Review

Future Perspective of Cardioplegic Protection in Cardiac Surgery

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Abstract

“Depolarized arrest”, induced by hyperkalemic (moderately increased extracellular potassium) cardioplegia is the gold standard to achieve elective temporary cardiac arrest in cardiac surgery. Hyperkalemic cardioplegic solutions provide good myocardial protection, which is relatively safe and easily and rapidly reversible. However, this technique has detrimental effects associated with ionic imbalance involving sodium and calcium overload of the cardiac cell induced by depolarization of the cell membrane. Hence, the development of an improved cardioplegic solution that enhances myocardial protection would be expected as an alternative to hyperkalemic cardioplegia. In this review, we assess the potential disadvantages of “depolarized arrest” and the suitability and clinical potential of “non-depolarized arrest”. “Magnesium cardioplegia” and “esmolol cardioplegia” has been shown to exert superior protection with comparable safety profiles to that of hyperkalemic cardioplegia. These alternative techniques require further examination and investigation to challenge the traditional view that hyperkalemic arrest is best.

Endogenous cardioprotective strategies, termed “ischemic preconditioning” and “ischemic postconditioning”, may have a role in cardiac surgery to provide additional protection. The elective nature of cardiac surgery, with the known onset of ischemia and reperfusion, lends it to the potential of these strategies. However, the benefit of preconditioning and postconditioning during cardiac surgery is controversial, particularly in the context of cardioplegia. The clinical application of these strategies is unlikely to become routine during cardiac surgery because of the necessity for repeated aortic crossclamping with consequent potential for embolic events, but offers considerable potential especially if “pharmacological” preconditioning and postconditioning could be established. (J Nippon Med Sch 2013; 80: 328–341)

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1. Introduction

Hyperkalemic (moderately increased extracellular potassium) cardioplegia that induces a depolarized arrest has been the cornerstone and gold standard of myocardial protection for more than 30 years. Despite this, hyperkalemia is known to have detrimental effects on both myocardium and endothelium, causing edema, increased energy utilization, and calcium overload. This may result in a complicated postoperative course after cardiac operation, particularly in patients with pre-existing left ventricular dysfunction. In addition, the demographic shift towards elderly patients with more impaired ventricular function has increased the operative risks. Thus, there is a need to explore improved methods of myocardial protection to delay the damaging effects of global myocardial ischemia, especially for high-risk patients. Consequently, the search for cardioplegic solutions to improve myocardial protection during ischemia and reperfusion continues, with current efforts concentrating on alternative concepts that avoid membrane depolarization and its detrimental effects.

This review describes the potential disadvantages of depolarized arrest and highlights “magnesium cardioplegia” and “esmolol cardioplegia” which are alternative arresting agents that may possibly be applicable in a clinical setting, together with the additional protective strategies of “ischemic preconditioning (IPC)” and “ischemic postconditioning (POC)” in the context of cardioplegia.

2. Depolarized Arrest: Hyperkalemic Cardioplegia

In 1955, Melrose and colleagues introduced the concept of “elective reversible cardiac arrest” using an intracoronary infusion of a high concentration of potassium citrate (77 mmol/L) added to blood. This arresting solution was used clinically by a number of centers in the late 1950s with apparently good results. However, subsequent studies claimed that the use of potassium citrate was associated with myocardial injury, including areas of necrosis, which had been observed at autopsy in patients who had died. Consequently, the use of hyperkalemic solutions was abandoned for almost 20 years. Over this time period, surgeons used various techniques to protect the heart during ischemia, including continuous or intermittent normothermic perfusion, electrically induced ventricular fibrillation, or topical (and profound) hypothermia; surgical results were generally good, but mortality rates were high (10–20%).

At St. Thomas’ Hospital in London, Hearse and colleagues reported a large series of experimental studies in which many individual components of a potassium-based cardioplegic solution were systematically characterized and optimized in the mid-1970s. From these studies, the St. Thomas’ group rationalized that three main components of effective cardioplegic protection were (a) the induction of rapid chemical arrest to conserve energy and provide a still operating field, (b) the use of hypothermia to reduce the rate of metabolism, and (c) the addition of anti-ischemic agents to enhance protection by combating specific deleterious ischemia-induced changes. The St. Thomas’ Hospital cardioplegic solution (STH) was first introduced into clinical practice at St. Thomas’ Hospital by Brainbridge in 1975. This solution was subsequently modified to become the St. Thomas’ Hospital cardioplegic solution No. 2 (STH2), which had a potassium concentration of 16 mmol/L, an elevated magnesium concentration of 16 mmol/L, and a normal ionized calcium concentration. Within several years, hyperkalemic cardioplegia became the predominant cardioprotective technique throughout the world, with the St. Thomas’ solution being the most widely used cardioplegic solution.

Elevation of the extracellular potassium concentration to around 10 mmol/L shifts the resting membrane potential of myocytes from ~85 mV to ~65 mV, at which level the voltage-dependent sodium channel is inactivated and thereby blocks conduction of the myocardial action potential, inducing “depolarized arrest”. Further increases in extracellular potassium will cause further depolarization of membrane potential; when the resting membrane potential reaches about ~40 mV
(at an extracellular potassium around 30 mmol/L), the L-type calcium channel will be activated and lead to calcium influx into the myocyte, promoting calcium overload. Thus, any beneficial effects of elevated extracellular potassium are restricted to a relatively narrow concentration window (10 to 30 mmol/L). However, even at these levels of depolarization, other ionic currents remain active. It is postulated that the voltage-dependent activation and inactivation of the sodium channel are governed by “gates” that operate at different rates and lead to a sodium “window” current that is a noninactivating current at these membrane potentials\textsuperscript{12}. This will tend to increase the intracellular sodium concentration which will increase calcium loading of the myocyte, leading to contracture and cell death.

Thus, although hyperkalemic cardioplegia is by far the most widely used technique, it has a number of disadvantages and is not necessarily the best and most optimally protective.

3. Non-depolarized Arrest

Alternative techniques that avoid the problems associated with depolarized arrest may provide superior protection. An increasing number of studies have investigated the potential of non-depolarized arrest; however, most of these strategies have not been applied to cardiac surgery because of reversibility and systemic safety profile. In this review, we focus on “magnesium cardioplegia” and “esmolol cardioplegia” as examples of non-depolarized cardioplegia.

3-1. Magnesium Cardioplegia

Elevated extracellular magnesium can induce myocardial arrest\textsuperscript{14}, which is thought to occur because magnesium acts as a “natural” L-type calcium channel blocker via displacement of calcium\textsuperscript{15}. Magnesium was used in the Kirsch solution at a concentration of 160 mmol/L, but this was in combination with a high (11.0 mmol/L) concentration of the sodium channel blocker procaine\textsuperscript{16}. Kirsch solution was poorly protective against both normothermic and hypothermic ischemia compared to St. Thomas’ Hospital solution\textsuperscript{15}; hence, Kirsch solution has not been currently used in clinical practice.

As with calcium antagonists, magnesium has been employed more frequently as an additive protective agent rather than as a cardiac arresting agent per se. Hearn and colleagues\textsuperscript{17} showed it to be an exceptionally powerful protective agent that, in the rat, exhibits a bell-shaped dose-response profile, with an optimal concentration at 16 mmol/L, irrespective of whether hearts are subjected to normothermic or hypothermic ischemia. Since this finding, magnesium has become a standard component of St. Thomas’ Hospital cardioplegic solution. The addition of magnesium to calcium-containing hyperkalemic cardioplegia has been shown to protect against calcium-induced hypercontracture during arrest\textsuperscript{17}, and the relationship between magnesium and calcium has been extensively studied. It has been demonstrated that, under normothermic condition, the required magnesium concentration is dependent on the calcium concentration\textsuperscript{18}; high calcium requires high magnesium and vice versa. However, the temperature influences the ionic balance such that the required calcium for a given magnesium concentration is reduced by hypothermia\textsuperscript{21}. Magnesium is thought to exert its anti-ischemic protective effect by influencing the high-energy phosphate content of the myocardium, resulting in improved ATP availability and reduced ATP utilization\textsuperscript{19}. These metabolic effects are associated with reduced intracellular calcium accumulation\textsuperscript{17}, which is linked to the calcium channel antagonistic effects of magnesium\textsuperscript{21,23}.

To our knowledge, the systematic characterization of an optimal magnesium concentration when used alone as a cardioplegic agent has not previously been studied. Thus, we recently compared the protective effect of different concentrations of magnesium (when used as a cardioplegic agent per se) to hyperkalemic STH2 in isolated Langendorff-perfused rat hearts subjected to a single initial arresting infusion before 50 min of global normothermic ischemia\textsuperscript{24}. Contracture development was slowest at a magnesium concentration of 25 mmol/L, as well as inducing the lowest magnitude of peak contracture (Fig. 1A). In addition, these
Contracture development and recovery of function in hearts subjected to 50 minutes ischemia with single infusion of cardioplegia and 60 minutes reperfusion. (A) Temporal profiles for ischemic contracture development during 50 minutes ischemia. (B) Recovery of left ventricular developed pressure (LVDP), expressed as a percentage of pre-ischemic control value at baseline, throughout the 60 minutes reperfusion duration. Filled circles=STH2; open circles=16-Mg: 16 mmol/L of magnesium; open triangles=25-Mg: 25 mmol/L of magnesium; open squares=35-Mg: 35 mmol/L of magnesium; open diamonds=50-Mg: 50 mmol/L of magnesium. Values are mean ± standard error of the mean of either 6 hearts in STH2, 25-Mg, and 35-Mg, 7 hearts in 16-Mg, or 8 hearts in 50-Mg. (*=p<0.05 for 50-Mg compared with all other groups)

Redrawn from Maruyama and Chambers.¹

Contracture-related parameters of magnesium cardioplegia were significantly better than that of hyperkalemic STH2 (Fig. 1B). Magnesium concentrations of 16 and 35 mmol/L also protected hearts to a similar extent after 60 min of reperfusion, but recovery was slower; in contrast, protection with 50 mmol/L magnesium was significantly lower than
all other groups (Fig. 1B). Thus, the optimal magnesium concentration was established at 25 mmol/L, with higher concentrations having detrimental effects. Surprisingly, when the ischemic duration was increased to 60 min, and multidose (every 20 min) infusions of cardioplegia were used, 25 mmol/L magnesium cardioplegia provided improved protection compared to STH2 (Fig. 2A and 2B). McCully and colleagues demonstrated that senescent myocardium is more sensitive to ischemia,
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experiencing a 30% more rapid rise in [Ca] than mature myocardium\(^a\). Recent studies have shown that elderly patients, especially octogenarians, undergoing cardiac surgery are at higher risk for operative mortality\(^b\). Thus, cardioplegia administered to elderly patients should include magnesium to reduce calcium overload and associated lethal ischemic injury. One potential limitation of magnesium cardioplegia is that the time to achieve arrest with 25 mmol/L magnesium was longer than with STH2; despite this, 25 mmol/L magnesium arrested all hearts within the 2 min infusion duration and also maintained mechanical cessation during ischemia. According to the relationship between magnesium and calcium depending on temperature as described previously, the optimal magnesium concentration in magnesium cardioplegia, under hypothermic conditions, would be higher than 25 mmol/L\(^c\). It also demonstrates a requirement to assess the ionic relationship during hypothermic conditions. Another problem is that the response to magnesium of human myocardium is less than rat myocardium\(^d\), which might indicate that a higher magnesium concentration would be required in human hearts. Consequently, caution should be exercised against extrapolating results from the rat heart to other species, especially human heart.

Magnesium cardioplegia provides superior cardioprotection with lower and slower ischemic contracture compared to hyperkalemic cardioplegia, and is a relatively simple and inexpensive way to protect the heart with systemic safety profiles.

3.2. Esmolol Cardioplegia

Most \(\beta\)-blockers have prolonged negative inotropic effects that last for hours, which render them unsuitable for use during acute situations, such as cardiac operations. However, esmolol, an ultra-short-acting cardioselective \(\beta\)-blocker, has an extremely short duration of action (half-life of about 9 min), which allows its negative inotropic effects to be abolished rapidly after reduction or cessation of infusion. Its main clinical use is to treat hypertension and tachycardia in critical care. Esmolol has also been shown to be cardioprotective in unstable angina patients\(^2\) and in cardiac surgery as a supportive drug\(^2\). These properties have been exploited in both experimental\(^2\) and clinical\(^2\) studies. Clinically, esmolol has been used during cardiac surgery as a means of inducing “minimal cardiac contraction” (profound bradycardia during maintained continuous normothermic myocardial perfusion to avoid ischemia) to allow coronary artery bypass surgery on the beating heart. These studies also showed that continuous coronary perfusion with warm esmolol-enriched blood provided better myocardial protection compared to conventional cardioplegic solutions\(^2\).

Esmolol, at high concentrations (1.0 mmol/L), was shown to be an effective cardioplegic agent by inducing cardiac arrest in Langendorff-perfused rat hearts\(^2\). When added to an oxygenated perfusate, esmolol cardioplegia provided superior cardioprotection in isolated rat hearts when compared to cross-clamp fibrillation\(^2\) or St. Thomas’ Hospital cardioplegic solution\(^2\). In addition, esmolol cardioplegia with multidose infusions (for 2 min every 15 min) completely protected isolated rat hearts for extended periods (up to 90 min) of global normothermic ischemia (Fig. 3)\(^2\). The \(\beta\)-blocking action of esmolol can explain the bradycardiac and negative inotropic effects of the in vivo studies above, but the arresting effect of esmolol at high concentrations in Langendorff-perfused rat hearts isolated from any catecholamine background must be explained by other mechanisms. Recent studies have shown that millimolar concentrations of esmolol inhibit the L-type calcium channels and the fast sodium channels, resulting in a pronounced negative inotropy, prevention of action potential conduction and induction of a diastolic non-depolarized arrest\(^2\). The fast hydrolysis of esmolol by the red cell esterases gives it independence from renal or hepatic clearance (which might be compromised after cardiopulmonary bypass) from the systemic circulation, with associated safety profile advantage over some of the other conventional sodium channel blockers or calcium channel blockers. Clinically, continuous infusion of esmolol at relatively high concentrations (0.3 mmol/L) has already been used safely in cardiac surgery without any systemic
adverse effects\textsuperscript{20}. Hence, we would speculate that the use of esmolol as a cardioplegic agent (short, multiple, high-dose infusion) is unlikely to have major systemic effects, although its safety requires verification. However, the reversibility of the negative inotropic effect of esmolol, in rat heart studies, was shown to be compromised when esmolol was used for prolonged infusion periods in excess of 20 min at high concentrations (1.5 mmol/L)\textsuperscript{5}; esmolol concentrations of 0.75 mmol/L were optimal for reversibility, suggesting that concentrations higher than 1 mmol/L (when used for prolonged continuous infusion) might not be useful.

The use of esmolol as a cardioplegic agent may be a beneficial alternative to conventional hyperkalemic cardioplegia and would be applicable to all types of cardiac operations. These potential advantages of esmolol need to be explored in a more clinically relevant in vivo model of cardiopulmonary bypass.

4. Additional Protective Strategies: “Preconditioning” and “Postconditioning”

Recently, “ischemic preconditioning (IPC)” and “ischemic postconditioning (POC)” have been established as a means of providing an endogenous cardioprotection in experimental studies. Additional cardioprotection of these strategies during cardiac surgery is discussed in this chapter.

4-1. Ischemic Preconditioning

IPC, first described by Murry’s group in a canine model of regional ischemia in 1986, is defined as multiple brief episodes of ischemia prior to a prolonged ischemic insult\textsuperscript{34}. In 1992, St. Thomas’ group has shown IPC provides cardioprotection in the setting of global ischemia\textsuperscript{2}; thereafter, additional protection of IPC in combination with cardioplegia has been extensively studied. Although numerous studies have proven the benefit of IPC in myocardial protection in regional or global models of unprotected ischemia, the efficacy of IPC in combination with cardioplegia is somewhat controversial\textsuperscript{35-41}. Clinically, IPC has been applied to coronary artery bypass grafting (CABG)\textsuperscript{42-44}. Some clinical studies have showed postoperative improvement of the cardiac index, reduced inotropic requirements and antiarrhythmic effects\textsuperscript{45}, whereas, other clinical studies have found that IPC does not enhance cardioplegic protection\textsuperscript{46} and might even be deleterious\textsuperscript{47}.

IPC, despite many positive experimental and clinical studies demonstrating its efficacy, has not yet been adopted during cardiac surgery\textsuperscript{48}. Many factors may account for this, such as the necessity for repeated aortic crossclamping with consequent potential for embolic events, the reluctance to prolong the surgical procedure, and evidence that volatile anesthetics or cardiopulmonary bypass per se may induce IPC. The use of cardiopulmonary bypass may be an important aspect of IPC efficacy in clinical situations. Ghosh and Galinanes have demonstrated that IPC is protective in patients undergoing off-pump CABG but offers no additional benefit in conventional CABG\textsuperscript{49}. Moreover, IPC may
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Fig. 4 Recovery of left ventricular developed pressure (LVDP), expressed as a percentage of pre-ischemic control value at baseline during 60 minutes reperfusion. (A) 30 minutes ischemia (+POC); (B) 45 minutes ischemia (+POC); (C) 60 minutes ischemia (+POC); (D) STH2 and 30 minutes ischemia (+POC); (E) STH2 and 45 minutes ischemia (+POC); (F) STH2 and 60 minutes ischemia (+POC). Open circles=ischemia alone, filled circles=ischemia+POC, open square=STH2 protection, filled square=STH2+POC. Values are mean ± standard error of the mean of 6 hearts per group. (*p<0.05 compared with the same ischemic duration in the non-postconditioned group.)

Redrawn from Maruyama and Chambers⁷.

be suitable for off-pump CABG because this procedure needs no repeated aortic crossclamping. However, even in the off-pump CABG, the efficacy of IPC is controversial⁶.

Pretreatment with pharmacological agents prior to ischemic insult, termed “pharmacological preconditioning”, can induce protective effects to mimic IPC⁴. The clinical application of pharmacological preconditioning to cardiac surgery offers the benefits of IPC without its disadvantages because this procedure needs no repeated aortic crossclamping and no additional intermittent ischemia. Since the efficacy of adenosine pretreatment in CABG was first reported clinically by Lee and colleagues in 1995⁶, various pharmacological agents, such as nicorandil⁷, diazoxide⁸, or bradykinin⁹, have been used in the clinical setting. However, clinical studies have yielded conflicting results⁹,¹⁰. Theoretically, pharmacological preconditioning may be the best way to provide an additional protection in combination with cardioplegic arrest, if optimal pharmacological agents could be established clinically.
4.2. Ischemic Postconditioning

POC, first described by Vinten-Johansen’s group in a canine model of regional ischemia in 2003, is defined as brief interruptions of reperfusion at the onset of reperfusion before complete reperfusion. More recently, POC efficacy after global ischemia has been demonstrated. Recent studies have shown that POC protects the heart against reperfusion injury by activating prosurvival kinases, termed the RISK pathway, through the activation of Akt and ERK. The activation of RISK phosphorylates downstream targets (such as GSK-3β, BAD/Bax, and endothelial NOS) leading to the inhibition of the mitochondrial permeability transition pore (mPTP). The inhibition of the mPTP plays a critical role in the cardioprotection elicited by IPC and POC. The mPTP has been shown to remain closed during ischemia and to open only in the first few minutes of reperfusion (by binding of cyclophilin D to the matrix side of a core protein) under conditions of high mitochondrial calcium overload, especially when it is accompanied by ATP depletion, elevated inorganic phosphate, and increased matrix pH.

Unlike IPC, POC offers the unique opportunity to be applied in clinical practice, because this procedure can be initiated at the time of reperfusion during percutaneous coronary intervention (PCI). As demonstrated initially by Staat and colleagues in a multicenter, randomized, controlled study and subsequently confirmed by other studies, POC during PCI was protective in patients who suffered acute myocardial infarction. As with “pharmacological preconditioning”, administration of various pharmacological agents, such as adenosine, opioids, bradykinin, cyclosporine-A, or sivelestat (a neutrophil elastase inhibitor), at the time of reperfusion, termed “pharmacological postconditioning”, can induce protective effects to mimic POC in experimental studies. In addition, “pharmacological postconditioning” using adenosine and cyclosporine-A has been successfully translated to clinical setting. These observations have raised the possibility that POC may enhance the efficacy of current methods of intraoperative myocardial protection (using hypokalemic cardioplegia) in cardiac surgery.

We examined whether POC exerted additional protection if the ischemia was preceded by cardioplegic protection in isolated Langendorff-perfused rat hearts. We found (Fig. 4 and 5) that
POC was effective after 30 min ischemia alone, but not after longer periods of ischemia; in contrast, POC was ineffective after cardioplegic protection with STH2 (hyperkalemic cardioplegia with elevated magnesium concentrations of 16 mmol/L) at all ischemic durations (even when the recovery at 60 min was equivalent to that after 30 min of ischemia alone). Magnesium, a natural L-type calcium channel blocker, protects the heart from reperfusion injury through preventing calcium overload, with elevated magnesium concentration suggested to also involve inhibition of mPTP opening. We speculated that the protective effect of increased magnesium in cardioplegia may inhibit mPTP opening, and hypothesized that the efficacy of POC following cardioplegic arrest may be related to magnesium concentration in cardioplegia. Our demonstration that POC was effective in hearts protected with cardioplegia containing either low-magnesium or zero-magnesium (Fig. 6 and 7) under specific conditions confirmed this possibility. However, recent clinical studies have demonstrated the

Fig. 6 Recovery of left ventricular developed pressure (LVDP), expressed as a percentage of pre-ischemic control value at baseline during 60 minutes reperfusion. (A) 30 minutes ischemia, low-Mg cardioplegia (±POC); (B) 45 minutes ischemia, low-Mg cardioplegia (±POC); (C) 60 minutes ischemia, low-Mg cardioplegia (±POC); (D) 30 minutes ischemia, zero-Mg cardioplegia (±POC); (E) 45 minutes ischemia, zero-Mg cardioplegia (±POC); (F) 60 minutes ischemia, zero-Mg cardioplegia (±POC). Open triangles=low-Mg cardioplegia, filled triangles=low-Mg cardioplegia+POC, open diamond=zero-Mg cardioplegia, filled diamond=zero-Mg cardioplegia+POC. Values are mean ± standard error of the mean of 6 hearts per group. (*p<0.05 compared with the same ischemic duration in the non-postconditioned group.) Redrawn from Maruyama and Chambers.

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efficacy of POC after valve replacement surgery and pediatric congenital heart surgery. These studies showed reduced release of markers of myocardial injury, reduced post-operative inotropic requirements and shorter ICU stay, and used blood-based hyperkalemic cardioplegia containing elevated magnesium. A number of factors could account for these contrasting results, including species differences in sensitivity to magnesium, species variability in the efficacy of POC, temperature and the use of young healthy rat hearts compared to aged and sick human hearts.

As with IPC, the clinical application of POC that uses repeated aortic crossclamping is unlikely to become routine during cardiac surgery because of the potential for embolic injury, but offers considerable potential if a pharmacologic means of induction (i.e., "pharmacological postconditioning") could be established.

5. Conclusions

The development of hyperkalemic cardioplegic solutions revolutionized cardiac surgery by providing good myocardial protection in the 1970s. Although hyperkalemic cardioplegia that induces "depolarized arrest" is the gold standard of myocardial protection in the 21st century, it has a number of disadvantages and is not necessarily the best and most optimally protective, especially for high-risk patients. Alternative cardioplegic agents that induce "non-depolarized arrest", such as "magnesium cardioplegia" and "esmolol cardioplegia", have been shown to exert superior cardioprotection to hyperkalemic cardioplegia; however, considerably more characterization and research are required before these strategies could be applied to routine use in cardiac surgery.

The role of IPC and POC in cardiac surgery is still uncertain. Although IPC and POC by repeated aortic crossclamping is unlikely to be applied for routine clinical use because of the inherent risks of embolic injury, "pharmacological preconditioning and postconditioning" would be optimal as an additional cardioproteective strategy to avoid the adverse consequences associated with repeated aortic crossclamping. The ultimate cardioprotective strategy in cardiac surgery might be a good
combination of “non-depolarized cardioplegia” and “pharmacological preconditioning and postconditioning”.

Conflict of Interest: None declared.

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