

Molecular Mechanisms of Cell Adaptation to Hypoxia and the Role of Ischemic and Anesthetic Preconditioning. Implications for the Anesthetist

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ABSTRACT

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Cell protection against hypoxia can be mediated by brief periods of sublethal ischemia, a phenomenon called 'preconditioning'. The molecular mechanisms that are responsible for cell protection are extremely complicated; however, extensive research in molecular biology and cellular physiology has uncovered many different signaling pathways, especially in cardiac tissues. Except for ischemia, it seems that many anesthetic medications, such as volatile anesthetics and opioids, can induce or alter different signaling cascade reactions associated with cell rescue from oxygen lack. The above phenomenon is called anesthetic preconditioning and is considered to be highly cardio-protective.

Several experimental and clinical studies have shown that specific biochemical and molecular pathways are involved in cell tolerance to acute and chronic oxygen lack. Hypoxic states of the human tissue belongs to the most frequent and dangerous diseases of modern times. They result from disturbed oxygen supply to cells, which is insufficient to meet their metabolic demands. Tissue protection against prolonged ischemia and hypoxia can be mediated by brief periods of sublethal ischemia, a phenomenon called 'preconditioning'. This protective adaptive mechanism is inherent to all tissues with high energy

consumption and aims in increasing cell survival in response to temporal shortage of nutrient supply and repetitive noxious stimuli. Except for ischemic preconditioning, different medications have been associated with pharmacological-induced preconditioning, especially in cardiac tissue. Particularly, there is substantial evidence that volatile anesthetics and opioids mediate similar cytoprotective mechanisms through different signaling cascade alterations. The aim of this review is 1) to focus on basic biochemical pathways being involved in cells suffering from oxygen lack and rescue mechanisms that are activated during pharmacological preconditioning and 2) to discuss experimental and clinical studies that provide evidence for perioperative anesthetic-induced preconditioning.

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Molecular mechanisms of ischemic and anesthetic preconditioning

Ischemic preconditioning is associated with two forms of protection, a first window lasting approximately 2-3 hours after ischemia has been preconditioned and a second window of protection (SWOP), that is induced 1 day after the first trigger and lasts 2-3 days [1,2].

1. Pathogenesis of ischemic preconditioning- The role of mitochondria

Mitochondria are the site of biochemical processes strictly involved in the cellular survival or death in conditions of hypoxia-mediated oxidative stress. All major biochemical and metabolic alterations activate specific signal transduction pathways which stimulate the nuclear response to oxidative injury. In the last years it has been assumed that a so called 'oxygen sensor' would be involved in the mitochondrial response to chronic and acute hypoxia [3]. There is substantial evidence implicating mitochondrial electron transport enzyme complexes (ETC) as the specific target of molecular oxygen altered availability [4]. The cytochrome oxidase that gives electrons from cytochrome c to oxygen is prone to morpho-functional adaptation to altered oxygen concentrations. In the first place, hypoxia inhibits electron transport chain at the inner membrane of the mitochondria. As a result, the lack of oxygen inhibits the transport of protons and thereby causes a decrease in the membrane potential. The final result is a reduced ATP synthesis, with a parallel hyperpermeability of the inner mitochondrial membrane, which leads to the release of Ca^{++} (membrane permeability transition pore-MPTP) and cytochrome c, through activation of the proteins Bax or Bak. The above mechanism can activate different enzymes called caspases which are involved in programmed cell death (apoptosis) [6,7]. In addition to energy deprivation, reactive oxygen species (ROS) generation contributes to hypoxia induced apoptosis [8]. In contrast to the proapoptotic effects of hypoxia, cells can become resistant to apoptosis during hypoxia. It is assumed that the translocation of the pro-

apoptotic protein Bax to the mitochondria is inhibited. At the same time, oxygen lack through ROS generation activates the transcription factor 'nuclear factor kB' (NF-kB) which induces an augmented production of the protein 'inhibitor of apoptosis protein 2' (IAP-2) [9,10].

Despite the above mechanisms of cell injury, brief (3-5 minutes) and repeated periods of ischemic hypoxia stimulate adaptive responses to hypoxic cells. Oxidative stress and increase in Ca^{++} concentrations during hypoxia and/or ischemia stimulate endothelial nitric oxide (NO) production, especially during the second window of protection (late preconditioning). Because of its gaseous nature, NO diffuses into the cell mitochondria and binds to the reduced form of cytochrome a_3 . This is the same site and the same form of the enzyme to which oxygen binds. As a result, cytochrome oxidase activity is inhibited while this inhibition is competitive with oxygen and reversible when oxygen concentrations are restored. In conclusion, the hypoxia induced NO generation and the subsequent cytochrome partial inhibition leads to a metabolic adaptation of the enzyme to the lower molecular oxygen availability. This mechanism can be considered as a limiting factor in the hypoxia-induced ROS mitochondrial generation [11-13]. At the same time, there is a down regulation of Na/K ATPase activity in order to sustain a reduced energy turnover state. The above large scale drop in Na/K ATPase activity (10%) does not alter electrochemical gradients due to a similar decrease in cell membrane permeability (channel arrest) [14].

Except for NO generation, ischemic preconditioning induces the release of adenosine nucleotide in cytosol with consequent adenosine A1 receptors stimulation. Adenosine and NO play a crucial role in the translocation and activation of membrane protein-kinase C (PKC), especially during the second window of preconditioning. In the inactive state, PKC is only loosely associated with membrane lipids. Activation results in PKC membrane association. During hypoxia all damaging fac-

tors (oxidants generation, ATP depletion, Ca⁺⁺ overload) activate the PKC isoform which phosphorylates serine and threonine groups in mitochondrial membrane channel proteins, leading to activation of ATP sensitive potassium (K⁺_{ATP}) channels. A number of reports suggest that these channels play an essential role in cell adaptation to hypoxic states [15-17]. The activation of sarcolemmal and mitochondrial K⁺_{ATP} channels results in a shortening of the action potential duration (APD) with significant reduction of Ca⁺⁺ in-

flux and attenuation of mitochondrial Ca⁺⁺ overload. It seems relevant to underlie that it is more and more evident that hypoxia induced endogenous NO generation is implicated in opening of K⁺_{ATP} channels. The above mechanisms seem very important for cardio-protection and limiting infarct size during chronic hypoxia [18,19]. However, it appears that cardio-protective mechanisms are species-dependent. Another possible link between hypoxia and opening of K⁺_{ATP} channels, especially in cardiac cells, seems to incorporate

Table 1. Different effects of medications on cardiac preconditioning (38)

Preconditioning ↑	Preconditioning ↓
Adenosine receptor agonists	Adenosine receptor antagonists (theophylline, minophylline)
K ⁺ _{ATP} channel openers (nicorandil, levosimendan, diazoxide) and uncouplers of oxidative phosphorylation (bupivacaine, ropivacaine, non-steroid anti-inflammatory drugs-NSAIDs)	K ⁺ _{ATP} channel blockers (sulfonylurea analogs, lidocaine)
Opioid agonists (morphine, fentanyl)	Opioid antagonists (naloxone)
β-adrenoreceptor agonists (isoproterenol, norepinephrine, epinephrine)	β-adrenoreceptor antagonists
α ₁ adrenoreceptor agonists (phenylephrine, norepinephrine)	α ₁ adrenoreceptor antagonists (phentolamine)
M ₂ muscarinic receptor agonists (acetylcholine esterase inhibitors)	M ₂ muscarinic receptor antagonists (atropine)
Nitric oxide releasers (nitroglycerine, nitroprusside)	Nitric oxide scavengers (vitamin E)
Ca ⁺⁺	Ca ⁺⁺ channel blockers (nifedipine)
B ₂ bradykinin receptor agonists (angiotensin converting enzyme inhibitors: captopril, enalapril)	
AT ₁ receptor antagonists	Digoxin
Statins	Aprotinin
Flumazenil	Cyclooxygenase-2 (COX-2) inhibitors
Amrinone	

ROS generation [20].

2. Changes in gene expression: HIF-1 and other factors

Other key mechanisms of cell adaptation to hypoxia include more permanent alterations of metabolic functions through different gene elements regulation. The most significant regulator of oxygen homeostasis is the hypoxia-inducible factor 1 (HIF-1). Its activity is induced by oxygen lack in all nucleated cell types via a novel posttranslational mechanism and plays critical roles in the responses of the cardiovascular and respiratory systems to hypoxia. HIF-1 is a heterodimeric protein composed of HIF-1 α and HIF-1 β subunits. HIF-1 α regulates the transcription of an extensive repertoire of genes, including many involved in angiogenesis and vascular remodeling, erythropoiesis, metabolism, apoptosis, control of ROS, vasomotor reactivity and vascular tone and inflammation [21]. HIF-1 α alters the transcription of these genes by dimerizing with the aryl hydrocarbon nuclear translocase (ARNT or HIF-1 β) and then binding to specific hypoxia response elements (HREs) in their regulatory regions. The final response is transcriptional activation. Under normoxic conditions, HIF-1 α undergoes propyl-hydroxylation, which produces a binding site being recognized by the von Hippel-Lindau protein (VHL). VHL is a subunit in an E3 ubiquitin ligase complex that polyubiquitinates HIF-1 α , thus targeting it for rapid destruction by the proteasome. When oxygen is less abundant, propyl-hydroxylation does not occur and consequently VHL does not bind to HIF-1 α . As a result, HIF-1 α associates with ARNT, binds the HRE in hypoxia-responsive genes and alters their transcription [22,23].

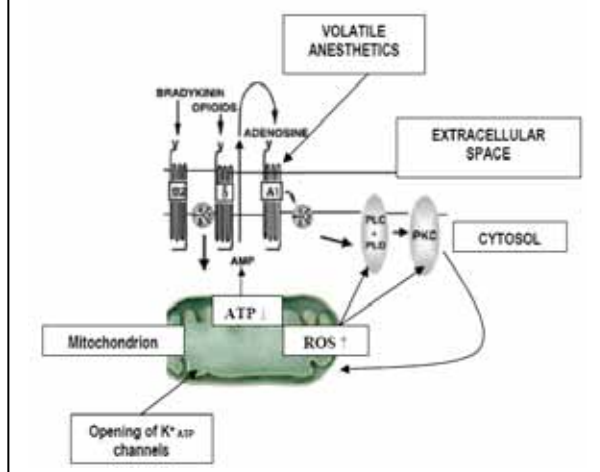
HIF-1 α can result in apoptosis by stabilizing the product of the tumour suppressor gene p53. This protein induces apoptosis by regulating Bax protein activity [10]. However, not only apoptotic but also necrotic cell death is induced during hypoxia, as a result of NF- κ B induction. It has been demonstrated that hypoxia acts via a signalling pathway common to that used by TNF and IL-1. Both these

cytokines transmit signals through the sphingomyelin (SM)-ceramide cycle, in which ceramide is generated from membrane SM with eventual activation of different kinases and phospholipases, and with final activation of NF- κ B production [24]. This factor leads to transcription of target genes that encode pro-inflammatory cytokines (interleukins 6 and 8, TNF- α). In parallel, NF- κ B inhibits programmed cell death via overexpression of the anti-apoptotic factor bcl-2 [24].

3. Mechanisms of anesthetic preconditioning - experimental studies

Strong evidence supports the preconditioning effects, especially in cardiac tissues, of volatile anesthetics, among other medications (Table 1). Isoflurane has been shown to reduce the infarct size in canine models of myocardial injury in vivo. Different studies demonstrate that isoflurane is capable of preconditioning rabbit and human myocardium whereas halothane can precondition only rabbit myocardial tissue [25]. It seems that ischemic and anesthetic pre-conditioning share common pathophysiological mechanisms (Figure 1) [26]. Toller et al have shown that both mitochondrial and sarcolemmal K⁺_{ATP} channels are important in desflurane-

Figure 1. A schematic depiction of preconditioning mechanisms. Different agonists of adenosine, bradykinin and opioid receptors, such as volatile anesthetics, trigger PKC which activates subsequently K⁺_{ATP} channels in the mitochondria. At the same time, ROS and AMP generation due to ATP depletion acts via the same signaling pathways.



induced preconditioning through alterations of mitochondrial Ca^{++} handling and ROS production [27]. It has been also demonstrated that volatile cardioprotective mechanisms were attenuated by adenosine A_1 receptor antagonists and PKC inhibitors. In addition, the activation of G_i proteins is implicated in isoflurane-induced preconditioning through inhibition of calcium entrance into the cytosol and reduction in the cAMP levels [28]. A growing body of evidence suggests that α_1 adrenoreceptors stimulation could mediate ischemic and desflurane-induced preconditioning in human myocardium, especially before ischemia, as desflurane has been shown to release intrinsic store of catecholamines in isolated rat and human myocardium [29,30]. Using DNA microarrays Lucchinetti et al studied transcriptional changes in isolated perfused rat hearts exposed to 40 minutes test ischemia, followed by 3 hours reperfusion, in response to anesthetic pre-conditioning. This was induced by 15 minutes of isoflurane 2.1 vol% followed by 10 minutes of washout [31]. It was shown that HIF-1, NF-kB and mitochondrial complexes I and III were downregulated, while the uncoupling protein (UCP), that is present in the inner membrane of mitochondria and bypasses ATP formation, was significantly overexpressed. This mechanism might be responsible for limiting the generation of ROS through uncoupling the respiration at complexes I and III and results in antioxidant defense. In addition, an anesthetic post-conditioning was induced by 15 minutes of isoflurane 2.1 vol% administered at the onset of reperfusion. This technique markedly increased the expression of many contractile proteins and gap junction proteins (connexins 32, 36 and 40) and reduced the inflammatory response, through a downregulation of different cytokines, chemokines and adhesion molecules. The same results were displayed by Zhong et al who studied different cytokines by Western blot analysis in similar experimental conditions, using sevoflurane-induced preconditioning [32]. In the above study it was also shown that volatile anesthetics attenuated the expression of inducible nitric oxide synthase

(iNOS), protecting the myocardium from ROS injury through inhibition of their interaction with NO and the subsequent production of the free radical peroxynitrate. At the same time, apoptosis of myocardial cells was markedly decreased due to an overexpression of the anti-apoptotic factor bcl-2.

Table 2. Anesthetic effects on mitochondrial and sarcolemmal K^+_{ATP} channels (38)

Anesthetic drug	Mitochondrial K^+_{ATP} channel activity	Sarcolemmal K^+_{ATP} channel activity
R-ketamine	↓	↓
S-ketamine	no effect	?
Propofol	no effect	no effect
Etomidate	no effect	?
Thiopental	↓	?
Midazolam	no effect	?

Except for volatile anesthetics, opioids have been linked to anesthetic preconditioning as well. Opioid receptors are present in cardiac myocytes whereas opioid agonists have been shown to protect the heart from ischemia through at least 2 mechanisms: 1) an increased production of inositol 1,4,5-triphosphate (IP_3) and a subsequent depletion of the sarcoplasmic reticulum from its calcium stores, leading to reduced cytosolic calcium accumulation during sustained ischemia and 2) an activation of PKC by diacylglycerol, that is formed from hydrolysis of membrane phospholipids in addition to IP_3 and the subsequent PKC-mediated opening of K^+_{ATP} channels [33]. Administration of morphine before an ischemic insult can mimic ischemic preconditioning while naloxone abolishes the above protective action [34]. Kato et al studied the effects of fentanyl on post-ischemic mechanical cardiac function and concluded that the heart was protected through fentanyl interaction with adenosine A_1 receptors and subsequent PKC and K^+_{ATP} channels stimulation [35]. Of the several known subtypes of opioid receptor agonists, δ opioid agonists seem to provide best protection against

ischemic injury while κ agonists appear to enhance cardiac ischemia [36].

Many anesthetics seem to prevent cardiac preconditioning (Table 2). Different studies have showed that barbiturates inhibit mitochondrial K^+_{ATP} channels while propofol, etomidate and midazolam have no effect on the above proteins and final myocyte survival in rat models [37].

anesthetic was administered for 5 minutes before aortic cross-clamp, followed by a 10 minute wash out period [39]. The major finding of this study was the higher 5-nucleotidase activity (an index of PKC activation) in the study cohort of patients. Pouzet et al studied the effects of preconditioning stimulus with sevoflurane in a similar patient population (study and control group=10 respectively) but without using a washout period [40].

Table 3. Clinical studies concerning volatile induced cardiac preconditioning (42)

Anesthetic agent	Protocol	Results
Isoflurane before aortic cross-clamp (2,5% MAC) <i>Reference 39</i>	Study group=10, Control group=10	Lower troponin I and CK-MB in study group (no statistical difference-NS) Higher PKC activity
Sevoflurane before aortic cross-clamp (2,5% MAC) <i>Reference 40</i>	Study group=10 Control group=10	Increased PKC activity
Sevoflurane before aortic cross-clamp (2% MAC) <i>Reference 41</i>	Study group=37 Control group=35	Decreased BNP release in study group
Enflurane before CPB <i>Reference 43</i>	Study group=8 Control group=8	Preserved cardiac function in study group
Isoflurane before CPB (1,5% MAC) <i>Reference 44</i>	Study group=20 Control group=20	Myocardial function similar between groups
Isoflurane before CPB (0,5-2% MAC) <i>Reference 45</i>	Study group=28 Control group=21	Better cardiac index in study group

Anesthetic preconditioning. Clinical studies

In contrast with the numerous experimental studies concerning anesthetic preconditioning, only a few clinical studies have addressed the potential cardioprotective impact of volatile anesthetics. This could be attributed to the standardized and reproducible way that is necessitated for an experimental protocol to be instituted, a situation that is only present in cardiac surgery.

Belhomme et al were the first who studied the preconditioning of isoflurane in 20 patients (control group=10, study group=10) undergoing cardiac surgery (Table 3), whereas the

Different enzymes, such as PKC were found increased in the study group but not in a significant way. In another study that included 37 cardiac surgery patients (study group=37, control group=35) Julier et al demonstrated significantly reduced levels of the brain natriuretic polypeptide (BNP), in the study group [41].

Since none of these studies addressed the issue of alterations in perioperative hemodynamic variables, Penta de Peppo et al used enflurane before cardiopulmonary bypass (CPB) in 16 patients (study group=8, control group=8) and determined pressure-area relations with the aid of transesophageal echo-

cardiography [43]. They showed that enflurane pretreatment preserved left ventricular function after CPB. The same group studied 40 patients using isoflurane preconditioning and their main results were that different hemodynamic variables such as cardiac index, left ventricular stroke work index and ejection fraction remained unchanged after CPB in both groups [44]. In another study Haroun-Bizri et al studied 49 patients (study group=28, control group 21) who were given also isoflurane (0.5-2%) before CPB. They concluded that the study group had a better cardiac index, but the need for inotropic support and the incidence of arrhythmias after release of aortic cross-clamp were similar between groups [45].

Although the above clinical studies have clearly indicated a protective role of volatile anesthetics in myocardium during coronary surgery, the impact of pharmacological preconditioning on postoperative morbidity and final outcome remains still unclear. Recently, in a large study including 320 cardiac patients it was demonstrated that the cohort that received volatile anesthetic regimens displayed a significant lower intensive care and hospital length of stay, compared with the group that received total intravenous anesthesia [46]. It seems that anesthetic preconditioning might have a positive impact in the vital functions of other organs, such as the kidney. Julier has noticed that sevoflurane preconditioning was associated with reduced release of cystatin C, a new marker of renal dysfunction [41].

Conclusions

Experimental and clinical studies have shown that all volatile anesthetic regimens, except for the already known indirect cardioprotective effects such as dose-dependent depression of myocardial function and subsequently oxygen demand, have also direct protective properties. The extensive research in molecular biology and cellular physiology has uncovered many cell protective mechanisms that are induced during hypoxia. The

ischemic and pharmacological preconditioning, that seem to share common signal transduction pathways, has been implicated in direct cardiac preservation after short periods of oxidative stress while different gene regulated elements can be altered by the above preventive tools. The potential clinical application of anesthetic preconditioning remains the subject of ongoing research. Many issues are still unresolved such as the differences between different volatile anesthetics, their interactions with other commonly used medications during general surgery, their impact on different than the heart organ protection, their optimal dose and the duration of administration. These issues need to be addressed by well designed, prospective and randomized studies in the near future.

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