesthetics may protect human hearts by anesthetic preconditioning. (14)

Preconditioning by anesthetics represents a promising new therapeutic strategy in patients undergoing PTCA, CABG surgery (including off-pump procedures) or valve replacement, and in the preservation of donor hearts. Pharmacological preconditioning may even exert better protection than ischemic preconditioning. However, in short surgical procedures with optimal cardioplegic protection or short ischemic periods, loss of function and cell death may be negligible. Furthermore, it remains to be established whether diseased and aged myocardium can be preconditioned in the same manner as healthy myocardium. Although it is possible to re-initiate preconditioning once it has worn off, there is currently sparse experimental evidence indicating that cardiac tissue can be constantly maintained in a protective preconditioned state. Dana and colleagues showed in a rabbit model that repeated administration of an adenosine receptor agonist, with a 48-h interval schedule, can maintain the heart in a protective state against myocardial infarction with no evidence of tachyphylaxis. However, continuous stimulation of the preconditioning mechanism may lead to tachyphylaxis. In this regard, late preconditioning may be more attractive, though less effective. Late preconditioning has been demonstrated for opioids, but not for volatile anesthetics. Moreover, silent ischemia, overt angina or warm-up angina may already precondition high-risk cardiac patients and thereby abrogate the beneficial effects of pharmacological interventions. Recently, Aitchison and colleagues presented experimental evidence that there may exist an ‘anti-preconditioned’ state of the myocardium. By means of pre-ischemic transient \( \kappa_1 \)-opioid receptor stimulation in isolated
perfused rat hearts, a sizeable increase in infarct size compared with ischemia alone was achieved. This observation implies that transient receptor stimulation may make the heart more vulnerable to necrosis (‘death memory’ vs ‘survival memory’ by preconditioning). The discovery of pro-injurious anti-preconditioning effects opens up a fascinating field for future studies in experimental and clinical cardioprotection. Some of the commonly used perioperative medications may induce anti-preconditioning in cardiac tissue and thereby affect outcome. Prophylactic treatment with pharmacological preconditioning should be used with extreme care. The combination of ischemic preconditioning and antecedent prophylactic treatment with nicorandil can abolish the protection afforded by ischemia in human trabeculae, and halothane can inhibit the effects of hypoxic preconditioning. No direct extrapolation should be made from theoretical experimental knowledge, and the effects of each preconditioning protocol need to be evaluated in randomized controlled trials.

**Conclusions**

Cardiac preconditioning is an area of basic research with clinical relevance. Human myocardium is amenable to this form of protection. Although the key signaling steps and ultimate cellular protective mechanisms underlying cardiac preconditioning have been unravelled, many questions remain unresolved, particularly with respect to the aged and diseased myocardium. The concept that many anesthetics interact with the endogenous cardioprotection elicited by preconditioning should be considered carefully in experimental and clinical medicine. Although there is some promising evidence that anesthetic preconditioning may improve the perioperative cardiovascular outcome in patients at high risk of cardiovascular complications, its definitive role in clinical practice needs to be established in randomized controlled clinical trials.
References:

1. Andriy Babsky*, Shahryar Hekmatyar*, Suzanne Wehrli†, Nicolai Doliba†, Mary Osbakken†,§ and Navin Bansal*†
   Influence of Ischemic Preconditioning on Intracellular Sodium, pH, and Cellular Energy Status in Isolated Perfused Heart


5. Steenbergen C, Perlman ME, London RE, Murphy E.

6. Chun-Mei Cao, Qiang Xia, Qin Gao, Mai Chen, and Tak-Ming Wong

   Calcium-Activated Potassium Channel Triggers Cardioprotection of Ischemic Preconditioning.

   Journal of Pharmacology And Experimental Therapeutics Fast Forward
   First published on September 2, 2004; DOI: 10.1124/jpet.104.074476
7. Raphael, Jacob M.D.; Zuo, Zhiyi M.D., Ph.D.; Abedat, Suzan M.Sc.; Beeri, Ronen M.D.; Gozal, Yaacov M.D.

Isoflurane Preconditioning Decreases Myocardial Infarction in Rabbits via Up-regulation of Hypoxia Inducible Factor 1 That Is Mediated by Mammalian Target of Rapamycin

Anesthesiology:
doi: 10.1097/ALN.0b013e318164cab1
Laboratory Investigations

8. Hong Liu, MD*, Lianguo Wang, MD†, Matt Eaton, BS‡, and Saul Schaefer, MDAnesth Analg 2005;101:349-355
Sevoflurane Preconditioning Limits Intracellular/Mitochondrial Ca^{2+} in Ischemic Newborn Myocardium
International Anesthesia Research Society

From the Department of Pharmacology and Toxicology, Medical Faculty, University of Tübingen, Tübingen, Germany

10. Ferdinandy, R. Schulz, and G. F. Baxter
Interaction of Cardiovascular Risk Factors with Myocardial Ischemia/Reperfusion Injury, Preconditioning, and Postconditioning
11. E. Lucchinetti, M. Jamnicki, G. Fischer, and M. Zaugg
Preconditioning by Isoflurane Retains Its Protection Against Ischemia-Reperfusion Injury in Postinfarct Remodeled Rat Hearts

12. S. R. Walsh¹,*, T. Tang¹, U. Sadat¹, D. P. Dutka² and M. E. Gaunt

Cardioprotection by remote ischaemic preconditioning†
British Journal of Anaesthesia 2007 99(5):611-616;
journals.permissions@oxfordjournals.org
†

13. J Chun-Mei Cao, Qiang Xia, Qin Gao, Mai Chen, and Tak-Ming Wong.
Calcium-Activated Potassium Channel Triggers Cardioprotection of Ischemic Preconditioning
Journal of Pharmacology And Experimental Therapeutics Fast Forward First published on September 2, 2004; DOI:
10.1124/jpet.104.074476

14. M. Zaugg¹³, E. Lucchinetti³, C. Garcia¹, T. Pasch¹, D. R. Spahn² and M. C. Schaub³

Anaesthetics and cardiac preconditioning. Part II. Clinical implications
British Journal of Anaesthesia, 2003, Vol. 91, No. 4 566-576
15. Cuihong Han *,†,1, Li Lin ‡,1, Weidong Zhang *, Li Zhang *, Shijun Lv *, Qiang Sun †, Hengyi Tao †, John H. Zhang § and Xuejun Sun †
Hyperbaric Oxygen Preconditioning Alleviates Myocardial Ischemic Injury in Rats Online ISSN 1471-6771 - Print ISSN 0007-0912