Myocardial protection in cardiac surgery: how limited are the options? A comprehensive literature review

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April 28, 2020

Abstract

For patients undergoing cardiopulmonary bypass, myocardial protection is a key for successful recovery and improved outcomes following cardiac surgery that requires cardiac arrest. Different solutions, components, and modes of delivery have evolved over the last few decades to optimise myocardial protection. These include; cold and warm, blood and crystalloid solution through antegrade, retrograde or combined cardioplegia delivery approach. However, each method has its own advantages and disadvantages, posing a challenge to establish a gold standard cardioplegic solution with an optimised mode of delivery for enhanced myocardial protection during cardiac surgery. The aim of this review is to provide a brief history of the development of cardioplegia, explain the electrophysiological concepts behind myocardial protection in cardioplegia, analyse the current literature and summarise existing evidence that warrants the use of varying cardioplegic techniques. We provide a comprehensive and comparative overview of the effectiveness of each technique in achieving optimal cardioprotection and propose novel techniques for optimising myocardial protection in the future.

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Disclosure: There are no conflicts of interest or sources of support

Funding : No funding obtained

Keywords : Myocardial protection, Cardioplegia, Cardiac arrest

Abstract:

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The aim of this review is to provide a brief history of the development of cardioplegia, explain the electrophysiological concepts behind myocardial protection in cardioplegia, analyse the current literature and summarise existing evidence that warrants the use of varying cardioplegic techniques. We provide a comprehensive and comparative overview of the effectiveness of each technique in achieving optimal cardioprotection and propose novel techniques for optimising myocardial protection in the future.

Introduction

Cardioplegia is an essential cardioprotective pharmacological therapy for electromechanical cardiac arrest during cardiac surgery[(1)]. This is achieved by altering cellular electrochemical gradients to reduce myocardial metabolic demands by inducing electrical quiescence. In addition, cooling of the myocardium to minimise ischaemia-reperfusion (I-R) injury associated with being on cardiopulmonary bypass, which is a significant cause of mortality and morbidity in cardiac surgery[(2)]. As well as myocardial protection, cardioplegia is also indicated for a bloodless and motionless operating field for prolonged periods of time.

There are many forms of cardioplegia that are currently used in clinical practice; this can be classified based on varying parameters such as temperature (cold, tepid or warm), solution (crystalloid or blood), delivery method (anterograde, retrograde or combined) and substances within the solution (glucose with insulin and potassium, Mg^{2+}, HCO_3^-, procaine etc.). This suggests that there are probably several methods to arrest the myocardium safely, prior to aortic cross-clamping. Nevertheless, there is still an ongoing debate on the relative effectiveness of these variable forms of cardioplegia.

Literature Search:

A comprehensive literature search was done on PubMed, SCOPUS, Embase, Cochrane database, google scholar and Ovid to identify the articles that discussed the use of myocardial protection methods during open heart surgery. Key words used were 'Cardioplegia' 'blood cardioplegia' 'crystalloid cardioplegia' 'warm cardioplegia' 'cold cardioplegia' 'myocardial protection' 'cardioplegia solutions' 'antegrade' 'retrograde'. The search terms were used as key word and in combination as MeSH terms to maximize the output from literature findings. A staged literature search was done, whereby a separate literature search was performed for each section within this article and all the relevant studies were identified and summarized separately. If a paper is reporting on many aspects of the myocardial protection, then the results have been shared between different parts of this review. The relevant articles are cited and referenced within each section separately. No limit placed on publication time or language of the article.

History of Cardioplegia in a Nutshell

Rapid cardiac arrest before cardiac surgery, and therefore the concept of cardioplegia, with a hyperkalaemic solution was introduced by Melrose et al. in 1955, and it enabled better post-ischaemic recovery of myocardial function compared to mere aortic cross clamping[(3)]. However, it also led to $[Ca^{2+}]_I$ overload, and Hearse et al. found that myocardial damage was related to ATP depletion along with this $[Ca^{2+}]_I$ overload[(4)]. Hence, Hearse proposed three components of myocardial protection by cardioplegia during cardiac surgery: (a) rapid

diastolic cardiac arrest to conserve energy by $[Na^+]_I$ and $[Ca^{2+}]_I$ depletion, extracellular K^+ and Mg^{2+} elevation and infusion of local anaesthetic agents or Ca^{2+} antagonists, (b) hypothermia to slow down cellular metabolic demands, and (c) application of substances (i.e. oxygen, energy substrates etc.) to prevent or reverse IR injury[5]. These principles now form the foundation for most cardioplegic solutions.

Bretschneider et al. developed Custodiol, an intracellular crystalloid cardioplegic solution which is Ca^{2+}-free with a low Na^+ concentration to reduce the Na^+ gradient causing the loss of action potential (AP) and consequently inducing cardiac arrest[6]. In comparison, Hearse introduced an optimal extracellular crystalloid cardioplegic solution, called the St. Thomas' Hospital solution, which mainly relies on depolarised hyperkalemic (16mM) arrest. In addition, Lolley et al. developed glucose cardioplegic solutions containing insulin and K^+ to enhance ATP production during I-R, which was later found to reduce myocardial injuries in animal models of I-R[7].

Cold blood cardioplegia was proposed by Buckberg et al. to arrest, perfuse then reperfuse the myocardium with different compositions of hyperkalaemic crystalloid cardioplegic solution mixed with blood in a 1:4 ratio[8]. Calafiore et al. later introduced warm blood cardioplegia containing K^+/Mg^{2+} which provides myocardial protection when applied continuously[9].

Cardioplegic delivery can be anterograde, retrograde or combined. Anterograde delivery involves running the cardioplegia solution down the coronary arteries and supplying the myocardium in the same fashion that blood normally does. In retrograde cardioplegia however, the flow of solution is administered in a retrograde manner, and it is indicated in cases such as critical coronary stenosis or when anterograde delivery does not provide sufficient cardioplegic solution to the myocardium distal to the occlusion[10]. Despite the extensive study of cardioplegia solutions over the last decades (Fig.1), the ideal myocardial protection method during cardiac surgery is still uncertain.

The Physiology of Cardioplegia

To rapidly arrest the myocardium in diastole and maintain it in a depolarised state, it is necessary to understand the underlying electrophysiology behind hyperkalaemia, which is a fundamental constituent of most cardioplegic solutions. Hyperkalaemia induces diastolic arrest by establishing a new resting membrane potential (RMP) that is more depolarised (i.e. more positive) than normal[11]. It is worth noting that the RMP is maintained by the ATP-driven Na^+/K^+ pump, which creates an electrochemical gradient across the sarcolemmal membrane (Fig.2).

In physiological states, AP generation occurs due to activation of voltage-gated channels which allow influx of cations. Following sinoatrial node stimulation, voltage-gated Na^+ channels (VGNCs) open, provided the -65mV threshold is reached which enables a rapid influx of Na^+ ions, depolarising cardiomyocytes to +20mV (Fig.2). This potentiates the opening of L-type Ca^{2+} channels (LTCCs) leading to a further influx of cations whilst the VGNCs become inactivated. Calcium-induced calcium release from the sarcoplasmic reticulum via ryanodine receptors allows electromechanical coupling, forming the characteristic prolonged plateau of AP in cardiomyocytes (Fig.2). As the membrane potential reaches more negative values, LTCCs close and delayed K channels return the RMP back to -85mV.

In the hyperkalemic states of cardioplegia, the constant influx of K^+ increase the RMP to -55mV which is beyond the VGNCs threshold thus they remain inactivated. Consequently, both adequate repolarisation and conduction of another AP are prevented – rapid cardiac arrest is induced. Additionally, the myocardial oxygen consumption and significant cellular ATP depletion, both of which are characteristic of I-R injury, are reduced as per Hearse's principles of cardioplegia[12].

Mitochondrial ATP-sensitive K^+ channels allow coupling of membrane potential to the cellular metabolism and therefore play a significant role in myocardial protection[13]. This is established by reducing post-ischaemic infarct size and apoptosis, possibly via altering mitochondrial Ca^{2+} and modulating reactive oxygen species formation[14].

Solutions for Myocardial Protection

Cardioplegic solutions can either be intracellular or extracellular[15]. Extracellular solutions contain high concentrations of potassium, magnesium and sodium ions and work by preventing repolarisation of myocytes[15]. Intracellular solutions contain low electrolyte concentrations and work by decreasing the sodium-potassium concentration gradients and stopping potassium efflux, thus preventing action potential generation[15]. There are several types of these solutions used in clinical practice, some of which are listed below.

Histidine-tryptophan-ketoglutarate (HTK)/Custodiol/Bretschneider's

The main advantage of HTK is the buffering capacity of histidine which enhances the efficiency of anaerobic glycolysis, providing better myocardial preservation[15,16]. The ketoglutarate component is an intermediary in the Krebs cycle and acts as a high energy ATP provider during reperfusion[15,16]. The tryptophan component stabilises cell membranes[15]. Mannitol, an osmotic diuretic is also added[15]. It decreases cellular oedema and has free radical scavenging properties, thus reducing ischaemic injury[15].

HTK induces cardiac arrest by lowering the sodium and calcium concentrations and preventing action potential depolarisation[15]. This means that longer time is required to initiate cardiac arrest, which causes greater ischaemic and reperfusion damage[16]. However, only a single dose is required which simplifies the procedure[16].

St Thomas's solution (STH) STH is an extracellular cardioplegic solution[15]. The original St Thomas's solution (STH1) was formed by Hearse and colleagues in the early 1970s[17]. This STH1 solution was then refined to form Plegisol or St Thomas's Hospital solution No. 2 (STH2) which is now the most widely used crystalloid cardioplegic solution in the world[17]. Many studies show STH2 to have better myocardial protective and antiarrhythmic effects than STH1.

Due to the high potassium and magnesium concentration in STH, it induces rapid cardiac arrest[15]. It is effective in providing myocardial protection in patients undergoing procedures like coronary artery bypass graft (CABG)[16]. However, it is less protective in patients requiring longer cross-clamp times. STH also increases cellular oedema and damages endothelial function. It thus needs repeated perfusion during ischaemia and must be administered every 20-40 minutes[16].

Del Nido solution In the early 1990s, Pedro del Nido and colleagues developed a cardioplegic solution that satisfied the requirements of the paediatric heart during surgery[18]. It has mainly been used in paediatrics and not very commonly for adults. Due to this there is scarce data available to support the safety and efficacy of its use in adult heart surgery[18].

Del Nido solution is very dilute and consists of lidocaine and magnesium and has lower concentrations of calcium[18]. It induces cardiac arrest during surgery and decreases intracellular calcium, slows down rate of energy consumption and scavenges free radicals[18]. It also reduces myocardial oedema, preserves high-energy phosphates and also promotes anaerobic glycolysis[18].

It allows uninterrupted surgery due to single cardioplegia dosing, thus reduced overall surgical times[18]. However, concerns regarding its use in adults exist due to lack of prospective randomised trials and evidence for safe use[18]. The properties of the different cardioplegic solutions are summarised in Table 1.

Cold versus Warm Cardioplegia

The cardioplegic solution for myocardial protection can be delivered at either cold ([?]4-100C) or warm ([?]35-370C) temperatures and there is still much debate regarding the optimal cardioplegic temperature[19]. Since the 1950s, cold crystalloid solutions were used to maintain the arrested state of the heart due to it lowering the myocardial oxygen demand and reducing the risk of ischaemic damage[20]. Potassium-induced electromechanical arrest lowers the oxygen demand of the myocardium by 90%. Lower temperatures of cardioplegic solution reduce this oxygen demand by a further 5-20% which is done by reducing the myocardial basal metabolic rate[19].

Lower temperatures of cardioplegia may cause membrane rupture, denaturalisation of proteins, inhibition of Na^{+}-K^{+} and Ca^{2+}ATP systems in the sarcolemma and sarcoplasmic reticulum, and lead to oedema and

calcium sequestration[21]. A longer period of time is needed to rewarm the heart by reperfusion, increasing the risk of reperfusion injury and arrhythmias[19].

Hypothermia also leads to right shift of the oxyhaemoglobin dissociation curve, causing lower oxygen availability for the myocardium in cold blood cardioplegia. At 200C only 50% of the total oxygen content in blood cardioplegia is available, falling to a further 30% when temperature is decreased to 100C[19]. Other disadvantages of cold cardioplegia include inadequate delivery of the cardioplegic solution due to sludging, cold agglutinin activation and rouleoux formation, leading to myocardial ischaemia and a delay in recovery of myocardial metabolism and function postoperatively[19].

To avoid these side-effects of cold cardioplegia, warm blood cardioplegia was brought in in the 1970s[20]. Giving continuous warm cardioplegia prevents hypothermic ischaemia and also minimises reperfusion injury[19]. A meta-analysis by Fan et al. found that warm cardioplegia was associated with improved postoperative cardiac index reduced cardiac markers (cTn and CK-MB) indicating less cardiocyte injury[20].

Lichtenstein et al. observed the outcomes in two groups of patients undergoing CABG post-MI. The warm group had lower 30-day mortality rate and a reduced need for postoperative IABP[19]. An Emory University study however found a significantly higher rate of postoperative neurological complications in warm versus cold cardioplegia (4.5% versus 1.4%), along with more perioperative strokes with warm cardioplegia (3.1% versus 1.0% with cold). They hypothesised this was due to use of blood cardioplegia in the warm group which had higher glucose level and caused hyperglycaemia, absence of neuroprotective benefits of hypothermia, and embolic events leading to stroke[19].

With warm cardioplegia there is need for larger total volumes of cardioplegic solution, increased use of high potassium cardioplegia to eliminate episodes of electric activity, higher risk of systemic hyperkalaemia, reduced systemic vascular resistance, as well as increased use of crystalloid and alpha-agonists to maintain perfusion pressures[19].

Kuhn et al. looked at the amount of endothelial injury with each technique, quantified by measuring circulating endothelial cells (CECs), von Willebrand factor (vWF) and soluble thrombomodulin (sTM). Concentrations of all these factors were much higher with warm cardioplegia, reflecting greater endothelial injury compared to cold cardioplegia[22]. The advantages and disadvantages of each technique is summarised in Table 2.

Blood versus Crystalloid Cardioplegia

Blood cardioplegia resembles normal physiology and causes an improved postoperative cardiac outcome[23]. It allows for rapid cardiac arrest in an oxygenated environment, intermittent reoxygenation of the myocardium when cardioplegic solution is delivered so anaerobic substrates like glucose and insulin are no longer needed. In a meta-analysis by Guru et al., blood cardioplegia was associated with decreased low-output syndrome (LOS) and creatine kinase-myocardial band (CK-MB) release therefore, a decreased mortality rate[23]. Additionally, blood cardioplegia preserves ventricular performance and systolic function. A meta-analysis by Zeng et al. found that cold blood cardioplegia also caused a significantly lower rate of perioperative MI compared to cold crystalloid cardioplegia[24]. Blood cardioplegia's oxygen carrying capacity is advantageous[23]. Hypothermia during cardiac surgery may offset this advantage by causing a left shift in the oxyhaemoglobin dissociation curve- so less oxygen is available for myocardial tissue[24]. At 200C only 50% of the total oxygen is released from blood cardioplegia, falling to 37% at 100C. This is a stark contrast to crystalloid cardioplegia which releases all of its oxygen at all temperatures.

There is, however, myocardial uptake of haemoglobin bound oxygen from the blood cardioplegic solution during hypothermia. This is due to the acidotic environment developing during cardiac arrest which shifts the oxyhaemoglobin dissociation curve to the right, along with a higher tissue affinity for oxygen in hypothermia. Delivering oxygen to the ischaemic myocardial tissue in blood cardioplegia may produce oxygen free radicals which cause ischaemia and reperfusion injury. However, blood also contains endogenous oxygen radical scavengers which protect against this[24].

It is important to note that haemoglobin has six times higher buffering capacity than plasma proteins. Whole blood also contains physiological oncotic pressure constituents. This minimises myocardial oedema, although this is not a significant issue with crystalloid cardioplegia either. Red blood cells present in blood cardioplegia are also critical for perfusion of the capillary bed due to improved rheologic effects which leads to better oxygen delivery.

With blood cardioplegia there is also avoidance of the cost and need to prepare a complex pharmacological mixture as in crystalloid. However, apparatus to deliver blood cardioplegia is more complicated and expensive than crystalloid. Due to these higher costs and impaired visualisation of the operating field some surgeons choose not to use blood cardioplegia[23]. A study by Gundry et al. concluded that blood cardioplegia was also associated with a higher rate of perioperative and postoperative conduction disturbances such as right bundle-branch block, than crystalloid[25]. On the contrary, crystalloid cardioplegia is widely used due to its simplicity, lower costs and good efficacy in the majority of patients[26]. It allows for good visualisation of the operating field due to being clear.

A strong argument against the use of crystalloid cardioplegia is it contains only one-fourth as much oxygen as blood cardioplegia[19]. It also decreases the oncotic pressure, increasing risk of oedema[26]. Some studies have found crystalloid cardioplegia causes intracellular oedema, depletion of glycogen stores and higher release of CK-MB. It also causes a higher degree of intra-operative haemodilution which is associated with increased blood transfusion requirement, significantly greater intensive care requirements, longer hospital stays, higher operative costs and higher mortality rates and postoperative organ failure e.g. renal failure[26]. Mullen et al. concluded in a study that although crystalloid cardioplegia was associated with higher incidence of MI and higher CK-MB release postoperatively, it lead to better right ventricular systolic function compared to blood cardioplegia[27]. The advantages and disadvantages of blood and crystalloid cardioplegia are summarised in Table 3.

Antegrade, retrograde or combined cardioplegia delivery

For optimal myocardial protection, homogeneous distribution of the cardioplegic solution is integral. This is influenced by the mode of delivery of the cardioplegia and the most common approach is through antegrade delivery of cardioplegia\sout via the aortic root[28]. This leads to rapid diastolic cardiac arrest and administration of cardioplegia seems to be straight forward, easy and rapid[29].

However, antegrade cardioplegia may cause inhomogeneous distribution if occlusion or significant stenosis of coronary arteries is present. This may lead to myocardial injury and delayed functional recovery as the myocardial areas distal to the lesion are poorly protected. Additionally, the antegrade perfusion can not only be delivered through the aortic root but also directly through the coronary ostia during aortic valve surgery, however it may cause coronary ostial injury during placement of the perfusion cannulae into each coronary ostia[30].

Retrograde cardioplegia delivery is via the coronary sinus. It can be used alternative to antegrade cardioplegia in the presence of occluded coronary arteries for better recovery of function in areas distal to the occlusion[31]. There is also elimination of operative interruptions, reduced risk of aortic root air, and air and debris flushing from the coronary arteries, especially during aortic valve surgery[29]. Retrograde cardioplegia is particularly beneficial for valve operations and redo-CABG. During aortic valve surgery, the coronary ostia are not cannulated, thus the operative field is clear and there is no ostial damage, intraoperative dissection or late ostial stenosis[30].

Some limitations of retrograde cardioplegia include coronary sinus injury and delay of cardiac arrest[32]. There is also requirement of large volumes of cardioplegic solutions[29] and myocardial oedema may occur[33]. Additionally, retrograde cardioplegia leakage through the coronary arteriotomy site may obscure the surgical field and prolong the operation, therefore coronary suction may be a necessity[34]. Due to absence of any direct connection between the coronary sinus and anterior cardiac veins there is inadequate protection of the right ventricle, which is worsened in patient with right ventricular dysfunction or poor venous collaterals[34].

As retrograde cardioplegia is associated with under perfusion of the right ventricle and antegrade cardioplegia homogenous delivery is affected by coronary lesions, combined antegrade-retrograde blood cardioplegia was brought about. It combines the advantages of both techniques[30]. Bhayana et al. found that compared to antegrade alone, combined cardioplegia lead to earlier recovery of left ventricular function and a shorter post-ischaemic stunned period so less damage to the myocardium[30].

Using combined cardioplegia may have a greater benefit in higher risk patients[30]. It may also provide better distribution in patients with hypertrophied cardiac tissue[34]. Radmehr et al. also found that there was reduced need for ionotropic support in combined cardioplegia compared to antegrade[34]. However, in situations such as right coronary artery occlusion, both antegrade and retrograde delivery would be compromised so the combined method would not be drastically more beneficial.

As each approach has its own benefits and drawbacks, treatment must be individually tailored to each patient. The properties of different cardioplegic delivery methods are summarised in Table 4.

Other methods of myocardial protection

Myocardial preconditioning

Described in 1986 by Murry et al. myocardial ischaemic preconditioning (IPC) is a process whereby the heart undergoes multiple cycles of ischaemia followed by reperfusion, prior to surgery to prevent subsequent ischaemic-reperfusion injury (IRI) during surgery[35]. Years later, the concept of remote IPC (RIPC) was introduced by Przyklenk and colleagues, which describes a procedural site away from the protected area, such as cross clamping the right side of the heart to protect the left[36]. Since the introduction of IPC, multiple studies have been conducted to determine the beneficial outcomes of its use. A trial conducted in 2013 by Thielmann and colleagues studied the prognostic effects of RIPC of the left upper arm, in patients CABG[37]. They concluded that all-cause mortality was reduced in patients treated with RIPC than those without[37].

Cross-clamp fibrillation

Cross-clamp fibrillation (XCF) involves cross-clamping the aorta and inducing ventricular fibrillation, to allow the heart to continue to beat during vessel occlusion. A 2019 comparative study on XCF and cardioplegia in patients undergoing CABG, reviewed 3,340 XCF patients to measure survival outcomes and post-operative complications[38]. Their results showed that when compared to cardioplegia, XCF reduced cases of atrial arrhythmias, post-operative inotropic use and conferred a mean survival advantage[38]. However, there was no reported difference in mortality between the two procedures[38].

Glucose-insulin-potassium cardioplegia

The use of a glucose-insulin-potassium (GIK) infusion was first detailed in 1962 by Sodi-Pallares et al. where it was used to treat acute myocardial infarction[39]. Its mechanism of cardioprotection has been extensively reviewed and studies indicate that insulin plays the key role by targeting the the reperfusion injury salvage (RISK) pathway, which plays a role in reducing IRI[40]. In 2002, the Insulin Cardioplegia Trial failed to demonstrate a significant difference in post-operative outcomes between patients receiving insulin solutions versus those in the placebo group in CABG surgery[41]. However, since then a randomised-control trial by Ellenberger et al. in 2018 researched GIK effects on patients undergoing on-pump heart surgery. They reported that GIK was associated with better left systolic ventricular function after weaning off bypass, reduced cardiovascular and respiratory complications, and shorter ICU stays compared with saline[42].

Biomarkers of myocardial protection

Laboratory parameters such as high sensitivity cardiac troponin I (cTnI),T (cTnT) and CK-MB are indispensable biomarkers utilised to define myocardial injury and predict prognosis amongst patients undergoing cardiac surgery[43-45]. cTnI is a gold-standard necrotic biomarker used for risk assessment post-cardiac

surgery as it is released almost exclusively in the myocardium in the presence of myocardial injury irrespective of the mechanism of injury[46]. Importantly, the release of cTnI post-cardiac surgery was found to be associated with increased mortality and morbidity[47]. cTnI elevation after cardiac surgery indicates multifactorial peri-operative myocardial injury, and it may be used as a biomarker reflecting cumulative intraoperative adverse effects on the myocardium[48]. CK-MB activity is also a valuable sensitive and specific indicator of reperfusion, myocardial injury, and infarct size, though inferior to cTnI[49].

In addition to cTnI and CKMB, a recent study demonstrated the elevation of the apoptotic biomarker caspase-3 p17 – this reflected that, along with necrosis, apoptosis also occurs during I-R in patients undergoing cardiac surgery with cardioplegia[50]. This puts forward a theory that caspase-3 p17 could therefore also be utilised as an indicator of the effectiveness of myocardial protection provided by cardioplegia in cardiac surgery.

Future Research

Despite advances in methods and mechanisms of myocardial protection, areas remain that could benefit from further exploration. The pathological process of ischaemic-reperfusion injury (IRI) is central to post-operative outcomes and therefore has potential for targeted therapeutic intervention, to minimise the effects of reperfusion injury on the heart.

The notion of IRI was first observed in 1960 by Jennings et al. who discovered extreme acceleration of necrosis in dog hearts following ischaemia and subsequent reperfusion[51]. The process of IPC, as described above, was the first of its kind that focused on mediating IRI as a method of cardioprotection, by making the heart resistant to ischaemia prior to surgery[35]. However, there remains scope to further refine therapeutic interventions that minimise the effects of IRI. This is possible due to the extensive research into the mechanism of IRI, which has identified various contributing pathways, with the long-term prospect to target each.

One such aspect for consideration is targeting the mitochondrial permeability transition pore (mPTP). The role of mPTP in IRI has been discussed since its first proposal in 1987 by Crompton et al.[52]. Opening of the mPTP is triggered in the reperfusion phase of IR by Ca^{2+} influx, oxidative stress and reversal of ischaemic induced acidosis[52,53] . Upon opening of the pore, cell swelling and apoptosis occurs, resulting in cardiomyocyte cell death. The mPTP is therefore a candidate for targeting by novel inhibitors. Cyclosporin A (CsA) and cyclophilin D (CyP-D) are two mPTP related molecules. CsA is a non-selective inhibitor of mPTP and acts by binding and inhibiting CyP-D, a mediator that facilitates the opening of the pore. Research into its cardioprotective use have proven somewhat beneficial. A study performed in 2015 found CsA reduced IRI in patients undergoing aortic valve surgery[54]. However, Cyclosporin to Improve Clinical Outcome in STEMI patient (CIRCUS), a phase III trial in MI patients, failed to show improvement in all-cause mortality with CsA use[55]. The limitations of CsA lie within its non-specific nature, resulting in inhibitory effects of other molecules such as cyclophilin A and B. These unwanted side effects reduce the clinical translatability of CsA into practice, and further research is needed to overcome these issues. Identifying more specific inhibitory molecules, or altering the structure of CsA[56] could prove useful in adapting its functionality.

Conclusion:

Each type and technique of cardioplegia has its own advantage and limitations; the choice of each solution should be based on ideal myocardial protection to provide safe outcomes. Future research should identify the use of solutions with better myocardial protection with less frequent administration.

Figures legends

Figure 1. Timeline of the key developments in the history of cardioplegia.

Figure 2. Electrophysiology Principles in Cardioplegia. Schematic diagram showing cardiomyocyte function including cation transport (Na^+/HCO_3^- symporter, Na^+-H^+ exchanger, LTCC, G-protein coupled receptor, VGCC, Na^+/Ca^{2+} exchanger, voltage-gated Na^+ channels, Na^+/K^+ pump, voltage-gated

K^+ channel), excitation-contraction coupling, acid-base balance regulation, and adrenergic and muscarinic receptors.

SR sarcoplasmic reticulum, *M2* muscarinic receptor 2, *A1* adenosine receptor 1, *R* -adrenergic receptor, *GLUT* glucose transporter 1, G_i inhibitory G protein, G_s stimulatory G protein, *AC* adenylate cyclase, *ATP* adenosine triphosphate, *cAMP* cyclic adenosine monophosphate, *ADP* adenosine diphosphate, K_{ATP} ATP-sensitive potassium channel, *PLC* phospholipase C, *PKC* phosphokinase C, *NF-kB* nuclear factor kappa B, *CICR* calcium-induced calcium release, *PDH* pyruvate dehydrogenase.‘

References

1. Chatrath R, Kaul T, Walker D. Myocardial protection during cardioplegia in open-heart surgery: a review. *Can Anaesth Soc J* . 1980; 27: 381–8.

2. Hausenloy D, Boston-Griffiths E, Yellon D. Cardioprotection during cardiac surgery. *Cardiovasc Res* . 2012; 94: 253–65.

3. Melrose D, Dreyer B, Bentall H, et al. Elective Cardiac Arrest.*Lancet* . 1955; 266: 21–3.

4. Hearse DJ, Garlick PB, Humphrey SM. Ischemic contracture of the myocardium: Mechanisms and prevention. *Am J Cardiol.* 1977; 39: 986–93.

5. Hearse DJ. Cardioplegia. *Postgrad Med J* . 1983; 59: 11–24.

6. Reidemeister JC, Heberer G, Bretschneider HJ. Induced cardiac arrest by sodium and calcium depletion and application of procaine. *Int Surg* . 1967; 47: 535–40.

7. Lolley DM, Hewitt RL, Drapanas T. Retroperfusion of the heart with a solution of glucose, insulin, and potassium during anoxic arrest.*J Thorac Cardiovasc Surg* . 1974; 67: 364–70.

8. Buckberg GD. Strategies and logic of cardioplegic delivery to prevent, avoid, and reverse ischemic and reperfusion damage. *J Thorac Cardiovasc Surg.* 1987; 93: 127–39.

9. Calafiore AM, Teodori G, Mezzetti A, et al. Intermittent antegrade warm blood cardioplegia. *Ann Thorac Surg.* 1995; 59: 398–402.

10. Gundry SR, Kirsh MM. A Comparison of Retrograde Cardioplegia Versus Antegrade Cardioplegia in the Presence of Coronary Artery Obstruction.*Ann Thorac Surg.* 1984; 38: 124–7.

11. Chambers DJ, Fallouh HB. Cardioplegia and cardiac surgery: Pharmacological arrest and cardioprotection during global ischemia and reperfusion. *Pharmcol Ther.* 2010; 127: 41-52.

12. Fey K, Follette D, Livesay J, et al. Effects of membrane stabilization on the safety of hypothermic arrest after aortic cross-clamping. *Circulation.* 1977; 56: 143–7.

13. Wakiyama H, Cowan DB, Toyoda Y, et al. Selective opening of mitochondrial ATP-sensitive potassium channels during surgically induced myocardial ischemia decreases necrosis and apoptosis. *Eur J Cardiothoracic Surg.* 2002; 21: 424–33.

14. Pain T, Yang XM, Critz SD, et al. Opening of mitochondrial K(ATP) channels triggers the preconditioned state by generating free radicals.*Circ Res* . 2000; 87: 460–6.

15. Singh S, Das DS, Spadaccio C, et al. An overview of different methods of myocardial protection currently employed peri-transplantation. *Vessel Plus.* 2017; 1: 213–29.

16. Lee K, Chang C, Chuang Y, et al. Combined St. Thomas and histidine-tryptophan-ketoglutarat solutions for myocardial preservation in heart transplantation patients: *Transplant Proc.* 2012; 44: 886–9.

17. Chambers D, Haire K, Morley N, et al. St Thomas' Hospital Cardioplegia: Enhanced Protection With Exogenous Creatine Phosphate.*Ann Thorac Surg.* 1996; 61: 67–75.

18. Cayir M, Yuksel A. The use of del Nido Cardioplegia for Myocardial Protection in Isolated Coronary Artery Bypass Surgery. *Hear Lung Circ.* 2020; 29: 301–7.

19. Mauney M, Kron I. The physiologic basis of warm cardioplegia.*Ann Thorac Surg.* 1995; 60: 819–23.

20. Fan Y, Zhang A, Xiao Y, et al. Warm versus cold cardioplegia for heart surgery: a meta-analysis. *Eur J Cardio-Thoracic Sur.* 2010; 37: 912–9.

21. Martin T, Craver J, Gott J, et al. Prospective, Randomized Trial of Retrograde Warm Blood Cardioplegia: Myocardial Benefit and Neurologic Threat. *Ann Thorac Surg.* 1994; 57: 298–304.

22. Kuhn E, Choi Y, Pyun J, et al. Endothelial Injury Associated with Cold or Warm Blood Cardioplegia during Coronary Artery Bypass Graft Surgery. *Biomed Res Int.* 2015; 2015: 256905.

23. Guru V, Omura J, Alghamdi A, et al. Is blood superior to crystalloid cardioplegia? A meta-analysis of randomized clinical trials.*Circulation.* 2006; 114: 331–8.

24. Zeng J, He W, Qu Z, et al. Cold blood versus crystalloid cardioplegia for myocardial protection in adult cardiac surgery: A meta-analysis of randomized controlled studies. *J Cardiothorac Vasc Anesth.* 2014; 28: 674–81.

25. Gundry SR, Sequeira A, Coughlin TR, et al. Postoperative conduction disturbances: A comparison of blood and crystalloid cardioplegia.*Ann Thorac Surg.* 1989; 47: 384–90.

26. Günday M, Bingöl H. Is crystalloid cardioplegia a strong predictor of intraoperative hemodilution? *J Cardiothorac Surg.* 2014; 9: 23.

27. Mullen JC, Fremes SE, Weisel RD, et al. Right Ventricular Function: A Comparison Between Blood and Crystalloid Cardioplegia. *Ann Thorac Surg.* 1987; 43: 17–24.

28. Borger M, Wei K, Weisel RD, et al. Myocardial perfusion during warm antegrade and retrograde cardioplegia: A contrast echo study. *Ann Thorac Surg.* 1999; 68: 955–61.

29. Chitwood WR, Wixon CL, Norton TO, et al. Complex valve operations: Antegrade versus retrograde cardioplegia? *Ann Thorac Surg.* 1995; 60: 815–8.

30. Bhayana JN, Kalmbach T, Booth FVM, et al. Combined antegrade/retrograde cardioplegia for myocardial protection: A clinical trial. *J Thorac Cardiovasc Surg.* 1989; 98: 956–60.

31. Quintilio C, Voci P, Bilotta F, et al. Risk factors of incomplete distribution of cardioplegic solution during coronary artery grafting.*J Thorac Cardiovasc Surg.* 1995; 109: 439–47.

32. Menasché P, Kural S, Fauchet M, et al. Retrograde Coronary Sinus Perfusion: A Safe Alternative for Ensuring Cardioplegic Delivery in Aortic Valve Surgery. *Ann Thorac Surg.* 1982; 34: 647–58.

33. Jasinski M. Comparison of retrograde versus antegrade cold blood cardioplegia: randomized trial in elective coronary artery bypass patients. *Eur J Cardio-Thoracic Surg.* 1997; 12: 620–6.

34. Radmehr H, Soleimani A, Tatari H, et al. Does Combined Antegrade-Retrograde Cardioplegia Have Any Superiority Over Antegrade Cardioplegia? *Hear Lung Circ.* 2008; 17: 475–7.

35. Murray C, Jennings R, Reimer K. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. *Circulation.*1986; 74: 1124–36.

36. Przylenk K, Bauer B, Ovize M, et al. Regional ischemic 'Preconditioning' protects remote virgin myocardium from subsequent sustained coronary occlusion. *Circulation.* 1993; 87: 893–9.

37. Thielmann M, Kottenberg E, Kleinbongard P, et al. Cardioprotective and prognostic effects of remote ischaemic preconditioning in patients undergoing coronary artery bypass surgery: a single-centre randomised, double-blind, controlled trial. *Lancet.* 2013; 382: 597–604.

38. Ariyaratnam P, Cale A, Loubani M, et al. Intermittent Cross-Clamp Fibrillation Versus Cardioplegic Arrest During Coronary Surgery in 6,680 Patients: A Contemporary Review of an Historical Technique. *J Cardiothorac Vasc Anesth.* 2019; 33: 3331–9.

39. Sodi-Pallares D, Testelli M, Fishleder B, et al. Effects of an intravenous infusion of a potassium-glucose-insulin solution of the electrocardiographic signs of myocardial infarction. *Am J Cardiol.* 1962; 9: 166–88.

40. Hausenloy D, Yellon D. New directions for protecting the heart against ischaemia-reperfusion injury: targeting the Reperfusion Injury Salvage Kinase (RISK)-pathway. *Cardiovasc Res* . 2004; 61: 448–60.

41. Roa V, Christakis G, Weisel R, et al. The insulin cardioplegia trial: myocardial protection for urgent coronary artery bypass grafting.*J Thorac Cardiovasc Surg.* 2002; 123: 928–35.

42. Ellenberg C, Sologashvili T, Kreienbühl L, et al. Protection by Glucose–Insulin–Potassium in Moderate- to High-Risk Patients Undergoing Elective On-Pump Cardiac Surgery: A Randomized Controlled Trial. *Anaesth Analg.* 2018; 128: 1133–41.

43. Katus H, Looser S, Hallermayer K, et al. Development and in vitro characterization of a new immunoassay of cardiac troponin T. *Clin Chem.* 1992; 38: 386–93.

44. Ohman EM, Armstrong PW, Christenson RH, et al. Cardiac troponin T levels for risk stratification in acute myocardial ischemia. *N Engl J Med.* 1996; 335: 1333–41.

45. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). *Eur Heart J.* 2019; 40: 237–69.

46. Gohar A, Chong JPC, Liew OW, et al. The prognostic value of highly sensitive cardiac troponin assays for adverse events in men and women with stable heart failure and a preserved vs. reduced ejection fraction.*Eur J Heart Fail.* 2017; 19: 1638–47.

47. Mauermann E, Bolliger D, Fassl J, et al. Association of Troponin Trends and Cardiac Morbidity and Mortality After On-Pump Cardiac Surgery. *Ann Thorac Surg.* 2017; 104: 1289–97.

48. Domanski MJ, Mahaffey K, Hasselblad V, et al. Association of myocardial enzyme elevation and survival following coronary artery bypass graft surgery. *J Am Med Assoc.* 2011; 305: 585–91.

49. Goodman SG, Steg PG, Eagle KA, et al. The diagnostic and prognostic impact of the redefinition of acute myocardial infarction: Lessons from the Global Registry of Acute Coronary Events (GRACE). *Am Heart J.*2006; 151: 654–60.

50. Kim M, Lorinsky MK, Gold CA, et al. Usefulness of Circulating Caspase-3 p17 and Caspase-1 p20 Peptides and Cardiac Troponin 1 During Cardioplegia to Gauge Myocardial Preservation. *Am J Cardiol.*2019; 123: 899–904.

51. Jennings R, Sommers H, Smyth G, et al. Myocardial necrosis induced by temporary occlusion of a coronary artery in the dog. *Arch Pathol.* 1960; 70: 68–78.

52. Crompton M, Costi A, Hayat L. Evidence for the presence of a reversible Ca2+-dependent pore activated by oxidative stress in heart mitochondria. *Biochem J.* 1987; 245: 915–8.

53. Griffiths E, Halestrap A. Mitochondrial non-specific pores remain closed during cardiac ischaemia, but open upon reperfusion.*Biochem J.* 1995; 307: 93-8.

54. Chiari P, Angoulvant D, Mewton N, et al. Cyclosporine protects the heart during aortic valve surgery. *Anaesthesiology.* 2014; 121: 232–8.

55. Cung T, Morel O, Cayla G, et al. Cyclosporine before PCI in Patients with Acute Myocardial Infarction. *N Engl J Med.* 2015; 373: 1021–31.

56. Malouitre S, Dube H, Selwood D, et al. Mitochondrial targeting of cyclosporin A enables selective inhibition of cyclophilin-D and enhanced cytoprotection after glucose and oxygen deprivation. *Biochem J.*2010; 425: 137–48.

57. Habertheuer A, Kocher A, Laufer G, et al. Cardioprotection: a review of current practice in global ischaemia and future translational perspective. *Biomed Res Int.* 2014; 2014: 325725.

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