Ischemic And Anesthetic Preconditioning Of The Heart: An Insight Into The Concepts And Mechanisms

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Abstract

Myocardial Preconditioning is the exposure of myocardial tissue to brief, repeated periods of vascular occlusion in order to render the myocardium resistant to the deleterious effects of prolonged episodes of ischemia or reperfusion. The period of pre-exposure and the number of times the tissue is exposed to ischemia and reperfusion vary, the average being 3 to 5 minutes. Ischemic preconditioning was first described more than a decade ago by Murray et al (1). They demonstrated a 75% reduction in infarct size caused by a 40 min coronary artery occlusion, when the occlusion was preceded by four episodes of 5 min ischemia and 5 min of reperfusion. This phenomenon has been described extensively not only in experimental animals but also in humans and has been responsible for an enormous amount of research over the last 15 years.

INTRODUCTION TO MYOCARDIAL PRECONDITIONING

Myocardial Preconditioning is the exposure of myocardial tissue to brief, repeated periods of vascular occlusion in order to render the myocardium resistant to the deleterious effects of prolonged episodes of ischemia or reperfusion. The period of pre-exposure and the number of times the tissue is exposed to ischemia and reperfusion vary, the average being 3 to 5 minutes. Ischemic preconditioning was first described more than a decade ago by Murray et al ([1]). They demonstrated a 75% reduction in infarct size caused by a 40 min coronary artery occlusion, when the occlusion was preceded by four episodes of 5 min ischemia and 5 min of reperfusion. This phenomenon has been described extensively not only in experimental animals but also in humans and has been responsible for an enormous amount of research over the last 15 years. Ischemic preconditioning not only reduces the size of infarct but also protects the heart against post-infarction left ventricular dysfunction ([2,3,4]) and ventricular arrhythmias ([5,6]).

MECHANISMS UNDERLYING ISCHEMIC 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 ([7,8]), adenosine receptors ([9,10,11]), nitric oxide (NO) ([12,13,14]), heat shock proteins (HSP) ([15,16,17]), the epsilon isoform of protein kinase C (PKC) ([18,19,20]), mitogen-activated protein kinases (MAPK) ([21,22,23]), the mitochondrial ATP-dependent potassium (K+(ATP)) channels ([24,25,26]), as well as others, including a paradoxical protective role of oxygen free radicals ([27,28]).

It is believed that ischemia induced release of endogenous agents such as adenosine and nitric oxide (NO), activation of adenosine receptors, protein kinase C (PKC), mitogen-activated protein kinases (MAPK) and opening of ATP-sensitive mitochondrial potassium (K+(ATP)) channels are the potential mechanisms of this preconditioning phenomenon.

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 ([29]). 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 ([29,30,31]). In the second window of protection (SWOP), the origin of nitric oxide is attributed to the activity of an endothelial Nitric Oxide Synthase (eNOS) ([13,14]). Adenosine-induced preconditioning involves p38 MAP kinase, and mitochondrial K+(ATP) channels ([7,32]). Recently, it has been suggested that the K+ (ATP) channels involved in the protection are mitochondrial rather than sarcolemmal ([24,26]).

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 ([31]). 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 ([50,51]). The stress inducible HSP70.1 and 70.3 mediate second window of protection (SWOP) ([15,16]), but the exact signaling pathway of this response is still under investigation.

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 ([33]). Halothane ([34,35]), Desflurane ([35]), Isoflurane ([34,35,36,37,38,39]), and sevoflurane ([35,40]) have been extensively studied and these studies reveal promising results with potential clinical implications.

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+(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+(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+(ATP) channels ([39,41,42,43,44]), by stimulation of adenosine receptors ([45]) and subsequent activation of protein kinase C (PKC) ([46,47]) and by increased formation of nitric oxide ([48]) and free oxygen radicals ([47,49]). Activated PKC then amplifies the preconditioning stimulus and by phosphorylation, stabilizes the open state of the mitochondrial K+(ATP) channel (which is believed to be the main end-effector in anesthetic preconditioning) and the sarcolemmal K+(ATP) channel. The opening of K+(ATP) channels ultimately confers cytoprotection by decreasing cytosolic and mitochondrial Ca (2+) overload ([50,51]).

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