Myocardial protection in adult cardiac surgery: current options and future challenges

Francesco Nicolini\textsuperscript{a,*}, Cesare Beghi\textsuperscript{a}, Claudio Muscari\textsuperscript{b}, Andrea Agostinelli\textsuperscript{a}, Alessandro Maria Budillon\textsuperscript{b}, Igino Spaggiari\textsuperscript{a}, Tiziano Gherli\textsuperscript{a}

\textsuperscript{a}Department of Cardiac Surgery, University of Parma, Parma, Italy
\textsuperscript{b}Department of Biochemistry 'G. Moruzzi', University of Bologna, Bologna, Italy

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Summary

Current techniques of myocardial protection are evolving with the use of less conventional modalities of cardioplegia and have reduced the morbidity and mortality of cardiac operations. Blood cardioplegic solutions appear superior to cold cardioplegia in terms of myocardial protection and adjuncts as glutamate/aspartate enhancement, antioxidant supplementation, nitric oxide donors and maintenance of calcium homeostasis seem effective. In the near future, further experimental and clinical investigations about pharmacological preconditioning, sodium–hydrogen exchangers inhibition and gene therapy need to be addressed to well define their potential role in the improvement of current techniques of myocardial protection that are suboptimal in high-risk clinical settings.

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1. Introduction

Myocardial protection during cardiac surgery aims to preserve myocardial function while providing a bloodless and motionless operating field to make surgery easier. Myocardial protection, since the original reports of Bigelow [1] has been obtained by decreasing myocardial oxygen demand as a consequence of hypothermia. Moreover, Melrose [2] described the use of electromechanical cardiac arrest induced by potassium infusion, permitting cardiac surgery to be performed on a non-beating flaccid heart. The combination of both of these techniques has been the ‘cornerstone’ in myocardial protection during surgery until now, allowing surgery with excellent clinical outcome [3].

In the 1980s, blood-based potassium solutions were advocated to further improve myocardial protection and to reduce myocardial enzymes release [4]: however, recent changing trends in the population at risk have resulted in increasing number of high-risk patients presenting for cardiac surgery, with a consequent rise in intraoperative and postoperative morbidity.

In spite of the improvement in myocardial protection accomplished in past years, there is a room for further improvement, in particular in high risk patients, in the hope of preventing postoperative ventricular dysfunction and improving overall outcome.

The available literature allows us to summarize the following current trends and the future perspectives in myocardial protection in cardiac surgery.

2. Current trends in myocardial protection

2.1. Warm heart surgery

Standard techniques of intermittent cold cardioplegia result in myocardial hypothermia, ischemia, and a delay in the recovery of postoperative myocardial metabolism and function [5]. Several authors have stressed the deleterious effects of hypothermia on enzymatic and biochemical systems, suggesting to abandon both systemic and myocardial ischemia [6]. Then the cold blood cardioplegia following Buckberg’s approach [7] has been improved by
associating warm induction [8] and warm substrate-enriched initial blood cardioplegic reperfusion [9], showing the efficacy of this technique. Moreover, preservation of ATP levels during ischemia likely translates into greater preservation of membrane integrity. Enhancement of cardioplegic solutions with Krebs’ cycle substrates such as glutamate or aspartate, is now often utilized because it has shown an improved ATP preservation in several clinical studies [10,11].

Since the late 1980s, there has been renewed interest in continuous coronary perfusion during cardiac surgery: Lichtenstein and coworkers in 1991 suggested that the heart could be maintained at a temperature of 37 °C throughout the cross-clamp period to enhance perioperative myocardial metabolic function [12]. In 1994 the Warm Heart Trial reported the results of a prospective randomized trial involving nearly 2000 patients undergoing coronary artery bypass grafting, randomized to either normothermic or hypothermic cardioplegic solutions. Patients in the normothermic group experienced lower incidence of postoperative low cardiac output syndrome, even if no differences in mortality or myocardial infarction were found between groups [13]. Therefore, the use of normothermic myocardial protection has increased and routinely achieved with excellent results by retrograde continuous warm blood cardioplegia [14] or by intermittent cardioplegia with antegrade warm blood [15].

Although cold crystalloid cardioplegia is associated with an excellent clinical outcome in elective surgery, blood cardioplegia techniques seem to offer superior cardioprotection in high risk situations, such as advanced left ventricular dysfunction [16,17], acutely ischemic myocardium [18], heart transplantation [19], hypertrophied myocardium [20,21].

2.2. Novel techniques of cardioplegic delivery

The use of normothermic cardioplegia necessitated the development of novel methods of cardioplegic delivery to permit near-continuous perfusion. The introduction of retrograde perfusion in coronary sinus has been demonstrated to decrease the need of cardioplegic interruptions, allowing distribution of cardioplegia to regions supplied by stenosed vessels and improving subendocardial cardioplegic delivery. Although the concept of retrograde cardioplegia is simple, its proper and safe use requires a correct catheter placement and a maintenance of acceptable perfusion pressure (≤40 mmHg) to prevent perivascular hemorrhage and edema. It is known that the effectiveness of this technique is limited by the shunting of blood directly into atrial and ventricular cavities due to the presence of thebesian channels and arterio-sinusoidal vessels. Indeed retrograde normothermic cardioplegia requires a delivery at flows greater than 100 ml/min to minimize myocardial lactate production [22] and compensate this physiologic shunting. Despite such limitations, coronary sinus perfusion has been used successfully for coronary artery bypass grafting [23] and for valvular procedures [24].

A combined antegrade and retrograde approach has been proposed to improve coronary perfusion [25]. The recent coronary artery bypass grafting Patch trial, enrolling a high-risk group of coronary artery disease patients with a depressed ventricular function, constituted an ideal group to study an optimal cardioplegic protection. Results from this trial showed a clear superiority of blood cardioplegia and combined antegrade and retrograde cardioplegia versus crystalloid and antegrade cardioplegia alone for postoperative morbidity, even if there was no significant difference in early or late survival among groups of enrolled patients [17].

Nevertheless, a recent prospective randomized study comparing the administration of intermittent antegrade cold blood cardioplegia to antegrade cold blood cardioplegia induction followed by retrograde cold blood maintenance in patients undergoing valve replacement failed to demonstrate a superiority of combined route of cardioplegic delivery. The study demonstrated equivalent release of ischemia myocardial markers and similar outcome in both groups of patients, even if the antegrade/retrograde approach was technically convenient, allowing a lower aortic cross-clamp time [26].

2.3. Optimal cardioplegic temperature

The controversy about the optimal temperature to perform the operation and for the delivery of cardioplegic solutions is probably obsolete since there is increasing evidence that the best physiological compromise for the heart and the brain can be obtained performing the operation at a temperature of 32–33 °C [27–29]. Hayashi et al. reported a randomized study comparing the effects of cold (9 °C), tepid (29 °C) and warm (37 °C) blood cardioplegia in 42 patients undergoing coronary artery bypass grafting. Myocardial oxygen consumption, lactate release and acid release were greatest with warm, intermediate with tepid and least with cold cardioplegia. Early postoperative left ventricular function was best preserved after tepid cardioplegia suggesting that this type of myocardial protection seems effective to reduce metabolic demands and to permit immediate recovery of cardiac function [30]. Moreover, tepid protection provides better results to those obtained with cold protection, with a decrease in ventricular rhythm disorders, need for post ischemic DC shock and blood loss [31].

3. New perspectives in myocardial protection

Despite the advances reported above, current cardioplegic techniques have shown suboptimal protection in high-risk patients. Recent perspectives likely involve the use of
cardioprotective additives or appropriate new formulations of cardioplegic solutions to further improve protective effects.

3.1. Beta-blockade addition in myocardial protection

It is known that β-adrenergic antagonists attenuate the extent of myocardial injury during ischemia and reperfusion, reducing myocardial oxygen consumption and sympathetic tone and stabilizing cell membranes [32]. Even if most β-blockers have prolonged negative inotropic effects, the ultra-short-acting and cardioselective β-blocker esmolol has a half-life of a few minutes, and its effects are abolished rapidly after cessation of infusion. Clinical studies have shown that esmolol can be used to obtain minimal myocardial contraction during surgery while maintaining continuous normothermic coronary perfusion to avoid ischemia [33]. This technique showed equivalent or better protection than that obtained with crystalloid or blood cardioplegia in elective coronary artery disease patients.

A recent animal experimental study in the rat presents evidence in favor of the use of oxygenated multidose crystalloid esmolol cardioplegia to induce cardiac arrest as an alternative to St. Thomas’ Hospital cardioplegia solution No. 2 [34]. The study demonstrated that esmolol infusion during global ischemia can provide complete protection obtained by an enhanced balance of myocardial oxygen supply/demand and increased blood flow to ischemic areas. The use of esmolol as a cardioplegic agent may be a beneficial alternative to standard techniques, even if the inability to deliver esmolol in blood cardioplegia because of inactivation requires further investigations for the determination of surgical relevance and applicability.

3.2. Glucose–insulin cardioplegia

Glucose–insulin–potassium solutions have been commonly used to treat ischemic myocardium in a variety of medical and surgical situations. Despite encouraging results obtained by smaller non-randomized studies [35] or by randomized trial in elective coronary artery surgery [36], the recent Insulin Cardioplegia Trial [37] failed to demonstrate a significant benefit of insulin–cardioplegic solution in the setting of high-risk patients undergoing isolated myocardial revascularization.

3.3. Additional strategies to limit reperfusion injury and to control inflammatory response

Increasingly, cardioplegic solutions have been designed to include antioxidants for the inactivation of free radicals generated during ischemia and for the provision of scavengers to the intravascular and interstitial compartments during initial reperfusion. Reduced glutathione seems one of the most effective natural scavengers; it is shown to improve myocardial recovery when administered as part of the cardioplegia solution or in the reperfusate [38].

It is well known that the relations between endothelial cells and neutrophils play a pivotal role in the damaging effects of inflammation after myocardial ischemia [39]: indeed several studies have been performed to prevent neutrophil-induced reperfusion injury.

The modalities for neutrophil depletion or neutralization of neutrophil-induced toxicity are not yet a routine part of clinical myocardial preservation. However, several investigators suggest that the prevention of neutrophil adhesion and diapedesis would provide a major increment in recovery following reperfusion. Effective reduction in neutrophil–endothelial adhesion in experimental models has been obtained by inhibition of neutrophil CD11b/CD18 up-regulation by monoclonal antibodies against CD18, pharmacologic blockade of the CD11/CD18 and administration of acadesine [40]. Reduction in postsischemic reperfusion damage has also been demonstrated experimentally with monoclonal antibodies against 1-selectin, P-selectin and ICAM-1 [41].

Filtering of leukocytes during early reperfusion has been demonstrated to provide a further increment in myocardial recovery [42,43]. Inhibition of complement activation with synthetic soluble complement receptors has shown in experimental animal models to decrease neutrophil accumulation in posts ischemic myocardium. Inhibition of neutrophil inflammatory mediators by inhibitors of elastase, cyclooxygenase, and platelet activating factor has been demonstrated to be promising for the blunting of neutrophil-induced posts ischemic injury [44].

Monoclonal antibodies against complement have been described effective in the limitation of reperfusion injury in animal models [45]. A clinical experience regarding a novel complement inhibitor therapy has been reported by Fitch et al. [46] who administrated intravenously a humanized, recombinant, single chain antibody specific for human C5 (h5G1.1-scFv) at different doses before cardiopulmonary bypass in order to prevent activation of complement and related inflammatory response. They found that C5 inhibition may represent a novel therapeutic strategy because it has demonstrated a significant attenuation of postoperative myocardial injury, cognitive deficits and blood loss. Leukotrienes synthesis was thought to be dangerous in posts ischemic inflammatory response because of direct negative myocardial inotropic and chronotropic effects: several substances have been reported to attenuate leukotriene synthesis: the lipoxygenase inhibitors and the leukotriene receptor antagonists [45]. It is known that tumor necrosis factor α reduces myocardial function after reperfusion and that its involvement in heart failure has been suggested. Adenosine, epinephrine and pentoxifylline have been used to counteract the tumor necrosis factor α activities; moreover, anti tumor necrosis factor α antibodies have also been used to reduce its associated effects in systemic inflammatory response [45].
3.4. Myocardial preconditioning

Ischemic preconditioning is a powerful protective endogenous adaptive response of the myocardium against a prolonged ischemia [47]. However, the application of ischemic preconditioning requires a temporary stop of the blood supply, which can be difficult to perform in many clinical situations. A method to avoid these potential problems associated with the clinical application of ischemic preconditioning may be the administration of pharmacological means simulating preconditioning or the manipulation of the signaling pathway involved in the protection. Several membrane receptors seem to be involved in the phenomenon of ischemic preconditioning including α-1 [48] and β-adrenoceptors [49], opioids [50] and adenosine A1 and A3 receptors [51].

Indeed, recent experimental [52] and clinical studies [53, 54] have suggested a possible role for adenosine in myocardial preconditioning because patients that underwent adenosine pretreatment showed less CPK-MB release and improved post-recovery cardiac index. Bellhomme et al. showed the results of their study related to 45 patients undergoing myocardial revascularization and randomized to receive a pharmacological preconditioning using adenosine versus a prearrest drug-free period [55]. The measurements were troponin I release and the activity of ecto-5′-nucleotidase, as a marker of protein kinase C activation. In this study, peak postoperative values of troponin I did not show any significant differences between groups, whereas postoperative values of ecto-5′-nucleotidase increased significantly only in the adenosine preconditioned group. These data confirm that adenosine can activate the protein kinase C preconditioning pathway but is not able to obtain an optimal myocardial protection, reducing significantly myocardial enzymes release after coronary reperfusion. Nevertheless uncertain results are related to unwanted side-effects due to lack of drug specificity/selectivity: it is known that adenosine agonists can induce hypotension, bradycardia, renal vasoconstriction and pain sensations [56].

The intracellular sequence of events that translate the binding of the various agonists to their membrane receptors into the protection of preconditioning remains under investigation. ATP sensitive potassium channels have also been implicated in the signal transduction mechanism of ischemic preconditioning and recent evidence has shown that the mitochondrial and not the sarcoplasmic potassium channels are involved [57]. Nevertheless, the effect of mitochondrial potassium channels openers remains controversial: indeed, whereas some studies have showed a significant reduction in mitochondria Ca2+ level after their use [58], other authors have reported little effect on membrane potential, bioenergetics or Ca2+ uptake [59]. Recently, Loubani and Galinanes [60] have demonstrated that mitochondrial KATP channels are not the end-effectors of cardioprotection by preconditioning: they showed that activation of p38 Mitogen Activated Proteine Kinase could be another important point in the comprehension of the transduction pathway of human myocardium preconditioning. These findings probably need further experimental investigations, so that any extrapolation to the clinical setting is difficult to make at the present time. On the other hand, the clinical use of potassium channel openers has been hampered by the fact that the only drug available for human use, i.e. nicorandil, cannot be used intravenously.

Several studies have demonstrated that opioid-like agents afford the ability of cardiac tissue to tolerate periods of ischemia and hypoxia [61]. Opioid receptor activation seems to improve myocardial protection with effects similar to ischemic and adenosine-induced preconditioning [62].

A recent experimental study on isolated working rat heart to assess the protective effect in myocardial preconditioning of δ-opioid receptor agonist D-Ala2–D-Leu5 enkephalin (DADLE) has shown that pharmacological activation of δ-opioid receptors allows improvement of functional protection similar to that conferred by classic ischemic preconditioning. The study has also shown that the combination of both pretreatments results in additional benefit with regard to postischemic functional recovery and that these effects are reversed by naloxone, providing evidence of the relation between ischemic preconditioning and opioid receptors-mediated pathway [63].

In addition, several studies have suggested that peptides recovered from the plasma of hibernating animals, called hibernation induction triggers, have properties similar to those of opioid-like agents in terms of enhancement of myocardium tolerance to cold ischemia. The administration of these peptides to non-hibernating animals has been reported to induce physiologic changes that mimic hibernation including bradycardia, increased ATP preservation, and decreased oxygen utilization [64].

Recent studies have convincingly shown that volatile anesthetics, including isoflurane, desflurane and sevoflurane can also be cardioprotective [65–67]. This cardioprotection, termed anesthetic-induced preconditioning, mimics ischemic preconditioning with mechanisms not yet completely elucidated. Studies in vitro have shown evidence about an indirect enhancement of ischemic preconditioning resulting in cardioprotection against myocardial infarction with the KATP channels playing an important role [68]. Recently, De Hert et al. [69] suggested that volatile anesthetics are cardioprotective in humans. This study has demonstrated that sevoflurane-anesthetized patients had reduced cardiac enzyme release and improved left ventricular function after coronary artery bypass surgery as compared to patients anesthetized with propofol. This preliminary clinical evidence suggest that anesthetic-induced preconditioning also occurs in humans even if larger and multicenter trials need to be addressed.
3.5. Na+/H+ exchange inhibition and myocardial protection

Protons accumulating during ischemia are extruded at the time of reperfusion in exchange for sodium ions. The resulting sodium overload cannot be adequately handled by the sodium/potassium pump because it is inefficient due to ischemia-induced shortage of energy. This excess of intracellular sodium is then extruded from cells through the sodium/calcium exchanger, which functions in a reverse mode. It brings calcium ions in the cells allowing a dangerous calcium overload, responsible for the ischemia/reperfusion tissue injury. Recent reports have shown that sodium–hydrogen exchangers play a central role in the regulation of intracellular sodium, calcium and pH homeostasis, and contribute to ischemia–reperfusion myocardial damage [70]. Specific inhibition of the sodium–hydrogen exchanger isoform 1, located on the plasma membrane of the cardiac myocyte, with HOE-642 (cariporide) [71,72], or with dimethyl amiloride (DMA) [73], seems to decrease myocardial infarct size and to improve postischemic functional recovery and reperfusion ion homeostasis in experimental animal studies.

Even if pilot studies in humans have been promising [74], the first large-scale trial to assess the potential protective effect of sodium–hydrogen exchanger inhibition in humans is the GUARDIAN trial [75]. The trial enrolled 11,590 patients with unstable angina or non ST elevation myocardial infarction or undergoing high-risk percutaneous or surgical revascularization: these patients were randomized to receive placebo or one of three established doses of cariporide for the period of risk. Really, the trial failed to show an overall clinical benefit of cariporide over placebo on the primary end point of death or myocardial infarction. Nevertheless, the stated highest dose of cariporide was associated to a significant risk reduction, limited only to patients undergoing bypass surgery, with no effect on mortality. This beneficial effect in the ischemia–reperfusion injury such as in coronary artery bypass grafting supports the necessity of further investigations in other important clinical settings as myocardial hibernation and stunning, apoptosis and left ventricular remodeling.

3.6. Nitric oxide/L-arginine supplemented cardioplegia

Nitric oxide, an endogenously produced labile gas, has been demonstrated to reduce myocardial ischemia–reperfusion damage in experimental animal models; moreover, it seems to exert a myocyte protective role as antiapoptotic factor and as mediator in ischemic preconditioning [76]. Several experimental studies have suggested that the administration of blood cardioplegia with L-arginine may improve myocardial protection increasing nitric oxide release [77,78], allowing a better ventricular function recovery in areas at risk [79] and increases myocardial tissue pH recovery [80] in animal models.

The clinical experience in cardiac surgery with L-arginine is limited: Wallace and colleagues, in a small randomized trial, found a significant decrease in coronary vascular resistance and an increase in blood flow through saphenous vein grafts in the group of patients in which L-arginine was administered after coronary artery bypass grafting [81]. Moreover, in this category of patients they also showed an increase in the serum level of L-citrulline, as a consequence of an increase in the production of nitric oxide after administration of L-arginine. A recent prospective randomized trial comparing standard blood cardioprotective solution to L-arginine enriched solution in patients undergoing coronary artery bypass grafting showed that patients who received L-arginine supplemented cardioplegia had lower release of serum cardiac troponin T after the operation [82]. The best results were obtained with the association of warm cardioplegia and administration of L-arginine, suggesting a beneficial effect of L-arginine in normothermic cardiac arrest, even if a larger number of patients seem to be necessary to define the effect of L-arginine in cold blood solutions.

4. Future challenges

Current techniques of intraoperative myocardial protection are constantly evolving with the use of less conventional modalities of cardioplegia and have dramatically reduced the morbidity and mortality of cardiac operations. Based on the experience with current cardioprotective techniques we can conclude that blood from cardioplegic solutions appears superior to cold cardioplegia in terms of myocardial protection and that additional adjuncts as glutamate/aspartate enhancement, antioxidant supplementation, nitric oxide donors and maintenance of calcium homeostasis seem effective and associated with post-operative improved results. In summary, to date, changes in cardioplegic composition, temperature and route of delivery allow elective cardiac surgery to be performed with a relatively low risk. Thus, in the near future, any further measures in myocardial protection will be necessary to improve current techniques that are not completely adequate in high-risk clinical settings.

The clinical experience with preconditioning is still limited. Indeed the intracellular sequence of events that translate the binding of the various agonists to their membrane receptors into the protection of preconditioning remains under investigation. Initial clinical studies on anesthetic-induced preconditioning are provocative but larger investigations of the impact of volatile anesthetics are now required to further establish the clinical significance of anesthetic-induced preconditioning in humans. Thus it is early to determine whether pharmacological preconditioning can be a routinely applicable method allowing effective myocardial protection.
Recent reports have shown that sodium–hydrogen exchangers play a central role in the regulation of intracellular sodium, calcium and pH omeostasis, and contribute to ischemia–reperfusion myocardial damage. The rationale behind the use of sodium–hydrogen exchangers inhibition and the analysis of available data allow us to reasonably predict that these drugs may contribute to improve cardioplegic protection. As a consequence of these findings, the multinational, double-blind, randomized, placebo-controlled sodium–hydrogen Exchange Inhibition to Prevent Coronary Events in Acute Cardiac Conditions (EXPEDITION) Trial was initiated in 2000. The purpose of this study was to test the hypothesis that the sodium–hydrogen exchange inhibitor cariporide will reduce all-cause mortality and non-fatal myocardial infarction after CABG surgery performed in high-risk patients (urgent or repeat CABG, multivessel disease, comorbidities). Other clinical end-points are the rate of new developed ventricular dysfunction, major arrhythmia, need for inotropic support or mechanical ventricular assist devices. The results of this trial are expected in 2003.

Ischemic reperfused myocardium may become a potential target for gene therapy in the near future because gene transfer could be an alternative pharmacological approach to protect the myocardium from ischemic injury. The fact that ischemic reperfused heart is a target for gene therapy is supported by the observation that intracoronary administration of an adenoviral vector encoding fibroblast growth factor could ameliorate ischemic reperfusion injury [83]. Although no attempts have been made to deliver genes into the heart, the perspective of gene therapy remains high. It is well known that ischemia–reperfusion results in the induction of the expression of mRNAs for heat shock proteins (HSP) and antioxidants including HSP 27, HSP 70, peroxidase were found to be resistant to ischemic reperfusion [85,86]. Moreover, reports are available for in vivo gene transfer of both Cu/Zn-SOD [87] or Mn-SOD [88]. Nitric oxide represents another potential candidate for gene therapy for myocardial protection; indeed, providing hearts with an excess amount of nitric oxide results in a decrease in ischemia–reperfusion injury [77]. In fact, direct gene transfer of nitric oxide synthase was reported recently [89]. However, clear definition of the target cell (myocytes, endothelial cells) and elimination of undesirable side effects (deleterious enzymes up-regulation) are necessary; moreover, this kind of therapy must be proven superior compared to other pharmacological interventions in myocardial protection before clinical application.

References


Schultz JJ, Hsu AK, Gross GJ. Ischemic preconditioning is mediated by a peripheral opioid receptor mechanism in the intact rat heart. J Mol Cell Cardiol 1997;29:1355–62.


Schultz JJ, Hsu AK, Gross GJ. Ischemic preconditioning is mediated by a peripheral opioid receptor mechanism in the intact rat heart. J Mol Cell Cardiol 1997;29:1355–62.


