Pre- and Post-conditioning in Cardiovascular Surgery

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The only perioperative strategies used so far in cardiac surgery patients were based on surgical -open or endovascular - or percutaneous treatments associated with a drug therapy. Associated drug therapies included antithrombotic agents (\textit{i.e.} anti-platelet drugs and anticoagulants) and agents for treating the risk factors or disease requiring surgery (\textit{i.e.} beta-blockers or lipid lowering) \cite{1, 2}. However, new perioperative therapies have emerged, which act on relevant mechanisms during this critical period and can influence the course of a disease \cite{3-5}.

It is widely accepted that surgery is associated with a higher risk for myocardial damage and cardiac dysfunction, and therefore with higher morbidity and mortality. Patients undergoing myocardial revascularization or valvular replacement have an abnormal heart anatomy and vasculature. These anomalies are associated with a higher risk for ischaemic damage due to insufficient myocardial protection, even when standard cardioprotective measures are adopted. Ischaemic damage may have a dramatic impact on the evolution of the patient during the perioperative period. Hence, any perioperative strategy reducing ischaemic damage may be contributing to patient survival. New perioperative strategies are based on the administration of mediators of ischaemic preconditioning, which reduce cellular damage. Cardiac cell survival in an oxygen-deprived environment is mediated by the activation of mitochondrial mechanisms (potassium-channel openers) that trigger the preconditioning pathway. Preconditioning occurs when the blood supply to the heart is blocked (non-pharmacological preconditioning), which exposes the heart to the risk of ischaemia. Yet, drug-induced ischaemic preconditioning has been demonstrated to be superior to non-pharmacological preconditioning in terms of safety and efficacy \cite{6-8}.

The administration of anaesthetics starts before myocardial ischaemia occurs and is maintained throughout the entire intervention. Multiple studies have demonstrated that halogenated anaesthetics have preconditioning effects, compared with intravenous anaesthetics. There is evidence suggesting that the use of halogenated agents reduces perioperative mortality in cardiac surgery patients. When blood supply is restored, damage may be further caused by ischaemic mediators released during blood supply blocking. Halogenated agents may also exert cardioprotective effects as a result of drug-induced post-conditioning \cite{9, 10}.

Recent studies have demonstrated that halogenated agents trigger enzymatic mechanisms that confer pre- and post-conditioning effects. Existing evidence supports their postoperative use while cardiac surgery patients are in the ICU \cite{11}.

During revascularization or valvular replacement surgery, ischaemic damage may extend beyond the heart. This is important, as ischaemic damage may affect other organs (\textit{e.g.} brain and kidneys) previously damaged by underlying risk factors. Postoperative damage to other organs affects the quality of life of patients and is an independent factor of perioperative mortality. In patients exposed to extracorporeal circulation, blood flow is linear. Even if blood flow is pulsatile, it is not as efficient as natural blood flow. Therefore, any strategy based on drug-induced organ pre- and post-conditioning is a promising avenue for future research. Conflicting results have been obtained in studies in cardiac surgery patients on the potential neuroprotective effects of drugs such as corticosteroids and erythromycin. It is worth mentioning that studies on erythromycin were developed in the field of basic science; yet, promising therapies and preventive strategies against brain damage in patients at high risk for perioperative neurological damage have emerged from the results of these studies, with minimal adverse events \cite{12, 13}.

Intensive research is being conducted on the role of other pharmaceutical groups (\textit{e.g.} calcium sensitizers) as preoperative optimization drugs in cardiac surgery, with contradictory results. These studies focus on patients with left cardiac systolic dysfunction, because they would benefit the most due to the haemodynamic profile. Also, calcium sensitizers have been suggested to have pre- and post-conditioning effects by their opening of K\textsuperscript{+} channels and reducing intracellular calcium overload caused by other inotropics. Some studies have investigated the cardioprotective effects of these drugs in patients with ischaemic heart disease when administered during the induction of anaesthesia. Thus, promising - albeit not conclusive - results have been obtained about their role in reducing mortality \cite{14, 15}.

Nevertheless, scarce clinical research has been conducted on the potential of this pharmaceutical group to provide systemic protection. So far, it has been demonstrated to have nephroprotective effects, and encouraging results have been obtained in relation to its neuroprotective effects. There are ongoing clinical studies evaluating the role of calcium sensitizers in providing...
systemic protection to high-risk patients. If the hypotheses of these studies were confirmed, the use of these agents could expand beyond inotropic support [16].

Other agents such as dexmedetomidine - with two-fold effects, as alpha-receptor agonists and as mediators of neuroprotection - and other perioperative drugs used in patients at high risk for organic dysfunction are promising perioperative treatments for surgical patients [17, 18].

The beneficial effects of perioperative statin therapy on postoperative outcome after cardiac surgery has been studied in several articles with different results; we need new randomized controlled trials (RCTs) to obtain further evidence about the potential benefits of this treatment [19].

Apart from their primary indication, when administered perioperatively, numerous drugs may have other uses for different groups of surgical patients. Potential uses should be the subject of future research. Some of the drugs usually administered intraoperatively for a specific purpose (e.g. halogenated agents as hypnotics) could also have therapeutic effects when administered as continuous therapy (e.g. halogenated agents for pharmacological pre- and post-conditioning), which involves a change in the basic concepts of perioperative strategies.

In conclusion, a paradigm shift is necessary in the perioperative use of a number of agents in cardiovascular surgery. Some of these agents may exert systemic protection vs other agents with different mechanisms of action. If the potential of these drugs for systemic protection was confirmed, their current indications would expand to other therapeutic purposes.

REFERENCES