

CARDIOPROTECTION BY VOLATILE ANAESTHETICS: ANAESTHETIC-INDUCED PRECONDITIONING

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REZUMAT

Precondiționarea anestezică a miocardului este un fenomen bine precizat prin care anestezele volatile induc un efect cardioprotectiv care persistă un anumit timp după întreruperea anestezicului. Anestezele volatile reduc necroza/apoptoza miocitelor cardiace prin activarea de multiple mecanisme moleculare care nu sunt încă pe deplin caracterizate. Materialul de față trece în revistă dovezile experimentale și clinice asupra posibilelor mecanisme ce mediază efectele protective cardiace ale precondiționării prin anestezice volatile.

ABSTRACT

Anaesthetic-induced preconditioning of the heart has now become a well accepted phenomenon, where the delivery of a volatile anaesthetic induces a longer lasting cardioprotective effect. Volatile anaesthetics can reduce necrotic/apoptotic myocardial cell death through activation of multiple molecular pathways. We are just at the beginning of understanding the precise mechanisms which mediate preconditioning by volatile anaesthetics. The present material provides an overview of our current knowledge of the mechanisms of cardioprotection by volatile anaesthetics.

INTRODUCTION

Patients with coronary artery disease are at risk for myocardial ischaemic events during non-cardiac surgical interventions. Moreover, for most cardiac procedures a limited period of myocardial ischaemia (i.e., during aortic cross clamping) is necessary, which will result in additional reversible and irreversible cardiac injury. In the recent years a variety of pathological mechanisms leading to ischaemia-reperfusion injury have been elucidated and there is growing evidence that the choice of the anaesthetic regimen may contribute to cardioprotection. The aim of this short review is to provide an update of myocardial

preconditioning by volatile anaesthetics.

Murry et al.¹ reported in 1986 the paradoxical finding that if a sustained 40 min occlusion of a major coronary artery was preceded by four additional shorter coronary occlusions, infarct size was not increased as expected but surprisingly reduced to 25% of that seen in the control group. The phenomenon was named "ischaemic preconditioning". Since then, extensive research in this field was performed to identify the potential mechanisms of this cellular memory which reduces injury after ischaemia-reperfusion. The above mentioned early phase of protection (*classic or early preconditioning, EPC*) lasts 2 to 3 hours. Twelve to 24 hours later, "a second window of protection" reappears and lasts up to 72 hours. This phenomenon has been termed *late preconditioning*.²

If one assumes that for the heart angina is the physiological equivalent of preconditioning, the findings of Kloner and co-workers³ underline the immense clinical importance of this phenomenon: patients in whom a myocardial infarction is preceded by angina have a much better outcome in terms of survival. (Fig. 1)

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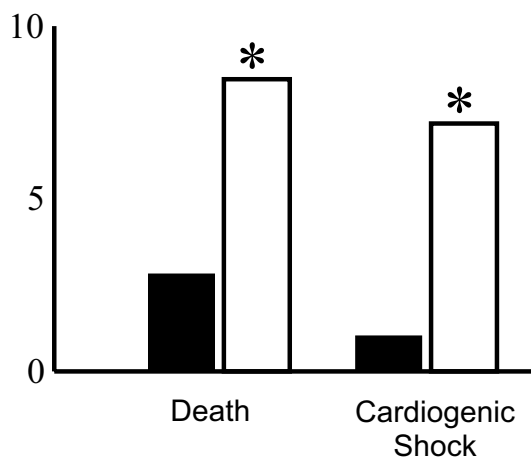


Figure 1. Patients with preceding angina (black columns) have a much better outcome after myocardial infarction. This finding underlines the clinical importance of the preconditioning mechanism (Modified from Klöner et al.³)

A lot of pharmacological agents (adenosine, nitric oxide donors, opioids, adrenergic agonists)⁴⁻¹¹ can induce a similar myocardial protective state by mimicking ischaemic preconditioning. Viewed from the clinical perspective, cardioprotection with pharmacological preconditioning may be more interesting than ischaemic preconditioning because short episodes of ischaemia may further damage the chronically ischaemic myocardium. However, some of the above mentioned pharmacological agents have serious unwanted side effects like hypotension (adenosine), arrhythmias (adenosine, adrenergic agonists, ATP-dependent potassium channel openers), or carcinogenic effects (protein kinase activators).

ANAESTHETIC PRECONDITIONING

As early as 1983 halothane was found to reduce myocardial infarct size in dogs, but the mechanisms remained unclear.¹² In 1987 two groups (Kersten et al. and Cason et al.) independently reported that isoflurane directly preconditions myocardium against infarction via activation of ATP-dependent potassium (K_{ATP}) channels in dogs, and this effect was named anaesthetic-induced preconditioning (APC).¹³⁻¹⁴ APC did not only reduce infarct size, but also post-ischaemic myocardial contractile dysfunction (“myocardial stunning”) and endothelial dysfunction in various experimental models. Figure 2 gives an example of the extent of infarct size reduction seen after only short administration of a volatile anaesthetic.¹⁵

The mechanism behind cardioprotection by volatile anaesthetic-induced preconditioning is not yet precisely defined. The net change in oxygen supply/demand balance induced *in vivo* by the volatile anaesthetics is not the action responsible for cardioprotection by preconditioning. This is supported by the fact that sevoflurane¹⁶ and desflurane¹⁷ induced APC in isolated cardiac muscle cells, too. Ischaemic preconditioning and APC share at least some of the mediating pathways, and these involve activation of A_1 adenosine receptors, protein kinase C (PKC), K_{ATP} channels and reactive oxygen species (ROS).

A lot of experimental evidence points to the mitochondria as being the convergence point for

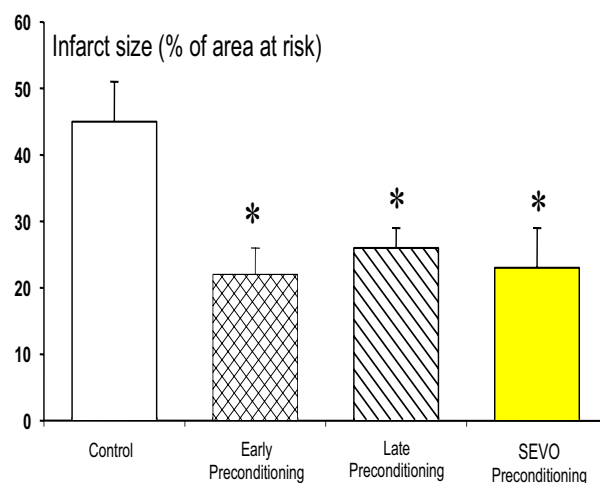
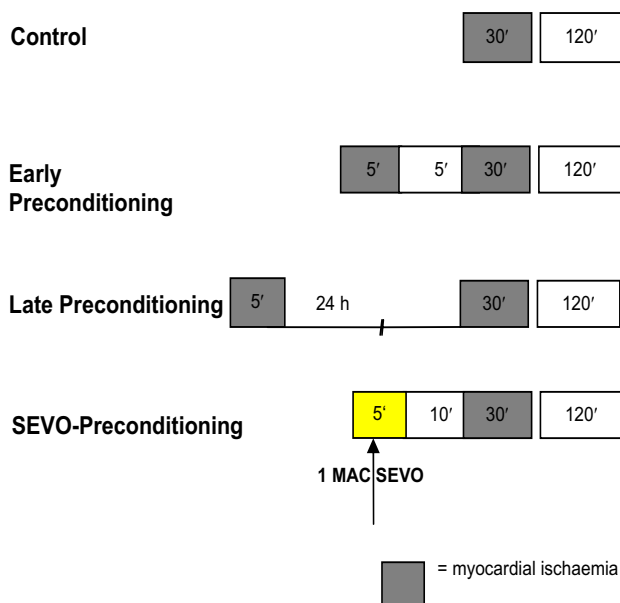
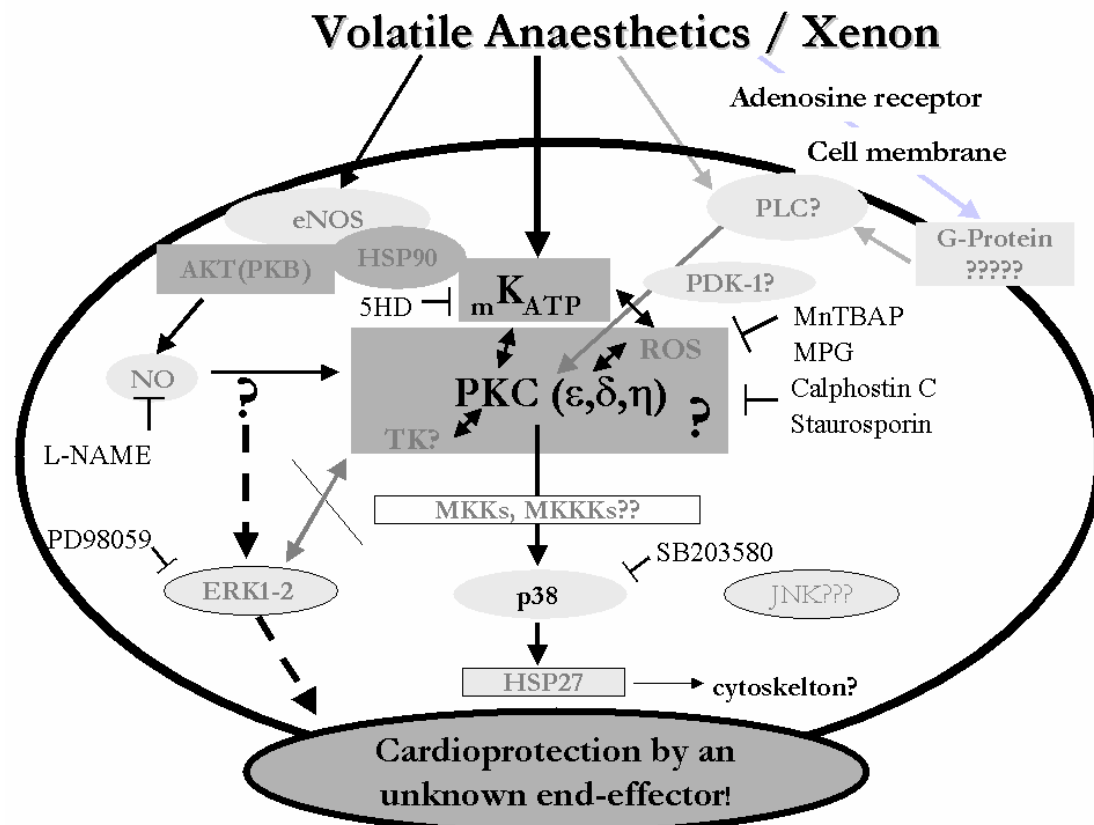


Figure 2. Five min. inhalation of 1 MAC sevoflurane have a similar infarct size reducing effect as the „endogenous“ cardioprotective mechanisms „early“ and „late preconditioning“ (Modified from Mullenheim et al.¹⁵).

many signalling pathways. Opening of mitochondrial (mito) rather than sarcolemmal (sarc) K_{ATP} channels seems to mediate APC,^{17,18} but there is also evidence that selective blockade of sarc K_{ATP} channels either attenuates¹⁶ or abolishes¹⁹ the protective effects of volatile anaesthetics. Zaugg *et al.*¹⁸ presented evidence that volatile anaesthetics mediate their protection by selectively priming mito K_{ATP} channels through multiple triggering protein kinase C-coupled signalling pathways. ROS directly generated in response to volatile anaesthetics lead to the activation of PKC- Σ who can modulate mito K_{ATP} channels opening.²⁰ Isoflurane-induced preconditioning depends on the release of free radicals²¹ and sevoflurane potentially leads to ROS formation by attenuation of mitochondrial electron transport.²²

PKC isoforms (at least epsilon and delta isoforms) are also essential for the protection seen after APC, but controversy exists about their activation sequence. APC would activate PKC either directly,¹⁸ via ROS formation,^{20,23} or after G-coupled receptor stimulation (similar with IPC) and this could lead to downstream modulation of mito K_{ATP} channel activity.^{20,23}

A different study made the evidence that, by contrary, mito K_{ATP} channels opening represents an upstream event that facilitates PKC activation via ROS.²⁴ Modulation of mitochondrial permeability transition²⁵ and mito K_{ATP} channel activity during APC induces changes that lead to preservation of mitochondrial integrity and function during reperfusion after lethal ischaemia. Figure 3 gives an overview of a possible concept of the intracellular signal transduction of anaesthetic preconditioning.



Treatment with volatile anaesthetics leads to an activation of the mito K_{ATP} (i.e., opening) - PKC (i.e., phosphorylation) complex which play a central role in ischaemic as well as in anaesthetic induced preconditioning. This complex is closely linked to activation of TK and release of ROS. Blockade of K_{ATP} channel opening, PKC activation, and intracellular release of ROS blocks the protection by anaesthetic induced preconditioning. Blocking the NO-synthesis, the activation of adenosine receptors, and the G-proteins also inhibit the protection. The definite order of activation in the signal transduction cascade is still a matter of debate. Downstream of K_{ATP} channel opening and PKC activation, phosphorylation of the mitogen activated protein kinase p38 and its downstream target HSP27 play an important role. The involvement of MKKs and MKKKs appear likely as there are needed to activate the mitogen activated protein kinase p38. If the activation of HSP27 is causally linked to the protection or only co-activated is not yet known. Another presumably parallel pathway seems to be the activation of ERK1/2, but only preliminary data about this pathway are yet available. The further steps to the still unknown end-effector mediating the protection by ischaemic and anaesthetic induced preconditioning are still under investigation.

AKT (PKB) = protein kinase B, eNOS = endothelial nitric oxide synthase, ERK1/2 = extracellular signalling regulated kinase 1 and 2, mito KATP = mitochondrial ATP-sensitive potassium channel, HSP27 = heat shock protein 27, HSP90 = heat shock protein 90, JNK = c-june NH2-terminal kinase, MKKs = mitogen activated protein kinase kinases, MKKKs = mitogene activated protein kinase kinase kinases, NO = nitric oxide, p38 = mitogen activated protein kinase p38, PDK = phosphatidylinositoltrisphosphat dependent kinase, PKC = protein kinase C, PLC = protein lipase C, ROS = free oxygen radicals, TK = tyrosine kinase, Calphostin C and, Staurosporin - blocker of protein kinase C, L-NAME - blocker of nitric oxide synthesis, MnTBAP and MPG - intracellular oxygen radical scavenger, PD98059 - blocker of ERK1/2 pathway, 5HD - blocker of mitochondrial ATP-sensitive potassium channels

Figure 3. Concept of the intracellular mechanisms of anaesthetic preconditioning.

POTENTIAL DELETERIOUS EFFECTS OF OTHER PERIOPERATIVE-ADMINISTERED DRUGS

Other anaesthetic drugs potentially interact with the signalling pathways of preconditioning and can abolish the protective effects of preconditioning. Barbiturates and ketamine can block K_{ATP} channels in isolated myocytes and thus may attenuate the cardioprotection mediated by K_{ATP} channels.^{26,27} While thiopentone did not interfere with ischaemic preconditioning,²⁸ ketamine blocked protection specifically through the R(-)-enantiomer^{29,30} and, as a consequence, it may be wise to avoid racemic ketamine in situations potentially associated with ischemia/reperfusion. Mito K_{ATP} channels were not blocked in different experimental settings by propofol, midazolam, etomidate, dexmedetomidine or mivazerol (for review see ref. 31).

Sulphonylurea drugs block the K_{ATP} channels in the pancreatic β cells to cause insulin release, but the same mechanism could impair the protective preconditioning effect in myocytes. A recent study indicates that, in patients with type 2 diabetes and coronary artery disease, stress-induced myocardial dysfunction is less severe during treatment with insulin than with glibenclamide.³²

Cyclooxygenase-2 (COX-2) inhibitors block the synthesis of PGE₂ and PGI₂, prostaglandins with vasodilator properties involved in acute and chronic pain signalling. COX-2 inhibitors seem to be associated with an increased risk of thrombotic cardiovascular events³³ and recent results also indicate that perioperative COX-2 inhibition may interfere with the cardioprotective effects of APC.³⁴

CAN I HAVE MY CAKE AND EAT IT, TOO ?

The two categories of patients who might have benefit from myocardial protective effects of APC were already mentioned. First, patients with coronary artery disease at risk for myocardial ischaemic events during noncardiac surgical interventions. Second, patients scheduled for cardiac procedures, where there is frequently a limited period of myocardial ischaemia (i.e., aortic cross clamping) that produces reversible and irreversible injuries. A better perioperative cardiac function following APC should lead to a better outcome in the above mentioned patients.

Several clinical studies have shown a preconditioning effect of volatile anaesthetics. Isoflurane,³⁵⁻³⁷ enflurane,³⁸ and sevoflurane³⁹ delivered to precondition the myocardium in patients who

underwent surgery with cardiopulmonary bypass improved different biochemical or functional postoperative markers of myocardial dysfunction compared with control. These studies either found a better postoperative myocardial function,^{37,38} a reduced release of troponins³⁵ (or only a tendency³⁶), or a reduced release of brain natriuretic peptide, a sensitive marker of myocardial contractile dysfunction.³⁹ Two of the studies also identified activation of important signalling pathways in bioptic specimens of preconditioned myocardium.^{36,39} Julier et al.³⁹ also reported that APC preserved renal function as assessed by release of biochemical markers.

An approach closer to the everyday use of volatile anaesthetics was to deliver inhalational anaesthetic regimens throughout the entire procedure and to compare the postoperative outcome with a group having total intravenous anaesthesia (TIVA).^{40,41} De Hert and colleagues⁴¹ observed that the use of desflurane or sevoflurane in high-risk coronary surgery patients resulted in better preservation of myocardial function with lower troponin I release after cardiopulmonary bypass.

CONCLUSION

A lot of recent experimental evidence demonstrates that volatile anaesthetics exert strong cardioprotective effects by preconditioning. The precise molecular mechanisms and the cellular end-effectors contributing to the protection remain to be unravelled. By carefully choosing the anaesthetic regimen the anaesthesiologist may influence the patient outcome in situations associated with ischaemia-reperfusion. First clinical studies seem to confirm the experimental data, however, the real impact on patients' outcome still need to be demonstrated.

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