

# Anesthetics and cardioprotection

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## ABSTRACT

*The prevalence of the cardiovascular disease significantly affects the outcome of both cardiac and non-cardiac surgery, and perioperative cardiac morbidity is one of the leading causes of death following anesthesia and surgery. The considerable incidence of myocardial infarction, congestive heart failure, myocardial ischemia, or serious dysrhythmias during the intraoperative or postoperative periods, has led many studies to examine medical factors and interventions for decreasing cardiac risk in patients with cardiovascular disease. An extensive amount of work has focused on whether any one anesthetic agent or technique is particularly beneficial for patients with coronary artery disease. Experimental studies conducted in our laboratory have clearly shown that volatile anesthetics may exert profound cardioprotection against myocardial ischemia and reperfusion injury. This article examines the recent evidence about the importance of mitochondria, reactive oxygen species and the  $K_{ATP}$  channels in cardioprotective signaling by volatile anesthetics. Moreover, the article addresses current concepts and controversies regarding specific roles of the mitochondrial and the sarcolemmal  $K_{ATP}$  channels in anesthetic-induced preconditioning.*

**Key words:** preconditioning, volatile anesthetics, heart, coronary disease, ischemia, myocardial infarction, mitochondria.

The cardiac tissue is very sensitive to hypoxia and short periods of ischemia, and could lead to extensive and permanent tissue death. Interestingly, short periods of ischemia (ischemic preconditioning-IPC) can lead to a reduced severity of cardiac injury. IPC has been studied extensively for the past two decades and has resulted in the publication of many studies, which have significantly increased our understanding of the cellular mechanisms of ischemia and reperfusion injury. IPC was initially described in 1986(1) by Murray et al, who

demonstrated that four 5-min periods of coronary artery occlusion interspersed with 5 min periods of reperfusion before a prolonged coronary occlusion produced a reduction in myocardial infarct size in dogs. Preconditioning could also be induced in humans undergoing percutaneous transluminal coronary angioplasty with a coronary occlusion of 2 min duration.(2) Many studies have shown that volatile anesthetics may precondition the myocardium against ischemia and infarction by activating the protective cellular mechanisms. This phenomenon was termed the anesthetic-induced preconditioning (APC). The cellular signaling of APC involves protein kinase C, protein tyrosine kinase, mitogen-activated protein kinases, protein

kinase B and the mitochondria. Finally, APC involves ion channels, in particular the mitochondrial and the sarcolemmal  $K_{ATP}$  channels. The mechanisms involved in APC have been a subject of several detailed review articles(3-12). Myocardial protection by volatile anesthetics is of clinical importance for patients with coronary artery disease because of their high morbidity and because of their mortality that is secondary to perioperative myocardial ischemia. The potentially beneficial effects of APC in patients have also been reported.(4,5,13-17) Initially, the mechanisms by which volatile anesthetics exert protective actions on ischemic myocardium have previously been attributed to an improvement in the relation between myocardial oxygen

supply and demand. For instance, our research has reported that volatile anesthetics are negative inotropes that decrease left ventricular contractility and depress sino-atrial nodal function. These actions decrease myocardial oxygen demand.(18,19) Although a portion of the cardioprotective effects of volatile anesthetics following ischemia and reperfusion demonstrated in our laboratory may be attributed to a reduction in energy requirements and ultimate preservation of energy-dependent vital cellular processes, other studies have demonstrated this not to be necessary for cardioprotection. For example, volatile anesthetics could exert cardioprotective effects even when administered during cardioplegic arrest and at reperfusion. Many components of the signaling pathway leading to cardioprotection are shared by ischemic and anesthetic preconditioning. Our laboratory and other studies have identified a signaling cascade that involves ROS, G-protein coupled receptors, protein kinases and ATP-sensitive potassium ( $K_{ATP}$ ) channels.(11,12,20-50)

Volatile anesthetics are very powerful agents in reducing infarct size and the ATP-sensitive potassium ( $K_{ATP}$ ) channels have long been considered essential components of cardiac preconditioning. There are two types of  $K_{ATP}$  channels in cardiac myocytes: the mitochondrial (mito $K_{ATP}$ ) channel which is located in the inner mitochondrial membrane, and the sarcolemmal (sarc $K_{ATP}$ ) channel which is located in the plasma membrane. After the discovery of the mito $K_{ATP}$  channels in the inner mitochondrial membrane and development of selective mito and sarc $K_{ATP}$  channel inhibitors, evidence suggested that mito $K_{ATP}$  channels rather than the sarc $K_{ATP}$  channels may play a more important role in cardioprotection. However, some of the recent studies that involved the use of sarc $K_{ATP}$ -specific inhibitors and genetic models of disrupted or knocked-out sarc $K_{ATP}$  channel subunits indicated that the role of sarc $K_{ATP}$  channel in cardioprotection should not be ignored.(51,52)

We have demonstrated that isoflurane can stimulate  $K_{ATP}$  channels in isolated ventricular myocytes.(20,40,41,48,49,53,54) In addition, our laboratory has shown that the  $K_{ATP}$  channel agonist pinacidil exerts greater effects to open the  $K_{ATP}$  channel in myocytes that were previously subjected to isoflurane. We also found that isoflurane may diminish the sensitivity of the  $K_{ATP}$  channels to inhibition by ATP and; therefore, increase the open state probability of the channel.(54) Recent findings suggest that an opening of the mitochondrial  $K_{ATP}$  channels is critically involved in IPC and induces reversible oxidation of mitochondria matrix.(55-59) Because the opening of mitochondrial  $K_{ATP}$  channels can dissipate the inner mitochondrial membrane potential established by the proton pump, our laboratory examined the effects of anesthetics on mitochondrial redox state by recording the fluorescence of FAD-linked enzymes. Our results indicate that isoflurane and sevoflurane dose-dependently increase the flavo-protein fluorescence.(29,30,34,35) Additional studies are being conducted in our laboratory to examine the human cardiac  $K_{ATP}$  channels using the artificial lipid bilayer.(60)

We have also examined the role of A<sub>1</sub>-receptor stimulation in the enhancement of recovery of contractile function of stunned myocardium by isoflurane.(61) These and other studies suggest that isoflurane either directly activates A<sub>1</sub> receptors or indirectly enhances the sensitivity of A<sub>1</sub>-receptors to reduced amounts of endogenously released adenosine.(62) This protection could be reversed by adenosine receptor antagonists, by G<sub>i</sub> protein blockers, PKC inhibitors, and  $K_{ATP}$  channel blockers. Therefore, it may be assumed that inhalational anesthetics could stimulate these receptors, proteins and signal transduction pathways including the  $K_{ATP}$  channels. Because our research has demonstrated that cardioprotection by anesthetics is not accompanied by augmented release of adenosine, it could be postulated that these receptor signal transduction pathways and  $K_{ATP}$

may be sensitized to the subsequent protein/channel modulators.

While it is evident that mitochondria play a crucial role in the phenomenon of anesthetic preconditioning, our most recent studies indicate that both the sarc $K_{ATP}$  and the mito $K_{ATP}$  channels are essential for the protection of myocytes from damage by oxidative stress since their inhibition completely abolished the protective effects of isoflurane preconditioning. Specifically, activation of the sarc $K_{ATP}$  channel was required for the cardioprotective effects of APC during the stress period but not during the preconditioning period. In contrast, activation of mito $K_{ATP}$  channel was found to be necessary during both isoflurane preconditioning and during exposure to oxidative stress. From these results it appears that although activation of both channels is important for the cardioprotective effects of preconditioning, each channel performs a distinct role: the sarc $K_{ATP}$  channel acts as an effector, while the mito $K_{ATP}$  channel plays a dual role as a trigger and an effector. The role of the mito $K_{ATP}$  channel as both a trigger and an effector, and the sarc $K_{ATP}$  channel as the effector of preconditioning could be explained by the following sequence of events: 1. Exposure to isoflurane can directly activate mito $K_{ATP}$  channels resulting in changes in the mitochondrial bioenergetics producing a small burst of ROS. 2. The ROS can activate cytosolic mediators such as PKC that translocate to the sarcolemma and phosphorylate the sarc $K_{ATP}$  channel and sensitize it to opening. 3. The primed sarc $K_{ATP}$  channel opens sooner during subsequent metabolic stress resulting in a greater  $K^+$  efflux, a more rapid repolarization of the cell membrane and action potential shortening, which leads to a decrease in cytosolic  $Ca^{2+}$  loading during ischemia/reperfusion. This can reduce or prevent mitochondrial  $Ca^{2+}$  overload, a major trigger of the cell death pathway. 4. The mito $K_{ATP}$  channel can also open during ischemia/reperfusion which may result in the depolarization of the inner mitochondrial membrane and thus further decrease driving force

for the mitochondrial  $\text{Ca}^{2+}$  entry and loading during ischemia/reperfusion.

## Conclusion

Results from our and other laboratories indicating that volatile anesthetics protect ischemic myocardium are important and clinically significant for patients with

coronary artery disease. It is very clear that their morbidity and mortality that is secondary to perioperative myocardial ischemia is disproportionately high. It is well documented that anesthetic preconditioning occurs and myocardium can be rendered resistant to ischemia and reperfusion injury for a prolonged

period after a prior, brief exposure to a volatile anesthetic. Anesthetic-induced protection has many similarities to ischemic preconditioning including a window of protection that has also been confirmed in patients undergoing coronary bypass graft and other surgeries.

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