

Cardiac Pre and Post Conditioning with Halogenated

Rodriguez Capitán MJ, Escalona Belmonte JJ, Guerrero Orriach JL*, Ramirez Fernandez A, Ramirez Aliaga M, Toledo Medina C, Malo Manso A, Rubio Navarro M and Cruz Mañas J

Department of Anaesthesia, Hospital Virgen de la Victoria, Málaga, Spain

Corresponding author: Jose Luis Guerrero Orriach, Hospital Virgen de la Victoria, Campus Universitario Teatinos C.P. 29010, Malaga, Spain, **E-mail:** guerreroorriach@terra.com

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Preface

Recently, many studies have shown a decrease in myocardial damage in patients undergoing coronary artery bypass surgery using an anaesthetic halogenated agent instead of propofol.

The basis for this protective effect on myocardium is at the mechanisms of preconditioning and post conditioning of halogenated agents. Both are related to the benefits of prior or subsequent administration of the drug (a halogenated anaesthetic agent) for myocardial cells, having very similar effects. It will be shown how this organic protection works and the clinical effects of halogenated at the postoperative period.

This issue will be one of the most important clinical points at anaesthesia and critical care, thus replacing the concept of anaesthesia from hypnosis to the therapeutic area.

Keywords: Halogenated; Cardiac surgery; Preconditioning; Post conditioning

Introduction

Preconditioning is a molecular mechanism by which an organ, after receiving a minor damage, may withstand a potentially lethal further one. Heart preconditioning is related with a brief hypoxic stimulus (ischemic preconditioning) or by using such drugs as volatile anaesthetics (pharmacological preconditioning) [1].

Preconditioning occurs in a biphasic manner: it is effective for two or three hours after drug application and then disappears and reappears at 12-24 hours to last up to three days afterwards. The first one of these phases, also known as classic preconditioning occurs through multiple intracellular signalling pathways based on phosphorylations, and the second one, also called second windows of protection, goes further by temporarily altering gene activity and protein expression. Both may affect myocytes, endothelial and smooth muscle cells [2].

There are several drugs used in anaesthesia which in addition to fulfilling its basic function are able to produce other effects in the field of cardio protection, specifically in the cardiac preconditioning, by reducing myocardial ischemia and opening this way many diverse research lines. Halogenated hypnotics are one of the most important drugs with preconditioning properties.

Several recent studies have described that the damage to the myocardial tissue occurs in two different moments. The first one is at the ischemia, and after this comes the reperfusion, when deleterious effect in cells of distinct organs are shown through a molecular response triggered like a leukocyte response, releasing inflammatory mediators and with oxidative stress, causing cellular damage both to the affected organ and at systemic level [3].

Some studies have shown that these protective effects not only happen when the drug is used before the ischemic injury. It also produces beneficial effects for ischemic and reperfusion damage and protective

effects when administered in the early stages of reperfusion, that is, at the pharmacological heart postconditioning. Pre and postconditioning share most of the molecular mechanisms [4-6]. The molecular mechanisms and clinical evidence about these effects will be discussed below.

Molecular Mechanisms

The final effects of the molecular actions are performed on mitochondria, exerting action through membrane receptors. Two enzymatic ways are very important to describe preconditioning and postconditioning mechanisms: The Reperfusion Injury Salvage Kinases (RISK) pathway via G-protein-coupled cell surface receptors and the Survivor Activating Factor Enhancement (SAFE) pathway, acting through the Tumour Necrosis Factor Alpha (TNF- α) receptor and activator of transcription STAT-3.

In mitochondria occurs the inhibition of the opening of the mitochondrial permeability transition pore (mPTP) and the opening of the ATP Dependent Potassium (KATP) channel. When normal function of mitochondria disappears, organic damage is knocking at the door. It may be inhibited by activating both pathways described before and stopping the levels of K inside the mitochondria and blocking the mPTP [7].

Argaud et al. reported a decrease in infarct size by 45% over the control in animals, inhibiting pharmacologically mPTP [8]. In the early stages of reperfusion damage cell reacts by activating a series of kinases that will protect against cell damage. These are the RISK group, and its effect will be exercised primarily on mPTP, inhibiting its opening [9]. K-ATP channels action during ischemic and reperfusion time is critical too.

Two types of channels may be described, that is the Sarcolemma (sK-ATP) channel and the Mitochondrial (mK-ATP) K-ATP one.

The sK-ATP has protective effects, as it seems left in a stream of potassium that hyperpolarizes the cell, thus decreasing the burden of

intracellular calcium and thereby decreasing the myocardial oxygen demand.

The mK-ATP works by slowing the flow of calcium into the mitochondria, thereby maintaining its intermembrane space and thus the link between the formation of high-energy phosphates and its cytoplasm use. This mitochondrial mechanism has a greater power than the protection mechanism that takes place in the sarcolemma. It shows that volatile anaesthetics do not get open these channels, but they could decrease the flow of K through these channels.

Other mechanism is an increase at the levels of oxygen free mediators expression, which is usually harmful to the membranes and cardio-depressant but can enhance the pre and postconditioning opening mitochondrial K channels [10]. Lu and his colleagues describe the activation of NF- κ B, a pivotal inducible transcription factor that regulates the expression on many genes involved in important biological processes including inflammatory stress responses and cell survival, with a consequent increased expression of antiapoptotic proteins such as Bcl-2 [11].

Concerning the second window of protection the key role remains at potassium channels. Even when they are not opened by acting through receptors these channels are temporarily opened directly through genetic modification and protein synthesis [10]. In late preconditioning decreases the expression of L-selectin (CD62L), a key molecule for the binding of leukocytes with the endothelium [12].

These actions on leukocyte adhesion and transmigration could also be understood as an endothelium effect, protecting against vascular injury and preventing the contribution of the endothelium in pro inflammatory and thrombogenic events associated with ischemia reperfusion injury [13].

More changes in gene expression result in changes in metabolic myocardial preferences, inhibiting fatty acid oxidation and thus improving the recovery of ischemic injury and even the long-term prognosis [12,14,15].

Changes in transcription are related to the activating SAFE pathway and TNF α . When TNF α binds to its receptor it activates the STAT pathway through phosphorylation of two Janus Kinases (JAKs), which will be translocated to the nucleus, thus resulting in gene transcription. The activation of the JAK/STAT pathway plays a crucial role in the expression of stress-responsive genes that could be participating in the protective effects on heart [16].

Sevoflurane at the postoperative cardiac surgery

Several studies have examined the effect of sevoflurane on the myocardium, highlighting the cardiac beneficial effect of the pharmacological mechanism when used after ischemia in patients with ischemic heart disease [17,18].

De Hert et al. demonstrated the cardioprotective effects of an anesthesia with sevoflurane by lowering the postoperative release of troponin I and NTproBNP. This effect was evident when the volatile aesthetic was administered through a surgical procedure. Sevoflurane also preserved left ventricular function after cardiopulmonary bypass with less evidence of myocardial damage in the first postoperative 36 hours period. This suggested a cardioprotective effect of sevoflurane at coronary artery surgery. Reductions in length of stay in intensive care unit were also detected [19-22].

Hellstrom et al. evaluated whether short-term sedation with sevoflurane in the intensive care unit could affect the release of cardiac troponin-T after coronary artery bypass grafting, comparing this with the propofol sedation. They found no statistically significant post-operative difference

between both groups in the cardiac troponin-T values at 12h, nor cardiac events or any need of hemodynamic support [23].

Steurer et al. suggested that sevoflurane could mediate cardiac protection, even using a low-dose postoperative application. They found lower troponin T values compared with propofol sedation. The use of these agents can offer an additional tool in the treatment or prevention of ischemic organ dysfunction in the postoperative period [24].

Soro et al. concluded that clinical results in cardiac surgery patients were controversial and might be related to the timing of administration of anaesthetics. They hypothesized that the cardioprotective effect of sevoflurane would be more intense if the administration during anaesthesia were continued in the intensive care unit, until weaning from mechanical ventilation. There were no significant differences in necrosis biomarkers, hemodynamic variables, and incidence of arrhythmias, myocardial ischemia and stay in the intensive care unit between the two groups, propofol and sevoflurane [25].

Guerrero JL et al. [5] concluded that at patients undergoing off-pump coronary artery bypass surgery exposure to sevoflurane during the immediate postoperative period has a beneficial effect on markers of myocardial injury. Patients anaesthetized with sevoflurane showed an important decrease in the levels of troponin I and NT-proBNP.

The use of sevoflurane showed a decrease of the ischemic area. This effect increased when the volatile anaesthetics in the postoperative period were maintained. The difference between this work and the previous ones is sedation with sevoflurane in the postoperative period with the AnaConDa Device. These results could be related to a prolonged effect in addition to preconditioning. The postconditioning would improve the cardioprotective effect of sevoflurane in the postoperative period [5,26].

Conclusions

Halogenated drug administration in the perioperative of cardiac surgery has shown the ability to reduce myocardial injury, the need for inotropic drugs and the length of stay in the ICU through mechanisms of myocardial conditioning, mainly through preconditioning and cardiac postconditioning in intra and immediate postoperative period. The longer duration of exposure to halogenate has been correlated with a greater benefit to patients.

Current studies try to identify what are the mechanisms by which this protection happens, also confirming an increase in myocardial protection through postconditioning which should reduce significantly the stay at the intensive care unit and the use of hospital resources and also mean an improvement in myocardial function assessed by hemodynamic data and biochemical markers of dysfunction and myocardial injury.

In the future this issue will be one of the most clinical important points of working in anaesthesia and critical care, changing the concept of anaesthesia from hypnosis to therapeutic area.

Conflicts of Interest: None

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