Cardiac (Pre)Conditioning: Concepts, Mechanisms, Perspectives

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In 1986, Murry et al. (1) described for the first time ischemic preconditioning in canine myocardium. They subjected hearts to four brief ischemic episodes (by ligating the circumflex coronary artery) interspersed with 5-min periods of reperfusion before a sustained ischemic insult of 40 min. This "conditioning" reduced infarct size from 30% to 7% of the area at risk. Since then, ischemic preconditioning has been described in almost all species including humans. In 1993, Marber and Kuzuya reported for the first time on a second delayed window of protection occurring 12–72 h after application of the initial preconditioning stimulus [for review see Ref. (2)]. While early or classic preconditioning is predominantly based on multiple fast-acting intracellular phosphorylation signaling steps, the second window is a result of altered gene expression in response to changes in transcription factors (such as NF-κB), and depends on *de novo* protein expression. Pharmacological preconditioning by halogenated ethers (volatile anesthetics)—a safer way of eliciting protection—was independently reported in 1997 by Kersten et al. (3) and Cason et al. (4). Tonkovic-Capin et al. (5) subsequently described the occurrence of a second window of protection after isoflurane preconditioning in a rabbit model. A completely different antiischemic strategy was reported in 2003 by Vinten-Johansen's group (6). These authors discovered that brief ischemic bouts similar to preconditioning but at the opposite site of the ischemic insult, i.e., during reperfusion, could protect the myocardium to a similar degree as observed in ischemic preconditioning (Fig. 1). This exciting phenomenon, subsequently called postconditioning in analogy to preconditioning, opened the possibility to provide successful protection even after the ischemic insult. Improved postischemic recovery of the myocardium in the presence of halogenated ethers during the early reperfusion phase was known by anesthesiologists for many years (7), but was not explicitly called postconditioning until the year 2005 (8). Since then, evidence has been accumulated that preconditioning and postconditioning elicited either by ischemia or volatile anesthetics share many signaling steps. Therefore, it is not surprising that both antiischemic strategies not only reduce infarct size, but also improve postischemic cardiac function and decrease arrhythmogenicity.

This brief review will give an introduction into the complex field of "cardiac conditioning" elicited by halogenated ethers with a special emphasis on recent findings. First, the most important signaling pathways and cytoprotective mechanisms will be discussed. Novel insights from genome-wide analysis will be also presented. Clinical studies providing evidence of anesthetic-induced conditioning in the heart will be reviewed later. Excellent reviews on this topic (2,9) have been recently published and can be recommended as further reading.

MECHANISMS OF "CARDIAC CONDITIONING" BY HALOGENATED ETHERS

Anesthetic Preconditioning

Although most anesthetics modify the effects of preconditioning, only halogenated ethers (volatile anesthetics), xenon, and opioids directly elicit a sustained preconditioned state in the myocardium. The main mechanisms are similar in ischemic and pharmacological preconditioning (Fig. 2). The vocabulary of triggers, mediators, and end-effectors has proven to be fruitful to understand the involved molecular mechanisms. The protection by preconditioning is typically present immediately after the triggering stimulus, but disappears within hours ("classic preconditioning"). The memory phase in anesthetic preconditioning may be less pronounced than in ischemic preconditioning. As low as 0.25 minimum alveolar concentration (MAC) is protective, but the maximum protective effect is usually reached at 1.5–2 MAC. Multiple G-protein coupled receptors (adenosine, opioids, and catecholamines) serve as triggers in anesthetic preconditioning, and activate a highly complex network of kinases (Fig. 2). Kinases such as protein kinase C (PKC) isoforms, cGMP-dependent protein kinase, protein tyrosine kinases, but also extracellular signal-regulated kinase-1/2 and protein kinase B (PKB/Akt) (together with its downstream targets endothelial nitric oxide synthase, 70-kDa ribosomal protein S6 kinase, glycogen synthase kinase-3β, pro- and antiapoptotic proteins) act as mediators (10–12). Most recently, the list of signaling components in anesthetic preconditioning has been expanded by vascular endothelial growth factor and hypoxia-inducible factor-1 (13). Finally, mitochondrial and sarcolemmal K_{ATP} channels

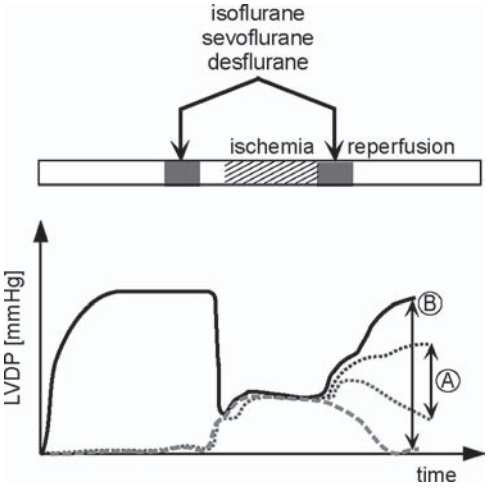

Figure 1. Concepts of pre- and postconditioning. Poor functional recovery (A) of cardiac systolic and diastolic function after ischemia/reperfusion is significantly enhanced (B) by either the preischemic exposure to halogenated ethers (anesthetic preconditioning) or by their application right at the onset of reperfusion (anesthetic postconditioning). LVDP, left ventricular developed pressure.

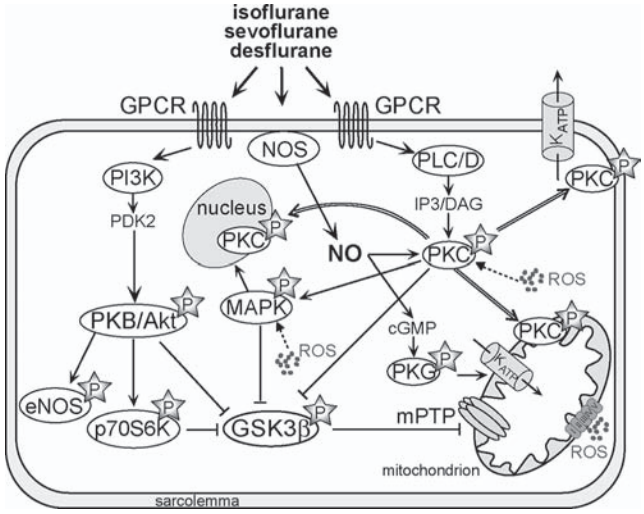

Figure 2. Signaling pathways involved in volatile anesthetic-induced cardiac conditioning. Beside their direct effects on mitochondria, volatile anesthetics activate G-protein coupled receptors (GPCRs) and modulate the production of nitric oxide (NO). These signaling pathways converge at the level of the protein kinase C (PKC) and induce its phosphorylation. Additionally, PKC (as well as mitogen-activated protein kinases or MAPKs) can be activated by reactive oxygen species (ROS) deriving from mitochondria in response to volatile anesthetics. PKC activates MAPKs and, on the other side, translocates to mitochondria, the sarcolemma, and nuclei (double-line arrows) interacting with mitochondrial and sarcolemmal adenosine triphosphate-sensitive potassium (K_{ATP}) channels as well as with the transcriptional machinery. Increased cGMP level activates PKG, which also affects mitochondrial K_{ATP} channel activity. K_{ATP} channel opening confers cytoprotection by preventing cytosolic and mitochondrial Ca^{2+} overload. Beside PKC, the phosphatidylinositol-3-kinase (PI3K)-PKB/Akt pathway also plays an important role in anesthetic protection. PKB/Akt phosphorylates several downstream targets, such as glycogen synthase kinase-3β, preventing the opening of the mitochondrial permeability transition pore. Abbreviations: cGMP, guanosine 3′,5′-cyclic monophosphate; DAG, diacyl glycerol; eNOS, endothelial nitric oxide synthase; GSK3β, glycogen synthase kinase-3β; IP3, inositol triphosphate; K_{ATP}, adenosine triphosphate-sensitive potassium channel; MAPK, mitogen-activated protein kinase; mPTP, mitochondrial permeability transition pore; NO, nitric oxide; NOS, nitric oxide synthase; PDK2, phosphatidylinositol-dependent kinase 2; PI3K, phosphatidylinositol-3-kinase; PKB, protein kinase B (also called Akt); PKC, protein kinase C; PLC/D, phospholipase C/D; PKG, cGMP-dependent protein kinase; p70S6K, 70-kDa ribosomal protein S6 kinase; ROS, reactive oxygen species.

serve as end-effectors by preventing cytosolic and mitochondrial Ca^{2+} overload (14–16). It should be noted that some investigators regard the mitochondrial K_{ATP} channel rather as a mediator or even trigger than an end-effector, mainly because the precise sequence of signaling events is still elusive. Volatile anesthetics are known to inhibit complex III of the respiratory chain (17) leading to the formation of reactive oxygen species (ROS) and the production of nitric oxide (NO), which activate K_{ATP} channels and multiple kinases. Hence, the ROS/NO can be regarded as triggers and the mitochondrial K_{ATP} channel as mediator. On the other side, opening of the mitochondrial K_{ATP} channel *per se* induces oxidative stress. Nonetheless, the most important end-effector in preconditioning is the mitochondrial permeability transition pore. Deleterious opening of this large multiprotein channel is prevented via inhibition of the metabolic master switch enzyme glycogen synthase kinase-3β. Additional mechanisms by which halogenated ethers can elicit preconditioning-like protection in the heart are i) activation of mechano-gated channels (18), ii) functional modulation of intercalated disks, iii) inhibition of leukocyte adhesion and migration (anti-inflammatory actions) (19), iv) metabolic substrate shift from fatty acid to glucose utilization (20), and v) direct protection of the endothelium (21).

Recent data provides evidence that a second window of protection occurs 12–24 h after exposure to volatile anesthetics, lasting for up to 72 h. Tonkovic-Capin et al. (5) demonstrated in a rabbit model that delayed protection by isoflurane is also dependent on K_{ATP} channels. Other animal models showed the involvement of cyclooxygenase-2, lipoxygenase-12, or inducible nitric oxide synthase in mediating these delayed effects (22). Important end-effectors of delayed protection are antioxidant enzymes and heat-shock proteins. Similar to early preconditioning, triggering of delayed protection can be abolished by administration of ROS/NO scavengers. Recent experimental data suggest that (delayed) protection by volatile anesthetics is gender-specific and more effective in male than female hearts (23).

Anesthetic Postconditioning

From a clinical point of view, postconditioning is particularly promising because no previous knowledge of the onset of the ischemic event is required to provide protection. However, to be effective, postconditioning must be established within the first seconds of reperfusion. A body of evidence supports the concept that

postconditioning activates signaling pathways in the heart similar to those observed in preconditioning (8,24). Specifically, postconditioning enhances the activation of PKC (via NO) and activates prosurvival kinases (PKB/Akt and ERK1/2) during early recovery from ischemia. Apart from ROS/NO, proinflammatory cytokines, tissue factor, and endogenous adenosine and opioids may also serve as triggers in postconditioning. Similar to preconditioning, mitochondrial K_{ATP} channels (25) and mitochondrial permeability transition pore (26) ultimately serve as end-effectors by preventing mitochondrial Ca^{2+} overload, a key event in cell death after ischemia-reperfusion.

Synergistic Effects by Pre- and Postconditioning

Current data suggests that anesthetic pre- and postconditioning exert synergistic effects. This is supported by clinical findings (27) and gene expression profiling of the two therapeutic strategies (28). Failure of synergistic protection by pre- and postconditioning in some studies may be due to the fact that additive effects can be only unmasked after sufficiently long ischemic insults.

TRANSCRIPTIONAL CHANGES IN ANESTHETIC PRE- AND POSTCONDITIONING

Given the complex interactions in cardioprotection, pre- and postconditioning might be better analyzed by the expression profiles of protective and antiprotective genes. Using a genome-wide approach, recent studies provided new insights into the molecular similarities and disparities between ischemic and anesthetic preconditioning on one side (29), and preconditioning and postconditioning on the other side (28). Gene cluster analysis showed that the myocardium preconditioned by isoflurane has a similar gene expression pattern comparable to healthy virgin myocardium. In contrast, hearts after ischemic preconditioning exhibited a gene expression profile closer to the unprotected state (29). Moreover, Lucchinetti et al. were able to show that the molecular outcome (i.e., at the gene expression level) of pre- and postconditioning is not interchangeable (Fig. 3) (28). Anesthetic preconditioning but not postconditioning prevented the activation of the deleterious remodeling program after prolonged ischemia in the heart. This finding is conceivable since a therapeutic intervention before the ischemic insult cannot have the same biological consequences as one initiated after ischemia. Thus in the future, it will be important to clarify whether differences in long-term outcome, i.e., weeks and not only hours or days after the ischemic hit, may indeed exist between pre- and postconditioning.

ANESTHETIC PROTECTION IN THE DISEASED HEART

Most experimental studies have evaluated the phenomenon of preconditioning in healthy juvenile hearts. However, this approach is far from clinical reality, as diseased myocardium would benefit most from this protection. Clinical and experimental studies provide evidence that diseased myocardium may be less receptive to protection by preconditioning. The following conditions have been associated with markedly reduced protection by preconditioning.

Ageing

Increased deleterious effects after sustained ischemia were reported in preconditioned aged rat hearts. This effect appears to be due to the insufficient translocation of PKC isoforms in response to the preconditioning trigger. Similarly, anesthetic-induced preconditioning is diminished in aged rats (30). These findings are supported by two clinical studies in which the antiarrhythmic and infarct-limiting effects of prodromal angina (clinical correlate of ischemic preconditioning) were lost in elderly patients with myocardial infarction. A clinical study in patients undergoing coronary angioplasty, comparing ischemic preconditioning in younger and elderly patients, also suggests that ischemic preconditioning is attenuated in the aged human myocardium, probably as a result of inhibitory effects upstream of the mitochondrial K_{ATP} channel.

Hypercholesterolemia and Diabetes

Rabbit myocardium loses its ability to respond to preconditioning triggers when exposed to a cholesterol-enriched diet for more than 4 wk. A loss of protection by preconditioning was reported in streptozotocin-induced diabetic rat hearts. Preconditioning by isoflurane was reported to be diminished in diabetic dogs (31). Markedly increased serum glucose concentrations (>500 $mg \cdot dL^{-1}$) can inhibit K_{ATP} channel activation *per se*. Some of these experimental results are consistent with clinical observations in which prodromal angina did not limit infarct size, enhance recovery of myocardial function or improve survival in diabetic patients with myocardial infarction, as opposed to nondiabetic patients.

Cardiac Remodeling

Loss of pre- and postconditioning could be involved in the poor prognosis of patients with postinfarct ventricular remodeling. Ischemic preconditioning is effective in three rat models of hypertrophied myocardium. Conversely, in a dog model of left ventricular hypertrophy, there was no evidence of cardioprotection after preconditioning. Results from muscle slices of human right atrial tissue of patients with a left ventricular ejection fraction <30% indicate that failing myocardium is not receptive to protection by ischemic preconditioning. In contrast to these disappointing results, data from our laboratory have demonstrated that infarct-remodeled rat myocardium is receptive to protection by anesthetic postconditioning (24). However, to date, it is unknown whether anesthetic preconditioning remains protective in postinfarct (compensated) remodeled hearts. Similarly, no data are available on delayed preconditioning ("second window of protection") in remodeled myocardium. It

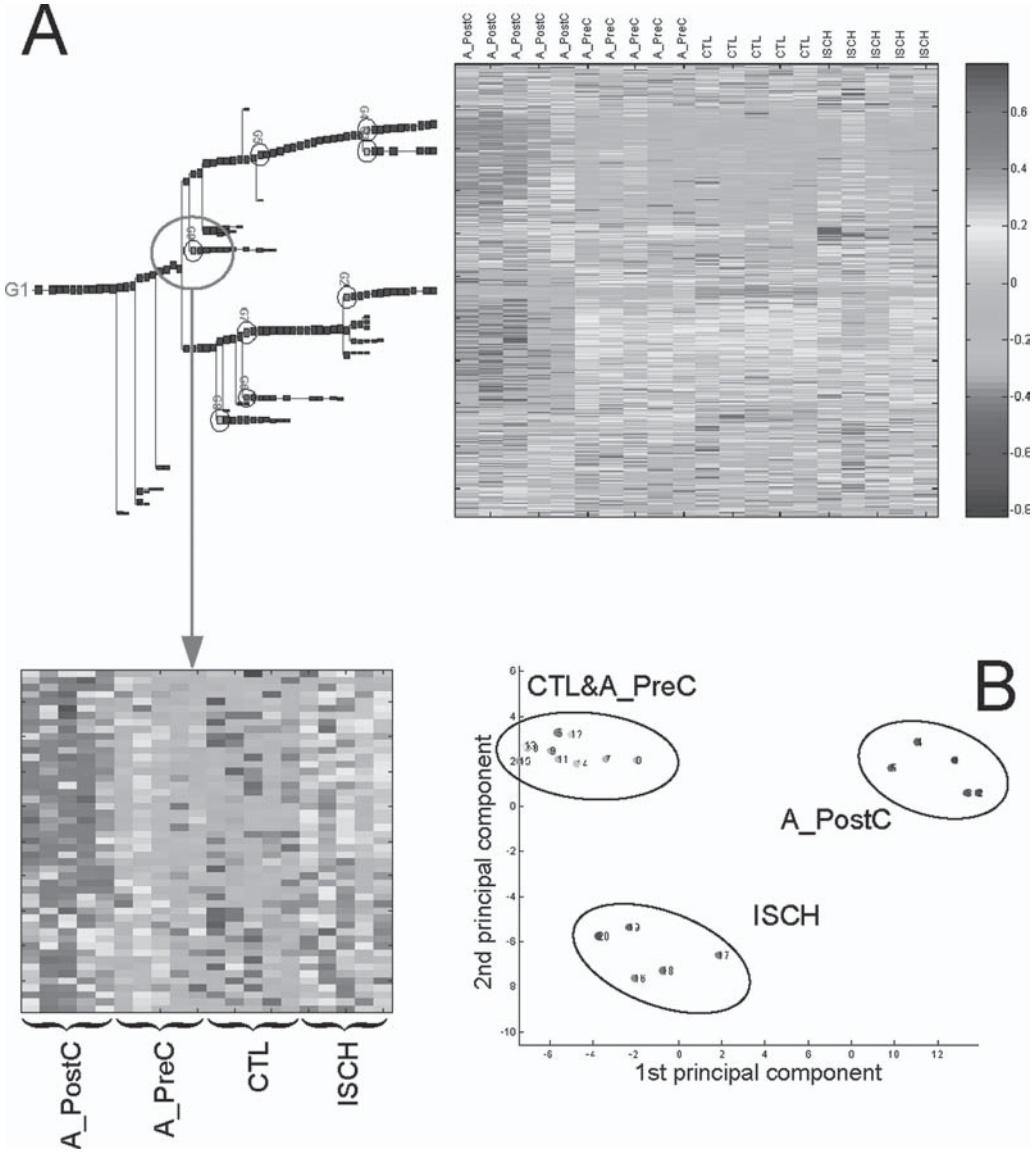

Figure 3. Pre- and postconditioning are not interchangeable with respect to their molecular outcome in the heart. Rat hearts were exposed to 40 min of ischemia and 3 h of reperfusion (ISCH), anesthetic preconditioning (A_PreC), anesthetic postconditioning (A_PostC), and time-matched perfusion (CTL). Panel A: Global gene expression matrix (heat map) of the 2133 differentially regulated genes. Rows correspond to the genes, and columns correspond to the samples. The color scale denotes the quantification for gene expression. Blue indicates least and red greatest degree of expression. Eight gene clusters (G2–G9) emerged from the mother cluster G1. Cluster G9 shows activation of the cardiac remodeling program in A_PostC but not A_PreC. Key transcripts were matrix metalloproteinase 7, collagen type V, tenascin X, elastin, collagen type I, fibromodulin, insulin growth factor-2, and proteoglycan NG2. Panel B: Principal component analysis of the various treatment groups. Note that A_PreC clusters with healthy virgin myocardium. Adapted from Ref. 28 with permission of Oxford University Press/British Journal of Anaesthesia.

could well be that the remodeling process may disrupt signaling pathways and reduce or even abolish innate protective cellular strategies, rendering the myocardium refractory to protection.

CLINICAL EVIDENCE OF CARDIOPROTECTION BY HALOGENATED ETHERS

While the number of pathways reported to be involved in the complex signaling of anesthetic cardioprotection keeps on increasing, more and more clinical studies point to halogenated ethers as being particularly beneficial in high-risk patients undergoing CABG surgery. Nevertheless, two recent meta-analyses evaluating myocardial protection with volatile anesthetics during CABG surgery concluded that additional studies need to be conducted (32,33). High-risk patients undergoing CABG surgery are ideal for studying the protective effects of volatile anesthetics, which can be administered via the ventilator or the cardiopulmonary bypass oxygenator and simultaneously serve to maintain the anesthetic state. Julier et al. (34) showed in the first placebo-controlled multicenter study that brief administration of sevoflurane on the cardiopulmonary bypass significantly ameliorates postoperative myocardial

function (as assessed by the biochemical marker brain natriuretic peptide) in patients undergoing on-pump CABG surgery. Surprisingly, sevoflurane-treated patients also exhibited improved long-term cardiovascular outcome (35). In a series of important clinical studies, De Hert and his group demonstrated that sevoflurane- and desflurane-based anesthetic regimens enhance cardiac function after cardiopulmonary bypass in elderly risk patients (27). Most recently, better preservation of myocardial function and reduced postoperative release of troponin I were reported by the use of sevoflurane in aortic valve surgery (36). Similar protection by volatile anesthetics could be shown in patients undergoing off-pump CABG surgery (20).

PROTECTION OF OTHER VITAL ORGANS BY HALOGENATED ETHERS

Recent experimental and clinical data extends the anesthetic protection observed in the heart to other vital organs. Renal functional and morphological protection by isoflurane preconditioning was recently reported in a rat model (37). Julier et al. (34) reported for the first time renal protection after sevoflurane preconditioning (as measured by reduced postoperative cystatin C serum levels) in patients undergoing on-pump CABG surgery. Similar protection of the liver could be observed by De Hert's group in patients undergoing on-pump CABG surgery with sevoflurane anesthesia (38). Notably, this is the first description of a successful hepatic preconditioning with sevoflurane in patients. Postoperative levels of sGOT, sGPT, and LDH were lower in the sevoflurane group compared with the propofol group. Current experimental data also suggest neuroprotective effects of volatile anesthetics, albeit predominantly in mild to moderate ischemia models, at lower concentrations of volatile anesthetics, and after shorter reperfusion times. However, a preliminary randomized study in patients undergoing CABG surgery did not show reduced neuronal damage (S-100β protein levels) by isoflurane as compared with propofol anesthesia (39). Recently, endothelial protection by even low doses of sevoflurane has been shown in humans *in vivo* (21). Since the endothelium is a key component in all body tissues, it can be speculated that sevoflurane inhalation may exert whole body protection.

PERSPECTIVES

Additional sufficiently powered, prospective randomized and controlled clinical studies should be conducted in the future. These studies should be extended to the setting of noncardiac surgery. Since halogenated ethers are readily available, they can be ideally used to directly translate basic science into clinical practice. The fact that anesthetic protection can be achieved under conscious sedation opens the possibility to administer halogenated ethers during diagnostic or interventional procedures in cardiology and endovascular procedures. On the other side, a detailed experimental exploitation of the protective mechanisms underlying volatile anesthetics may result in the discovery of novel antiischemic strategies. Based on similarities between ischemic and anesthetic preconditioning, inhibition of LINE-1 (long interspersed nuclear element 1) activity was recently found to reduce ischemic damage in the heart (40). Detailed genomic and proteomic analyses will help to uncover many additional fascinating biological effects of volatile anesthetics in the future.

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