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Desfluorane and Cardioprotection

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INTRODUCTION

The haemodynamic effects of desflurane can be categorised as direct and indirect1. Direct effects include reduced myocardial contractility, cardiac output and blood pressure, together with decreased peripheral resistance by vasodilation. Theindirect effects, on the other hand, are mediated by sympathetic activation which releases adrenaline and noradrenaline, and increases both heart rate and blood pressure. This response is related to the expired concentration of the drug (>1.25 MAC) and the velocity acquired. However, the sympathetic response stabilises after a few minutes. The prior administration of sympatholytic drugs such as fentanyl, alfentanil, sufentanil, clonidine or beta-blockers can minimise the sympathetic response.

The use of halogenated anaesthetics in cardiac surgery patients has been shown to reduce both mortality and complications. Accordingly, ten years ago the American College of Cardiology and the American Heart Association included these drugs as part of the anaesthetic plan for patients undergoing cardiac surgery. However, it remains to be determined whether patients at high cardiac risk undergoing noncardiac surgery also benefit from this treatment. In the following text, we explain the mechanisms by which this improvement occurs in the evolution of the patient.

PHARMACOLOGICAL PRE-AND POSTCONDITIONING

Preconditioning consists in conducting a non-lethal short-duration aggression against the myocardial cells, thus provoking a phenomenon of endogenous adaptation which enables these cells to resist subsequent ischaemic insults which would otherwise have a fatal impact. This "training" decreases the cells' energy and metabolic requirements, improves homeostasis and tolerance to reperfusion, limits the release of reactive oxygen mediators and reduces cell apoptosis and microcirculation perfusion.

Cardioprotection is divided into two phases, an early one that is powerful but which only lasts one or two hours, and a later one of a lesser magnitude, which starts at 24 hours and lasts for72 hours.

It has been shown that halogenated anaesthetics can mimic ischaemic preconditioning, thus decreasing cardiac dysfunction2-5 and avoiding the side effects provoked by other drugs, such as the agonists of adenosine receptors, activators of protein kinase, ethyl alcohol, opiates and natural substances such as acetylcholine, bradykinin, angiotensin II, noradrenaline and even platelet activating factor.

During ischaemia, the primary aim is to limit the consequences of ischaemia-reperfusion and any worsening of the lesion. Accordingly, cardioprotection could be directed against myocyte-injuring mechanisms that are mediated by the formation of free radicals, by calcium and by the deterioration of coronary vasculature, through the modulation of ion cell gradients, the activation of inhibitors of the complement systems, and the activation of neutrophils and antioxidants. Most of these mechanisms have been tested in experimental situations, with diverse drugs, none of which have been shown to have a clinically significant protective effect. From the standpoint of anaesthesia, few agents clearly present a direct protective action when administered during ischaemia. It has been suggested that propofol may reduce the oxidation of free radicals, by suppressing harmful neutrophil activity and reducing the intracellular concentration of calcium. For this reason, it is believed that propofolmay be cardioprotective, despite its not presenting the pre- or postconditioning effects offered by halogenated anaesthetics.

Ischaemic postconditioning arises when short periods of ischaemia-reperfusion occur during myocardial revascularisation. This reduces the reperfusion-induced damage and alleviates the harmful oxidative effect and the local inflammatory response. It limits the infarct size, byreducing apoptosis, by activating neutrophils and through endothelial dysfunction6-7. This phenomenon may be caused by volatile anaesthetics when applied after ischaemia during the reperfusion period.

CARDIOPROTECTION MECHANISMS

Pre- and postconditioning are based on the protection of mitochondria and on reducing the impact of inflammatory mediators. Mitochondrial damage occurs primarily through its permeability transition pore (MPTP). Under conditions of mitochondrial homeostasis, this pore is closed. During ischaemia and reperfusion, the MPTP opens, but it does not allow the passage of the intramitochondrial proteins, and this increases the colloid osmotic pressure, provoking the lysis of the outer mitochondrial membrane and making the inner membrane permeable to protons. This process decouples the respiratory chain and decreases the production of ATP. This prolongation of the normal opening of the MPTP is mediated by caspases 3, 6 and 9 and causes the apoptosis of the myocardial cell.

Postconditioning seems to produce a smaller opening of these channels, by reducing the activation of the coronary vascular endothelium, the production of cytokines and reactive oxygen species, and neutrophil adherence, although to date our knowledge of the question is limited by the fact that all studies in this

respect have been carried out using animal models.

Significant mediators include bradykinins, which are precursors of kininogens within the vascular and cardiac endothelium8. Myocardial bradykinin receptor B1 and B2 are overexpressed in myocardial ischaemia and also appear to be related to postconditioning. The mechanisms underlying the effect of bradykinins appear to be nitric oxide and prostacyclins.

In turn, two groups of kinases are related to postconditioning, namely the RISK group (reperfusion injury salvage kinase), which is formed by the PI3, Akt and ERK 1/2 proteins, the overexpression of which is associated with reductions in infarct size of up to 50% in animal models, and the SAFE group (surviving enhancement activating factor), which includes STAT 3. The protein kinases C and G also exert a significant influence. Postconditioning through protein kinase C has been demonstrated in animal models, and protein kinase G has been related with preconditioning9.

EVIDENCE OF CARDIOPROTECTION BY DESFLURANE IN CARDIAC SURGERY

De Hert2-5 conducted several studies to evaluate the preconditioning offered by halogenated anaesthetics and showed that they decreased ICU and hospital stay time compared with intravenous anaesthetics,and concluded that the advantages obtained from halogenated anaesthetics were related to the increased duration of exposure. In elderly patients undergoing high-risk coronary surgery, desflurane presented a better preservation of ventricular function and produced less myocardial damage, in comparison with propofol.

Guarracino et al.10 conducted a multicentre study comparing the use of propofol and desflurane in off-pump myocardial surgery, and developed a theoretical model of human myocardial ischaemia. Thepatients were randomised into two groups, according to the anaesthetic to be administered during surgery; 57 patients were assigned to the desflurane group and 55 patients to the propofol group. The results were a decrease in the plasma levels of troponin, a decrease in the need for inotropic medication (35% vs. 56%) and a decrease in extended hospital stays (defined as those with a duration exceeding seven days), in the patients who were anaesthetised with desflurane, compared to propofol.

Landoni et al.11 studied whether the beneficial effect of preconditioning was also apparent in mitral valve surgery. Postoperative troponin levels were compared between 59 patients who had received desflurane 30 minutes before a cardiopulmonary bypass, and 61 such patients who received propofol. These authors reported that the patients with associated coronary lesions obtained a greater benefit from the intervention, as a result of the preconditioning.

Tritapepe et al.12 conducted a multicentre study to evaluate preconditioning in myocardial revascularisation surgery, with a randomised population of 150 patients. Significantly lower levels of troponin and of inotropic support were recorded, together with a shorter period of mechanical ventilation, ICU stay and hospital stay, in the desflurane group in comparison with the propofol group.

Meco et al.13 demonstrated the preconditioning effect of desflurane in patients undergoing coronary artery bypass surgery, with significantly decreased postoperative levels of troponin and Nt-proBNP.

De Hert et al., in the first meta-analysis to be conducted in this field, concluded that halogenated anaesthetics (desflurane and sevoflurane) decrease morbidity and mortality and improve the prognosis of cardiac surgery patients.Landoni et al.14 conducted a second meta-analysis in 2013, and concluded that halogenated anaesthetics reduce mortality in cardiac surgery, compared to propofol (2.6% vs. 1.3%) although the small number of studies examined did not allow this claim to be made for the individual halogenated anaesthetics. In fact, virtually no studies have been made to specifically compare the different halogenated anaesthetics, but sevoflurane and desflurane have been associated with greater reductions in mortality, compared with propofol, in patients undergoing cardiac surgery.

Andrews et al.15 conducted the only study carried out to date in which diastolic dysfunction is evaluated with respect to diverse anaesthetics. These authors observed, with desflurane, reduced post-ischaemic cardiac stiffness and reduced left ventricular end-diastolic pressures, in comparison with sevoflurane and propofol.

Postconditioning has mainly been studied in animals. Lemoine et al.16,17 carried out several studies to examine postconditioning mechanisms, and concluded that they produced an improvement in atrial contractility.

Stumpner et al.18 recently analysed the mechanisms of cardiac postconditioning, and observed that desflurane acts on the mitochondria to produce this improvement.

CONCLUSIONS

The use of halogenated anaesthetics in cardiac surgery decreases morbidity and mortality, the need for inotropic medication, and the length of stay in the ICU and in hospital, thus enabling significant savings in resources. Myocardial protection is determined by the mechanisms of pre- and postconditioning.

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