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Drugs mediating myocardial protection

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Introduction

Two critical factors determine the outcome after an acute ischaemic cardiac event: the occurrence of life-threatening arrhythmias and the extent of myocardial tissue damage. Adequate prevention and/or treatment of such events may greatly improve the outcome of patients at risk of peri-operative myocardial ischaemic events. A number of drugs used in anaesthetic practice may protect the myocardium in the peri-operative setting [1]. Conceptually, protective measures against such events can be subdivided in three phases: measures taken *before* the period of myocardial ischaemia, measures *during* the ischaemic period, and measures instituted *after* the ischaemic period. For years the maintenance of a favourable myocardial oxygen balance has been the cornerstone of peri-operative myocardial protective strategies. While this is still true, there is now both experimental and clinical evidence that other protective mechanisms such as preconditioning and postconditioning may play an important role.

Myocardial oxygen balance

The intimate relationship between the determinants of myocardial oxygen supply and demand and the occurrence of myocardial ischaemia has resulted in the identification of a number of therapeutic approaches that may help in the prevention of peri-operative myocardial ischaemia. The ultimate goal of such treatment is to reduce the oxygen demand of the myocardium at risk while simultaneously maintaining or increasing the oxygen supply to this tissue. Myocardial oxygen demand is dependent on heart rate, myocardial contractility and ventricular loading conditions. Myocardial oxygen supply depends on the adequacy by which the blood is capable of providing sufficient oxygen to the different regions of the ventricles.

To date, β -blocker therapy has been extensively studied with regard to its potential protective action against the occurrence of peri-operative myocardial ischaemia. Putative mechanisms for this protective action include a decrease in myocardial oxygen demand secondary to lower heart rates and a decrease in myocardial contractility, anti-arrhythmic effects, coronary plaque-stabilizing effects, anti-inflammatory effects, a shift in energy metabolism, and anti-renin-angiotensin effects [2]. Although several clinical studies have suggested a reduced postoperative cardiac morbidity and mortality in the presence of peri-operative β -blocker therapy, others have failed to confirm these findings (reviewed in ref. 3). Based on the available data the ACC/AHA has published a recent update on the peri-operative use of β -blockers [4]. Class I recommendation was given for patients already receiving β -blockers and in patients undergoing vascular surgery who were at high cardiac risk because of cardiac ischaemia on stress testing. Class IIa recommendation was given for patients with coronary artery disease undergoing vascular surgery and patients with coronary artery disease or who are at high risk and are undergoing intermediate, high-risk, or vascular procedures. Class IIb recommendation was for patients undergoing intermediate or high-risk procedures who are considered to be at intermediate cardiac risk or patients considered to have low cardiac risk undergoing vascular surgery. Finally, class III recommendations include those patients with an absolute contraindication to β -blockers.

Increasing evidence indicates that statins may also protect against the occurrence of peri-operative cardiac events. Proposed mechanisms for this action include anti-inflammatory and anti-thrombotic effects, scavenging of reactive oxygen species, and decreasing endothelial cell apoptosis [5]. In this respect the effects of anaesthetic agents and techniques on the myocardial oxygen balance deserve some attention. Undoubtedly anaesthetic agents decrease myocardial oxygen consumption by a decrease in ventricular contractility and loading conditions related to their negative inotropic and vasodilating effects. Unfortunately, this beneficial effect on consumption may be accompanied by an adverse effect on oxygen supply related to the hypotension that may result from their vasodilating properties.

Protection before ischaemia: preconditioning

The concept of preconditioning refers to the phenomenon that pre-treatment with a potentially noxious stress-stimulus can increase the cellular tolerance to subsequent stress-stimuli. At the level of the myocardium, ischaemic preconditioning represents an adaptive endogenous response to brief sub-lethal episodes of ischaemia leading to a paradoxical pronounced protection against subsequent lethal ischaemia. The protective effects offered by the ischaemic preconditioning are of limited duration and can typically be divided into two phases. The early phase occurs immediately and induces a strong protection but has a limited duration of 1 to 2 hr, whereas the late phase occurs about 24 hr after the initial stimulus, induces less protection, but lasts for as long as 3 days. In addition, this protective action may be present when the stimulus is applied just before the ischaemic insult (early preconditioning) but may also be active when the preconditioning stimulus has been applied some hours before the actual ischaemic insult (late preconditioning). Finally, recent data indicate that preconditioning stimuli at the level of other organ systems may have a protective effect at the level of the ischaemic myocardium (remote preconditioning). A detailed discussion on the mechanisms involved in the phenomenon of preconditioning is beyond the scope of this article and the reader is referred to a number of recent reviews on the subject [6].

Different experimental studies have shown that ischaemic preconditioning could be either abolished or mimicked by the use of pharmacological agents that respectively block or stimulate certain steps in the intracellular cascade. This has led to the concept of pharmacological preconditioning. During the last few years, experimental studies have shown that volatile anaesthetics and opioids demonstrate such pharmacological preconditioning effects. The mechanisms involved in anaesthetic preconditioning closely resemble those involved in ischaemic preconditioning. For further details on this subject the reader is referred to different excellent recent reviews on the subject [7-10].

Do these anaesthetic preconditioning effects translate into a clinically relevant peri-operative myocardial protection? Over the years several clinical studies in cardiac surgery patients have analyzed the effects of anesthetic agents during the preconditioning phase (reviewed in ref. 1 and 9). The data from the various anaesthetic preconditioning studies show highly variable results and fail to demonstrate an unequivocal beneficial effect on the extent of post-ischaemic myocardial function and damage.

Protection during ischaemia

The ultimate goal of peri-operative cardioprotective strategies is to limit the extent and the consequences of the myocardial ischaemia-reperfusion injury. The mechanisms behind this injury are numerous and may be linked. The three main culprits, however, seem to be free radical formation, calcium overload, and impairment of the coronary vasculature [11]. Protective strategies aim to target one or more of these underlying mechanisms. These include strategies to preserve or replenish myocardial high energy phosphate stores, strategies to modulate intracellular gradients, free radical oxygen scavengers and / or antioxidants, inhibitors of the complement systems and the neutrophil activation, and many others [12-14]. While most of these approaches (adenosine modulators, cardioplegia solution adjuvants, Na^+ / H^+ exchange inhibitors, K_{ATP} channels openers, anti-apoptotic agents, and many others drugs with proven or anticipated effects on the complement – inflammation pathways) have been shown to be effective in some experimental and even observational clinical settings, none of them have, until now, unequivocally been proven to demonstrate a clinically relevant protective action. Of interest, anaesthetic agents have been claimed to have a direct protective action when administered during ischaemia (reviewed in ref. 1 and 9).

Protection after ischaemia – during reperfusion: postconditioning

After a transient decrease, or even an interruption, of blood flow, the subsequent injury results from two components: the direct damage occurring during the ischaemia and the subsequent damage related to the reperfusion. The restoration of blood flow induces a second series of harmful events that produce additional injury. The goal of protection at this stage is to reduce or prohibit the metabolic, functional and structural changes that occur after restoration of coronary perfusion, by modification of the reperfusion conditions [15].

In 1996, a specific protection against myocardial-reperfusion injury by volatile anaesthetic agents was described for the first time [16]. This was subsequently confirmed for other volatile anaesthetic agents and it appeared that cardioprotection was maintained even if other measures of protection against myocardial ischaemia were already applied such as preconditioning and cardioplegia (for a review see ref 17).

Little is known about the potential protective effects of intravenous anaesthetic agents when administered at the end of myocardial ischaemia and during early reperfusion. Despite its properties of free oxygen radical scavenging and inhibition of calcium influx across plasma membranes, propofol does not seem to have a cardioprotective effect when administered during the reperfusion period. Of note, the solvent of the clinically used propofol (Intralipid) reduced infarct size [18].

Clinical cardioprotection: is there a role for anaesthetic agents

The major obstacle to translate experimental observations to the clinical setting is that myocardial ischaemia has to be present in a predictable and reproducible manner. Cardiac surgery constitutes a suitable, but still sub-optimal, model for the study of potential cardioprotective effects of anaesthetic agents. The first studies that were performed had a protocol where the anaesthetic agent was administered before the ischaemic episode. As discussed above, highly variable results were obtained with regard to the cardioprotective effects. Part of the variability between studies can be attributed to differences in protocols, such as choice of the anaesthetic agent, duration of the administration, inclusion of a washout period, etc. Taken together, it would appear that none of these 'preconditioning' studies, although suggesting some protective action on either a biochemical or a functional variable, unequivocally demonstrate that the use of a volatile anaesthetic regimen resulted in a clinical benefit for the patients.

The absence of clinically straightforward data from anaesthetic preconditioning studies has initiated the question of whether the choice of the anaesthetic regimen during the surgical procedure would really influence myocardial outcome. The first study, by De Hert et al, compared the effects of sevoflurane and propofol on myocardial function during and after coronary artery surgery [19]. Before cardiopulmonary bypass, all haemodynamic variables were comparable between the two treatment groups. However, after cardiopulmonary bypass, patients who received the volatile anaesthetic regimen had preserved cardiac performance, evident from a preserved stroke volume and dP/dt_{max} , and the preservation of the length-dependent regulation of myocardial function. In addition, the need for inotropic support in the early postoperative period was significantly less with the volatile anaesthetic, and postoperative plasma concentrations of cardiac troponin I were consistently lower when compared with patients who received a total intravenous anaesthetic regimen. This data suggested, therefore, that volatile anaesthetics provided a cardioprotective effect that was not observed with the intravenous anaesthetic regimen. This was confirmed in a subsequent study by the same authors in a group of elderly, high-risk patients with documented impaired myocardial function [20]. Sevoflurane and desflurane preserved myocardial function after cardiopulmonary bypass with less evidence for myocardial damage and a better postoperative myocardial function compared with the intravenous anaesthetic regimen.

The cardioprotective effects of a volatile anaesthetic regimen during coronary surgery have been confirmed in other reports that used different anaesthetic and surgical protocols [21–24]. All these clinical studies clearly indicated that volatile anaesthetics protect the myocardium during coronary surgery. However, one study in patients undergoing off-pump coronary surgery observed no significant difference in incidence of myocardial ischaemia [25]. In this study, however, intra-operative remifentanyl concentrations were consistently higher and bispectral index values lower in the propofol group compared with the sevoflurane-treated patients, indicating that there were probably differences in anaesthetic depth that undoubtedly influenced the results.

Does anaesthetic cardioprotection affect outcome?

Although all these clinical observations clearly indicate that volatile anaesthetics protect the myocardium during coronary surgery, the impact of this phenomenon on postoperative morbidity and clinical recovery remains to be definitively established. This is mainly related to the fact that sample size of the different studies is too small to address these issues. Recently Jakobsen et al [26] published a retrospective study from a Danish national registry of 10 535 patients who had undergone cardiac surgery in one of three cardiac centres with either a volatile or an intravenous anaesthetic regimen. While there was no difference in 30-day total mortality, cardiac-related mortality seemed to be lower with a volatile anaesthetic regimen but non-cardiac death seemed to be higher in this patient population. Correct interpretation of these data remains difficult because of a number of methodological issues which are inherent to this type of analysis such as the retrospective design including patients over a period of 6 years, the lack of information on the different surgical and anaesthetic techniques, the differences in patient collection between centres, etc.

A recent meta-analysis [27] focused on the data obtained with the newer volatile anaesthetics desflurane and sevoflurane. The authors included 22 trials with a total of 1922 patients, comparing a volatile with an intravenous anaesthetic regimen. With the volatile anaesthetic regimen, postoperative troponin release was lower, cardiac index was better with less need for inotropic support, the incidence of peri-operative myocardial infarction was lower, and mechanical ventilation time, intensive care length of stay, and hospital length of stay were shorter.

Future directions and conclusions

Many questions remain to be definitively elucidated. The available clinical data on cardioprotective effects of volatile anaesthetics to date are largely confined to coronary surgery patients, mostly with an ejection fraction >50%. Non-cardiac surgery is also associated with a risk of peri-operative cardiac events. The observation that anaesthetic cardioprotection with volatile anaesthetics is also observed during off-pump coronary surgery may suggest that this phenomenon may also be present in patients at risk of myocardial events undergoing surgical procedures without cardiopulmonary bypass. Among these non-cardiac procedures, arterial vascular surgery is considered as high risk for the development of peri-operative cardiac events. Recently, a retrospective analysis has compared the effects of a volatile anaesthetic to a non-volatile anaesthetic regimen on the incidence of postoperative cardiac events, including the postoperative elevation of troponin I values after vascular surgery in high risk patients. The data were obtained from a phase II study that compared the Na⁺/H⁺ exchanger type I inhibitor zoniporide to placebo on the occurrence of cardiac events. This multi-center study was conducted in 105 sites throughout the United States, South America, Europe and Asia. The type of anaesthesia was retrieved from the database and patients were subdivided in two groups: inhalational vs non-inhalational anaesthetic regimen. The incidence of postoperative cardiac events and maximum postoperative troponin I levels were not different between the two groups in the total population nor in the patients undergoing peripheral arterial surgery. In patients undergoing aortic surgery the incidence of elevated troponin levels greater than 1.5 and greater than 4 ng.ml⁻¹ tended to be lower in the inhalational group but this difference did not reach statistical significance [28]. The results of this hypothesis-generating study suggested that potential beneficial effects on extent of postoperative myocardial damage in high risk patients undergoing arterial surgery will probably be more apparent in abdominal aortic surgery than in peripheral vascular surgery. Further sufficiently powered studies using a standardised protocol should now be performed to definitively address this question. The potential beneficial cardioprotective effect of volatile anaesthetics may also extend to some non-surgical revascularisation procedures, such as percutaneous transluminal coronary angioplasty. However, a recent study failed to demonstrate a protective effect of volatile anaesthetic agents in this setting [29].

In conclusion, over the years various cardioprotective strategies have been developed to reduce the incidence of peri-operative cardiac events. The great majority of these strategies showed promising results in experimental settings but mostly failed to provide convincing significant clinical effects. Anaesthetic cardioprotection, however, seems to be an exception to this. The experimentally observed protective effects seem to translate also to a clinically relevant cardioprotection with a beneficial effect on patients' outcome. Although the initial data seem to be promising, further studies will have to confirm these beneficial effects.

Key Learning Points

- Peri-operative administration of β -blockers and statins may improve postoperative outcome
- Application of preconditioning and postconditioning protocols may attenuate the extent of myocardial damage after ischaemia
- Experimental data have clearly demonstrated that volatile anaesthetics have a protective effect against the consequences of myocardial ischaemia
- The myocardial protective effects of volatile anaesthetics have also been seen in clinical protocols

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