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

**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.

**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. Additionally, cooling of the myocardium is thought to minimise the ischaemia-reperfusion (I-R) injury associated with 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, Mg2+, HCO3-, 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.

All the relevant articles were identified and screened by three authors; the results are summarized in narrative manner in each relevant section within the text of this review. A summary table of each section is provided where appropriate.

**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 [Ca2+]I overload, and Hearse et al. found that myocardial damage was related to ATP depletion along with this [Ca2+]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 [Ca2+]I depletion, extracellular K+ and Mg2+ elevation and infusion of local anaesthetic agents or Ca2+ 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 Ca2+-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(7–9).

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(10). Calafiore et al. later introduced warm blood cardioplegia containing K+/Mg2+ which provides myocardial protection when applied continuously(11). Blood cardioplegia has been demonstrated to have potent myocardial protective effects against I-R injury due to improved parameters compared to crystalloid cardioplegia, such as greater oxygen supply and better acid-base balance(12).

Cardioplegic delivery can be anterograde, retrograde or combined. Anterograde delivery involves running the cardioplegia solution down the right and left coronary arteries and supplying the myocardium in the same fashion that blood normally does. In retrograde cardioplegia however, solution is administered in a retrograde manner and perfusion is by the coronary sinus in the opposite direction to normal blood flow. Retrograde cardioplegia 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(13,14). However, retrograde cardioplegia has a low flow rate to avoid damaging the coronary sinus(15,16). Hence, combined cardioplegic delivery has been used frequently as a more effective approach in cardiac surgery to preserve the myocardium(17,18). Despite the extensive study of cardioplegia solutions over the last decades (***Fig.1***), evidence on the ideal myocardial protection method during cardiac surgery is still uncertain.

Effectiveness of cardioplegia delivery is measured by several methods including myocardial temperature and pH assessment through probe insertion into the left ventricular wall(19). Cardioplegia line pressure should be measured to investigate possible obstructions during infusion to prevent accidents such as circuit rupture and avoid high pressures usually associated with haemolysis(20). Direct intravascular measurement is the most reliable method to determine aortic pressure during cardioplegic infusion and to ensure effectiveness and safety(21). A double lumen catheter allows for simultaneously administration of antegrade cardioplegia and aortic root pressure assessment, though care should be taken to minimise the effects of interfering variables such as flow velocity, viscosity, and temperature of the infused solution(20,21). The precise optimal pressure for antegrade cardioplegia delivery is poorly described, but is assumed to be in the range between normal diastolic and normal mean blood pressure(21). During retrograde delivery of solutions, coronary sinus pressure may be assessed because of its fragility and possibility of rupture(22). The pressure at which retrograde cardioplegia can be safely delivered is thought to be 50 to 60 mm Hg(22).

**The Physiology of Cardioplegia**

To rapidly arrest the myocardium in diastole and maintain it in a depolarised state, voltage-gated channels can be pharmacologically targeted. In physiological states, AP generation occurs due to the activation of voltage-gated channels in the sarcolemmal membrane which allow the 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 and depolarises cardiomyocytes to +20mV (***Fig.2***)(23). This potentiates the opening of L-type Ca2+ 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 – this forms the characteristic prolonged plateau of the AP in cardiomyocytes (***Fig.2***). As the membrane potential reaches more negative values, LTCCs close and delayed K channels return the resting membrane potential (RMP) back to -85mV.  Hyperkalaemia is a fundamental characteristic of most cardioplegic solutions. Hyperkalaemia induces diastolic arrest by establishing a new RMP that is more depolarised (i.e. more positive) than normal – from -85mV to about -55mV(23). 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 the hyperkalemic states of cardioplegia, the influxes of K+ (induced by repeated bolus infusion) 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 – and 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(24,25). Reversing cardiac arrest is simple as the solution diffuses by washout, and electrical activity slowly resumes; if clinically indicated, re-dosing of cardioplegia is required. Cardioplegic arrest may be tolerated for several hours and Engelman et al.(26) supported the safety of arrest up to 3 hours. The upper limit has progressively increased since Engelman’s study in 1980 to approximately 6-8 hours, though ischaemic-tolerance time is dependent on circulatory temperature in cardiopulmonary bypass(27). As well as arrest duration, the perfusionist should remain cautious of cardioplegic overdose which can lead to systemic hyperkalaemia, a potentially life-threatening state which can cause muscle paralysis and lethal cardiac arrhythmias(28). This is a particular concern with continuous crystalloid-based cardioplegia administration as this can result in significant haemodilution which is counteracted by maintaining potassium at supranormal levels, resulting in a large potassium load to the patient(29).

The Na+/Ca2+ exchanger (NCX) also plays an essential role in the [Ca2+]i overload seen during ischaemia(30). In physiological states, NCX removes cytoplasmic Ca2+ in exchange for Na+ (***Fig.2***). During ischaemia however, acidosis occurs due to anaerobic metabolism and ATP depletion which causes Na+ influx through the Na+/H+ antiporter and Na+/HCO3- symporter as a compensatory mechanism(30,31). Elevated [Na+]i levels drive NCX in reverse mode and consequently lead to [Ca2+]i overload which causes hypercontractility and mitochondrial damage – this is hypothesised to be the main mechanism through which I-R injury occurs(30,31).

Mitochondrial ATP-sensitive K+ (mitoKATP) channels allow coupling of membrane potential to the cellular metabolism and therefore play a significant role in myocardial protection(32–34). This has been shown to be established by reducing post-ischaemic infarct size and apoptosis, possibly via altering mitochondrial Ca2+ and modulating reactive oxygen species (ROS) formation(35–37).

Other ions such as Ca2+, Na+ and Mg2+ are all associated with myocardial protection and contractility reduction. Furthermore, some studies have shown supplementing cardioplegic solutions with adenosine has beneficial effects on improving clinical outcomes, along with reducing apoptosis and cellular injury(38–40).  Adenosine acts on adenosine A1 receptors to increase the potassium permeability of nodal tissues, increasing potassium efflux and thus hyperpolarising the membrane potential to induce atrioventricular block(39). Adenosine receptor activation has been associated with reduced infarct size and attenuated endothelial activation, conferring cardioprotective effects(38). Exogenous adenosine administration is thought to delay endogenous adenosine washout in the first minutes of myocardial reperfusion and this explains the observed favourable effects of adenosine administration on clinical outcomes(38).

**Solutions for Myocardial Protection**

Cardioplegic solutions can either be intracellular or extracellular based on the cellular environment that they reflect(41). Extracellular solutions are characterised by moderately elevated potassium and sodium and relatively normal calcium concentration and work by preventing repolarisation of myocytes(41,42). Intracellular solutions are characterised by high potassium, relatively low sodium and very low calcium concentration(42). These work by decreasing the sodium-potassium concentration gradients and stopping potassium efflux, thus preventing action potential generation(41). There are several types of these solutions used in clinical practice, some of which are listed below(42).

*Histidine-tryptophan-ketoglutarate (HTK)/Custodiol/Bretschneider’s* solution

Custodial solution(41) is an intracellular cardioplegic solution first used by Bretschneider in the 1970s(43). The solution contains the additives HTK which are histidine and two amino acids- tryptophan and ketoglutarate(43).

The main advantage of HTK solution is the buffering capacity of histidine which enhances the efficiency of anaerobic glycolysis, providing better myocardial preservation(41,43). The ketoglutarate component is an intermediary in the Krebs cycle and acts as a high energy ATP provider during reperfusion(41,43). The tryptophan component stabilises cell membranes. Mannitol, an osmotic diuretic is also added(41). It decreases cellular oedema and has free radical scavenging properties, thus reducing ischaemic injury(41).

HTK solution induces cardiac arrest due to its intracellular sodium concentration of 15mmol/L and slightly elevated extracellular potassium concentration of 10mmol/L which prevents action potential depolarisation(44).It is useful in patients needing longer clamping times(43).  Due to the buffer effect of histidine only a single dose is required, which simplifies the procedure(43). However, the lack of calcium in solution means that longer time is required to initiate cardiac arrest, which causes greater ischaemic and reperfusion damage(43).

*St Thomas’s solution (STH)*   
STH is an extracellular cardioplegic solution(41). The original St Thomas’s solution (STH1) was developed by Hearse and colleagues in the early 1970s(45). 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(45). Many studies show STH2 to have better myocardial protective and antiarrhythmic effects than STH1. However due to cost implications, most of the cardiac centres in the UK use STH1(45). One of the main differences between STH1 and STH2 is that STH1 contains procaine hydrochloride, which is a membrane stabiliser with known cardioplegic effects, so STH1 patients may have fewer reperfusion-induced arrhythmias than STH2 patients(45).  Due to the high potassium and magnesium concentration in STH, it induces rapid cardiac arrest(41). It is effective in providing myocardial protection in patients undergoing procedures like coronary artery bypass graft (CABG)(43). 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(43). Repeated dosing is cumbersome and interrupts the surgical flow(46).

*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(46). This del Nido solution is an extracellular solution(47). It has mainly been used in paediatrics and not very commonly for adults4. Due to this there is scarce data available to support the safety and efficacy of its use in adult heart surgery(46).

 Del Nido solution is very dilute compared to traditional crystalloid cardioplegia solution- (1 : 4, blood : crystalloid) as compared to the traditional 4 : 1 blood cardioplegia(46). Del Nido consists largely of magnesium and mannitol with some lidocaine(46). The final calcium concentration of Del Nido diluted in blood is defined as trace because the base solution contains no calcium(46). Del Nido induces cardiac arrest during surgery and decreases intracellular calcium, slows down rate of energy consumption and scavenges free radicals(46). It also reduces myocardial oedema, preserves high-energy phosphates and also promotes anaerobic glycolysis(46).

It allows for uninterrupted surgery due to single cardioplegia dosing, reduced surgical times, reduced blood glucose level changes and easier glycaemic control(46). There is also reduced need for systemic cooling and lower total volume of administered cardioplegic solution is required(46). However, concerns regarding use of del Nido solution in adults exist due to lack of prospective randomised trials and evidence for safe use(46). 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(48).  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(49). 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%. This is done by reducing the myocardial basal metabolic rate(48). Although, some studies have observed higher oxygen delivery than predicted from cold blood cardioplegia due to factors improving oxygen unloading such as acidosis of myocardial tissue and hypercarbia(48).  However cold cardioplegia may inhibit myocardial enzymes and delay recovery of heart function in the postoperative period(49). Lower temperatures of cardioplegia may also cause membrane rupture, denaturalisation of proteins, inhibition of Na+-K+ and Ca2+ ATP systems in the sarcolemma and sarcoplasmic reticulum, and lead to oedema and calcium sequestration(50). A longer period of time is needed to rewarm the heart by reperfusion, increasing the risk of reperfusion injury and arrhythmias(48).

 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(48). 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(48).

To avoid these side-effects of cold cardioplegia, warm blood cardioplegia was introduced in the 1980s(49). Giving continuous warm cardioplegia prevents hypothermic ischaemia and also minimises reperfusion injury(48). A meta-analysis by Fan et al. 41 found that warm cardioplegia was associated with improved postoperative cardiac index reduced cardiac markers (cTn and CK-MB) indicating less cardiocyte injury(49).

Lichtenstein et al.(51) observed the outcomes in two groups of high-risk patients undergoing CABG post-MI. The warm group had lower 30-day mortality rate and a reduced need for postoperative IABP. Another study showed 99.2% of patients receiving warm blood cardioplegia had spontaneous return of normal sinus rhythm after removal of the aortic cross-clamp in contrast with only 10.5% of patients receiving cold cardioplegia(52). On the contrary, an Emory University study 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 that the 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(48).

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(48). Other disadvantages include poor visualisation, making it more cumbersome(48).

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(53).  The advantages and disadvantages of each technique are summarised in Table 2.

**Blood versus Crystalloid Cardioplegia**

Blood cardioplegia resembles normal physiology and allows for rapid cardiac arrest in an oxygenated environment(54). Blood cardioplegia delivery also allows intermittent reoxygenation of the myocardium so anaerobic substrates like glucose and insulin are no longer needed(12).  In a meta-analysis by Guru et al.(54), blood cardioplegia was not associated with a difference in mortality. However, reductions in creatine kinase-myocardial band (CK-MB) and low-output syndrome (LOS) incidence were observed. Blood cardioplegia was noted to have favourable effects on LOS incidence in 8 of 10 studies, supporting the use of blood rather than crystalloid cardioplegia. Additionally,  blood cardioplegia preserves ventricular performance and systolic function(12). A meta-analysis by Zeng et al.(55) found that cold blood cardioplegia also caused a significantly lower rate of perioperative MI compared to cold crystalloid cardioplegia. Blood cardioplegia’s oxygen carrying capacity is advantageous(54). 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(55). At 20⁰C only 50% of the total oxygen is released from blood cardioplegia, falling to 37% at 10⁰C(12). This is a stark contrast to crystalloid cardioplegia which releases all of its oxygen at all temperatures(12).

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(12).  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(55).

It is important to note that haemoglobin has six times higher buffering capacity than plasma proteins(12). Whole blood also contains physiological oncotic pressure constituents(12). This minimises myocardial oedema, although this is not a significant issue with crystalloid cardioplegia either(12).  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(12).

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(12). Due to these higher costs and impaired visualisation of the operating field some surgeons choose not to use blood cardioplegia(54). 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(56).  On the contrary, crystalloid cardioplegia is widely used due to its simplicity, lower costs and good efficacy in the majority of patients(57). 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(48). It also decreases the oncotic pressure, increasing risk of oedema(57). Some studies have found crystalloid cardioplegia causes intracellular oedema, depletion of glycogen stores and higher release of CK-MB(12). 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(57). 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 leads to better right ventricular systolic function compared to blood cardioplegia(58). 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, via the aortic root(52) as its administration is simple and convenient and it induces rapid diastolic cardiac arrest(59).

Although antegrade cardioplegia is a safe and effective method of myocardial protection during elective CABG, it may cause inhomogeneous distribution if occlusion or significant stenosis of coronary arteries is present(52).  Thus, the myocardial areas distal to the lesion are poorly protected, causing myocardial injury and delayed functional recovery(52). An obstacle of delivering cardioplegia in this method is the presence of concomitant aortic regurgitation with ischaemic heart disease. Antegrade cardioplegia may cause reduced coronary perfusion and thus fail to achieve a full diastolic arrest with adequate cardioplegia(52). The antegrade perfusion is not only delivered through the aortic root but can also be delivered directly through the coronary ostia during aortic valve surgery and thus it may cause coronary ostial injury during placement of the perfusion cannulae into each coronary ostia(60).

Jasinski et al. observed that during CABG ischaemic events, need for inotropic support and ventricular fibrillation rates on reperfusion were more common with antegrade cardioplegia than retrograde(61). Retrograde cardioplegia comparatively led to better myocardial function recovery and less ischaemic injury(61).  However clinical studies have not shown any superiority between antegrade or retrograde cardioplegia usage(12).

Retrograde cardioplegia delivery is via the coronary sinus. In certain occasions it can be used alternative to antegrade cardioplegia in the presence of occluded coronary arteries, allowing better recovery of function in areas distal to the occlusion(62). There is also elimination of operative interruptions, reduced risk of aortic root air, and flushing of air and debris from the coronary arteries, especially during aortic valve surgery(59).   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(60). Borger et al. observed that retrograde cardioplegia also decreased the risk of atheroembolism during redo-CABG(52). Some limitations of retrograde cardioplegia include coronary sinus injury and delay of cardiac arrest(63). There is also requirement of large volumes of cardioplegic solutions and myocardial oedema may occur(59,61). Additionally, retrograde cardioplegia leakage through the coronary arteriotomy site may obscure the surgical field and prolong the operation, therefore even during retrograde cardioplegia, coronary suction may be a necessity(64).  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 patients with right ventricular dysfunction or poor venous collaterals(64).

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(12). It combines the advantages of both techniques. Bhayana et al.(60) found that compared to antegrade alone, combined cardioplegia led to earlier recovery of left ventricular function and a shorter post-ischaemic stunned period so less damage to the myocardium.

 Using combined cardioplegia may have a greater benefit in higher risk patients(60). It may also provide better distribution in patients with hypertrophied cardiac tissue(64). Radmehr et al.(64) also found that there was reduced need for ionotropic support in combined cardioplegia compared to antegrade. 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(12).

As each approach has its own benefits and drawbacks, treatment must be individually tailored to each patient(59). For example, in low risk patients having uncomplicated procedures, antegrade cardioplegia may be sufficient but for complex operations combined cardioplegia is preferred, whereas in redo-CABG retrograde cardioplegia alone is beneficial to avoid embolisation(59). 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.(65) myocardial ischaemic preconditioning (IPC) is a process whereby the heart undergoes multiple cycles of ischaemia followed by reperfusion to prevent subsequent ischaemic-reperfusion injury (IRI) following regional ischaemia. The report, conducted in dog models, found infarct sizes were reduced by 75% following repetitive cross-clamping of the left circumflex coronary artery. Years later, the concept of remote IPC (RIPC) was introduced by Przyklenk and colleagues(66), which involves cross clamping a procedural site away from the protected area, such as cross clamping the right side of the heart to protect the left. Since the introduction of IPC, multiple studies have been conducted on animal and human hearts, to determine the beneficial outcomes of its use. A trial conducted in 2013 by Thielmann and colleagues(67) studied the prognostic effects of RIPC of the left upper arm, in patients CABG. They concluded that all-cause mortality was reduced in patients treated with RIPC than those without(67). A systematic review and meta-analysis conducted by Walsh et al. reported that IPC was associated with shortened intensive care unit (ICU) stays and reduced incidence of ventricular arrhythmias(68).  However, the multi-centre randomised ERICCA trial showed no benefit of RIPC on mortality or adverse effects(69).

*Cross-clamp fibrillation*

Cross-clamp fibrillation (XCF) involves cross-clamping the aorta and inducing ventricular fibrillation to allow the heart to be relatively still for surgery. A 2019 comparative study on XCF and cardioplegia in patients undergoing CABG reviewed 3,340 XCF patients to measure survival outcomes and postoperative complications(70).  Their results showed that when compared to cardioplegia, XCF reduced cases of atrial arrhythmias, postoperative inotropic use and conferred a mean survival advantage(70).  However, there was no reported difference in mortality between the two procedures(70). A comparison of postoperative outcomes in XCF versus antegrade-retrograde cold blood cardioplegia was led by Alex and colleagues(71). A retrospective trial was conducted of 1,454 patients over a 5-year period, who were undergoing CABG(71). They found both methods comparable for postoperative myocardial infarctions (MI), arrhythmias, multi-organ failure and mortality(71).

*Glucose-insulin-potassium adjunctive cardioplegia*

The use of a glucose-insulin-potassium (GIK) infusion as an adjunctive treatment for acute myocardial infarction was first detailed in 1962 by Sodi-Pallares et al.(72). Its mechanism of cardioprotection has been extensively reviewed and studies indicate that insulin plays the key role, whilst glucose and potassium prevent insulin-induced hypoglycaemia and hypokalaemia, respectively(73). Insulin targets the reperfusion injury salvage (RISK) pathway, which plays a role in reducing IRI(73). Implementing GIK as an effective method for cardioprotection has since been studied. The Insulin Cardioplegia Trial of 2002 failed to demonstrate a significant difference in postoperative outcomes between patients receiving insulin solutions versus those in the placebo group in CABG surgery(74). However, since then a randomised-control trial by Ellenberg et al.(75) in 2018 researched GIK effects on patients undergoing on-pump heart surgery. They compared GIK to a control of saline infusion, and reported that GIK was associated with better left systolic ventricular function after weaning off bypass, reduced cardiovascular and respiratory complications, and shorter ICU stays(75).  Additionally, a meta-analysis of 33 papers involving 2,113 patients, assessed the effectiveness of GIK in cardiac patients(76). They concluded that GIK was associated with reduced perioperative MI, reduced postoperative ionotropic support use and shortened ICU stays(76).

*Microplegia devices*

The basis for microplegia devices was proposed by Calafiore as an alternative technique to the standard 4:1 dilution of blood to crystalloid solution(11). These devices mix minimally diluted oxygenated pump blood with concentrated arresting agents and have been shown to provide clinical benefits(77). A systematic review found that microplegia outperformed standard blood cardioplegia in many regards, especially in respect to haemodynamics(77). It was also found to cause fewer cases of oedema, lower incidence of LOS and an overall improved cardiac index. However, Albacker et al.(78) found no significant difference in morbidity and mortality between patients given blood cardioplegia and microplegia after propensity matching. In fact, in-hospital mortality was higher in the microplegia group. They also reported similar levels of postoperative peak troponin I levels which translated into similar inotropic requirements postoperatively. This was supported by Onorati et al.(79) who observed no difference in hospital mortality, LOS incidence, acute myocardial infarction incidence or need for intra-aortic balloon pumping. However, microplegia resulted in lower levels of lower troponin-I and lactate from coronary sinus in patients undergoing CABG during the postoperative course(79). Microplegia was also associated with lower rates of transfusion and hospitalisation and a lower need/duration of inotropes and ICU-stay, which may counteract the greater economic burden of microplegia compared to traditional blood cardioplegia(79). One of the major advantages of microplegia is the avoidance of haemodilution and the higher haematocrit level which leads to better oxygen delivery and buffering capacity, resulting in a myocardial protective effect(78). Clinical studies should ensure that anaesthetists limit fluid administration so as to achieve this advantage and maximise the myocardial benefits of microplegia.

**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(80–82). 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(83). Importantly, the release of cTnI post-cardiac surgery was found to be associated with increased mortality and morbidity(84). 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(85). CK-MB activity is also a valuable sensitive and specific indicator of reperfusion, myocardial injury, and infarct size, though inferior to cTnI(86).

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(87). 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 postoperative outcomes and therefore has potential for targeted therapeutic intervention to minimise the effects of reperfusion injury on the heart. Research towards gene therapy is another possible avenue for consideration.

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(88). 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(65). 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.(89). Opening of the mPTP is triggered in the reperfusion phase of IR by Ca2+ influx, oxidative stress and reversal of ischaemic induced acidosis(89,90). Upon opening of the pore, cell swelling and apoptosis occur, 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 that have already been subject to use in clinical trials. 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 has proven it somewhat beneficial. A randomised-controlled trial conducted by Hausenloy and colleagues(91) in 2014, reported a significant reduction (P = 0.049) in peri-operative myocardial injury in high-risk patients treated with CsA, undergoing CABG. A separate study performed in 2015 found CsA reduced IRI in patients undergoing aortic valve surgery(92). 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(93). The limitations of CsA lie in 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 could prove useful in adapting its functionality(94).

An alternative method of therapy that could be applicable not only to improving CsA or CyP-D, but other IRI pathways, is gene therapy. Several successful gene therapy studies have been reported so far. A paper released in 2018, described an in-vivo experiment of the overexpression of DUSP1 gene (dual-specificity protein phosphatase1) in mice models(95). The gene conferred an improvement in myocardial function and reduced infarct sizes, when compared to wild-type mice. Studies like these have the potential to be translated clinically in the future, but questions remain about the accessibility and reproducibility of gene therapy in clinical practice. Larger scale trials are required to answer these questions.

**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 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+/HCO3- symporter, Na+-H+ exchanger, LTCC, G-protein coupled receptor, VGCC, Na+/Ca2+ 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, *Gi* inhibitory G protein, *Gs* stimulatory G protein, *AC* adenylate cyclase, *ATP* adenosine triphosphate, *cAMP* cyclic adenosine monophosphate, *ADP* adenosine diphosphate, *KATP* ATP-sensitive potassium channel, *PLC* phospholipase C, *PKC* phosphokinase C, *NF-kB* nuclear factor kappa B, *CICR* calcium-induced calcium release, *PDH* pyruvate dehydrogenase.`

Table 1: Properties of HTK, STH and Del Nido cardioplegic solutions. All units are expressed in mmol/L unless otherwise indicated.

|  |  |
| --- | --- |
| Histidine-tryptophan-ketoglutarate (HTK) | * Intracellular * Na+:15, K+:9, Mg2+:4, Ca2+:0.015, Mannitol:30, Histidine:198, Tryptophan:2, Ketoglutarate:1(96) * Contains histidine (buffer), tryptophan (membrane stabiliser), ketoglutarate (high energy ATP provider), mannitol (osmotic diuretic, free radical scavenger) * Single cardioplegic dose required so uninterrupted surgery * Longer time needed to initiate cardiac arrest due to low potassium |
| St Thomas’s solution (STH) | * Extracellular * Na+:110, K+:16, Mg2+:16, Ca2+:1.2(96), Bicarbonate:10(41) * Original solution STH1 was refined to form STH2 * STH2 is the most widely used cardioplegic solution, but most UK cardiac centres use STH1 * STH1 contains procaine hydrochloride, a membrane stabiliser with cardioplegic effects * Induces rapid cardiac arrest due to high potassium content * Repeated dosing is needed which interrupts operative procedure |
| Del Nido solution | * Extracellular * Na+:140, K+:26, Mg2+:3, Cl\_:98, lidocaine; 130mg * Used mainly for paediatric open-heart surgery; scarce evidence and research for safe use in adult cardiac surgery * Induces cardiac arrest, reduces energy consumption rate, scavenges free radicals, reduces myocardial oedema, promotes anaerobic glycolysis * Single cardioplegic dose needed so uninterrupted surgery and lower total volume of solution needed |

Table 2:  Advantages and Disadvantages of Cold and Warm Cardioplegia.

|  |  |  |
| --- | --- | --- |
| Type | Advantages | Disadvantages |
| Cold | * Lowers oxygen demand of myocardium * Oxygen unloading is enhanced due to acidosis and hypercarbia * Neuroprotective | * Inhibits myocardial enzymes * Delays postoperative recovery of metabolism and function * Membrane rupture * Denaturalisation of proteins * Inhibition of Na-K and calcium ATP systems * Myocardial oedema * Increased risk of reperfusion injury * Causes right shift of oxyhaemoglobin dissociation curve so lower oxygen availability * Inadequate delivery due to sludging, rouleaux formation and cold agglutinin activation |
| Warm | * Minimises ischaemia and reperfusion injury if given continuously | * Increased risk of postoperative neurological complications * Higher risk of hyperkalaemia * Increased use of high potassium cardioplegic solution * Larger volumes of cardioplegic solution needed * Increased use of crystalloid and alpha-agonists to maintain perfusion pressures * Poor visualisation * Greater endothelial injury * Must be given continuously |

Table 3: Advantages and Disadvantages of Blood and Crystalloid Cardioplegia.

|  |  |  |
| --- | --- | --- |
| Type | Advantages | Disadvantages |
| Blood | * Better delivery of oxygen due to haemoglobin * Better buffering capacity * Delivers nutrients present naturally in blood so anaerobic substrates not needed * Free oxygen radical scavengers present * Improved rheologic effects causing better flow * Oncotic pressure constituents present which prevents oedema * Acidotic environment during cardiac arrest may shift oxyhaemoglobin dissociation curve to the right and improve myocardial oxygen uptake * No cost or need to produce complex pharmacological mixture for cardioplegia | * Obscures operative field * Hypothermia may cause left shift of oxyhaemoglobin dissociation curve and reduce oxygen availability * Production of oxygen free radicals * Apparatus to deliver blood cardioplegia is expensive |
| Crystalloid | * Temperature has no effect on oxygen delivery * Lower costs * Good visualisation of operating field | * Contains less oxygen than blood * Decreases oncotic pressure and increases oedema risk * Causes more haemodilution |

Table 4:  Advantages and Disadvantages of Antegrade, Retrograde and Combined

|  |  |  |
| --- | --- | --- |
| Type | Advantages | Disadvantages |
| Antegrade | * Rapid and easy administration * Rapid cardiac arrest | * Inhomogeneous distribution in presence of coronary occlusions or stenosis, causing poor perfusion and injury to myocardium * Can form coronary emboli during redo-CABG * Can cause coronary ostial injury * Cannot be used in patients with type A aortic dissection or aortic insufficiency * Increased risk of ionotropic support and fibrillation |
| Retrograde | * Can be used in presence of coronary occlusions * No operative interruptions * Flushes air and debris from coronary arteries. So reduces embolisation risk in redo-CABG * No ostial injury | * Slower cardiac arrest * Coronary sinus injury * Myocardial oedema * Large volumes of cardioplegic solution required * Atriotomy and bicaval cannulation required * May leak and obscure operative field * Inadequate perfusion of right ventricle |
| Combined | * Combines advantages of antegrade and retrograde cardioplegia * Shorter post-ischaemic stunned period so less myocardial damage during CABG * Can be used for complex operations in high-risk patients * Reduced need for ionotropic support compared to antegrade alone * Better cardioplegic distribution in hypertrophied tissue | * May not be drastically more beneficial where both antegrade and retrograde cardioplegia are compromised |

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