Narrating Myocardial Protection: A Comprehensive Review of Cardioplegia Strategies

Abstract

This article comprehensively reviews cardioplegia strategies and their efficacy in protecting the myocardium during cardiac surgery. The article discusses the history of cardioplegia, including the development of various techniques and the drawbacks of hyperkalemic solutions. The article also describes the pathophysiology of myocardial ischemia during aortic cross-clamp placement and how it can lead to myocardial injury and cell necrosis. The use of hypothermia and cardioplegia is explored as potential myocardial protection strategies. The article concludes that although myocardial injury can occur during cardiopulmonary bypass, the incidence of frank myocardial infarction is relatively low. The article emphasises the importance of myocardial protection strategies to minimise the risk of myocardial damage during cardiac surgery. However, be aware that each cardioplegic solution has wide variations in the composition and protocols. I tried to narrate the composition with references and some modifications for each.

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Introduction

Cardioplegia refers to the intentional induction of cardiac arrest during cardiac surgery to facilitate surgical procedures while minimising the risk of myocardial damage. The term was first introduced in 1957 by Lam, building upon earlier experiments by Sidney Ringer in 1883, who demonstrated potassium-induced "diastolic arrest" in the frog heart. Lam initially used an intraventricular injection of potassium chloride (KCl) to induce cardiac arrest in hypothermic dogs but abandoned the method due to adverse events like ventricular fibrillation and myocardial ischemic reperfusion injury [1].

In the 1950s, Melrose pioneered the "Melrose Technique," utilising potassium citrate to induce cardioplegic arrest during cardiac surgery to enhance surgical precision and minimise myocardial injury. However, subsequent research unveiled the drawbacks of hyperkalemic solutions, leading to their temporary abandonment. Alternative methods, including hypothermia, posed risks such as the "stone heart" phenomenon. Bretschneider's HTK solution offered a potential alternative for organ preservation. In the mid-1970s, cardioplegic solutions with high-to-moderate potassium concentrations resurfaced, with St. Thomas' Hospital cardioplegia becoming widely adopted. Developed by Hearse and Braimbridge, this technique induced diastolic arrest through membrane depolarisation. Buckberg's multi-dose 4:1 cold bloodcardioplegia, introduced later, remains a commonly used solution in cardiac surgery, marking significant advancements between the 1950s and mid-1970s [2].

Pathophysiology of Myocardial Ischemia Under Aortic Cross-Clamp

Coronary blood flow dynamics play a pivotal role in supplying oxygen to the myocardium, with a biphasic pattern distributing 25% of flow during systole and 75% during diastole for the left ventricle (LV) and a more evenly balanced 50:50 distribution for the right ventricle (RV). At rest, total coronary blood flow ranges from 80 to 160 millilitres per 100 grams of myocardial tissue per minute (ml/100g/min), constituting around 5% of the cardiac output. This translates to an oxygen delivery of 13 to 20 millilitres per minute, contingent upon variables like blood oxygen-carrying capacity and arterial oxygen saturation (SpO2) [3].

Myocardial oxygen consumption, calculated as the product of coronary blood flow and the arteriovenous oxygen difference, varies across physiological states. Under cardiac arrest conditions, it dwindles to a mere 2 ml/100g/min, while at rest, it elevates to 8 ml/100g/min, surging to 90 ml/100g/min during maximal inotropy. With an oxygen extraction ratio hovering around 75%, which remains relatively stable across a spectrum of myocardial workloads, the myocardium predominantly allocates 60% of its oxygen consumption to contraction, 15% to relaxation, 20% to basal metabolism, and 3-5% to electrical activation. This intricate metabolic landscape can be illustrated as the area enclosed within the pressure-volume loop, representing the heart's " external " work [4].

The relationship between myocardial oxygen uptake, indicative of oxygen demand, and temperature is a critical aspect of cardiac physiology with implications for myocardial protection strategies. According to Vinten-Johansen and Thourani (2000), eliminating cardiac work by venting the beating heart during bypass surgery substantially reduces oxygen demand, ranging from 30% to 60% compared to a normally beating heart. Additionally, arresting the heart further decreases oxygen demand by an additional 50%, resulting in an impressive total

reduction of 90%. (Vinten-Johansen & Thourani, n.d.). Hypothermia and cardioplegia have shown benefits in protecting the myocardium from ischemia and reperfusion injury. These interventions reduce myocardial oxygen consumption (MVO2) by optimising the myocardium's metabolic state. With CPB, the reduction in cardiac work decreases MVO2 by 30% to 60%, which can be further reduced with subsequent temperature reduction, cardiac arrest, and hypothermia, resulting in up to 90% reduction in metabolic requirements [6].

Myocardial injury and cell necrosis can occur during cardiopulmonary bypass (CPB), evidenced by the release of troponin, which may lead to myocardial stunning and dysfunction. However, frank myocardial infarction is relatively uncommon in this context, with changes in cardiac enzymes indicating specific myocardial injury post-cardiac surgery becoming more detailed. With the placement of the aortic crossclamp after the initiation of CPB, myocardial tissue hypoxia ensues, resulting in acidosis, increased lactate due to adenosine triphosphate (ATP) consumption, and calcium accumulation. Severe ischemia can disrupt the muscle cell membrane, causing intracellular components to leak into the extracellular compartment [7]. The duration of ischemia during cardiac surgery, particularly during aortic cross-clamping, is a critical determinant of the extent of myocardial injury. Prolonged ischemia can result in irreversible damage to cardiac tissue through the following mechanisms.

a) **Cellular Energy Depletion:** The interruption of blood flow deprives cells of oxygen and glucose, disrupting aerobic respiration and ATP production. ATP depletion impairs cellular functions vital for maintaining membrane integrity, ion homeostasis, and protein synthesis [8].

b) **Anaerobic Metabolism and Lactic Acidosis:** Without oxygen, cells switch to anaerobic metabolism, accumulating lactic acid and other metabolic byproducts. Lactic acidosis lowers intracellular pH, impairing enzyme activity and disrupting cellular metabolism [9].

c) **Ion Dysregulation:** Ischemia disrupts ion gradients across cell membranes, leading to intracellular accumulation of sodium (Na+) and calcium (Ca2+) and depletion of potassium (K+). Increased intracellular calcium triggers multiple cellular pathways, including activation of proteases, phospholipases, and endonucleases, contributing to cell damage [10].

d) **Oxidative Stress and Reactive Oxygen Species (ROS):** Ischemia-reperfusion injury leads to generating reactive oxygen species (ROS) through various pathways, including mitochondrial dysfunction, xanthine oxidase activation, and leukocyte activation. ROS, including superoxide anion (O2•−), hydrogen peroxide (H2O2), and hydroxyl radical (•OH), damage cellular membranes, proteins, and DNA, exacerbating tissue injury [11].

e) **Inflammatory Response:** Ischemic injury triggers an inflammatory response characterised by releasing pro-inflammatory cytokines, chemokines, and adhesion molecules. Infiltration of leukocytes, such as neutrophils and macrophages, further amplifies tissue damage by releasing inflammatory mediators and proteolytic enzymes [12].

f) **Endothelial Dysfunction and Microvascular Injury:** Ischemia impairs endothelial cell function, leading to vasoconstriction, microvascular thrombosis, and increased vascular permeability. Endothelial dysfunction contributes to tissue hypoxia, inflammation, and impaired tissue perfusion, exacerbating ischemic injury.

g) **Mitochondrial Dysfunction and Apoptosis:** Prolonged ischemia disrupts mitochondrial function, leading to mitochondrial membrane depolarisation, cytochrome c release, and activation of apoptotic pathways. Apoptosis, or programmed cell death, contributes to tissue injury and remodelling in response to ischemic insult [13].

Overall, ischemic injury involves a complex interplay of cellular and molecular events, resulting in tissue dysfunction and damage. Understanding the mechanisms underlying ischemic injury is crucial for developing therapeutic strategies to mitigate tissue damage and improve outcomes in conditions associated with ischemic injury [14].

Sequalae of Myocardial Ischemia After Aortic Closs Clamp

Stunning: Myocardial stunning is a reversible form of mechanical dysfunction following brief ischemia and subsequent reperfusion periods. During ischemia, myocardial oxygen supply is inadequate to meet demand, leading to a depletion of high-energy phosphate stores and accumulation of metabolic byproducts. Upon reperfusion, despite restoration of blood flow, myocardial contractility remains depressed, contributing to transient left ventricular dysfunction. The stunning mechanisms are multifactorial and may involve alterations in calcium handling, mitochondrial dysfunction, oxidative stress, and inflammatory responses [15].

No-Reflow Phenomenon: The no-reflow phenomenon occurs when previously ischemic myocardial tissue fails to reperfusion adequately despite restoration of blood flow. It is characterised by microvascular dysfunction, impaired tissue perfusion, and persistent myocardial ischemia. Factors contributing to the no-reflow phenomenon include microvascular obstruction, endothelial dysfunction, leukocyte plugging, and distal embolisation of microthrombi or atheromatous debris. No-reflow can exacerbate myocardial injury and increase the risk of adverse outcomes, including myocardial infarction and heart failure [16].

Reperfusion Arrhythmias: Reperfusion of ischemic myocardium can trigger various arrhythmias, including ventricular tachycardia, ventricular fibrillation, and atrial fibrillation. The sudden reintroduction of oxygen during reperfusion can lead to electrical instability and aberrant conduction within the myocardium. Reperfusion arrhythmias may result from alterations in membrane ion channels, such as delayed after-depolarizations, triggered activity, and reentry circuits [17]. The response of the myocardium to ischemia-reperfusion injury during cardiac surgery is

complex and involves interactions between multiple cellular and molecular pathways. While cardioprotective strategies, such as cardioplegia and pharmacological agents, aim to mitigate ischemia-reperfusion injury, further research is needed to understand the underlying mechanisms better and develop more effective therapeutic interventions to improve patient outcomes [18].

Two Mechanisms Behind Cardioplegia-Induced Cardiac Arrest

A. **Depolarizing arrest:** They increase extracellular potassium to 16 mM, which results in membrane depolarisation from approximately -80 mV to -50 mV. At this level, voltage-dependent Na+ channels become inactivated, preventing the rapid sodium-induced spike and propagation of the action potential, leading to diastolic cardiac arrest. Moreover, at -50 mV, the high Na+ driving force promotes Na+ entry through the Na+ "window currents," which remain open at these depolarised potentials. Consequently, an elevation in intracellular Na+ causes a reversal of the voltage-dependent Na+/Ca2+ exchanger, facilitating the extrusion of 3 Na+ ions in exchange for 1 Ca2+ ion entry, ultimately resulting in intracellular Ca2+ overload [19].

B. **Polarized arrest:** The concept of "polarised arrest" is appealing because it maintains the membrane potential close to the resting potential value of about -80 mV, thereby reducing the adverse effects of calcium (Ca2+) loading. Both sodium (Na+) and calcium channels are closed at resting membrane potentials, minimising transmembrane fluxes and preventing intracellular Ca2+ overload. This preservation of mitochondrial function and ATP balance is crucial for myocardial preservation and recovery, as it helps avoid oxidative stress, cell death, and endothelial activation during reperfusion [20]. Polarised arrest is also associated with increased resistance to ischemia and inflammation, as demonstrated by several in vitro and animal studies. Notably, polarising solutions have significantly reduced porcine neutrophil priming

by suppressing superoxide anion generation, thus mitigating inflammatory responses [21].

Mechanisms of Induction of Polarised Cardiac Arrest Include

1. **Na channel blocker:** Local anaesthetic agents like lidocaine and procaine have been utilised alongside other agents to induce cardiac arrest. Procaine is a component of the St. Thomas cardioplegia solution, contributing to membrane stabilisation and offering benefits such as reducing the incidence of arrhythmias and rhythm disorders. However, there is a notable risk of postoperative convulsions associated with its use. Tetrodotoxin (TTX), another sodium channel blocker, is highly toxic but has demonstrated high efficacy in reversing cardiac arrest. It is preferred over hyperkalemic arrest due to its ability to reduce energy consumption and maintain a more physiological state of rest [22].

2. **K channel opener:** Adenosine can induce cardiac arrest through its hyperpolarising effect, particularly on conduction tissue. This property has been shown to offer good myocardial protection when adenosine is used alone as a cardioplegic agent at concentrations of 10 mmol/L or when added at one mmol/L to cardioplegic solutions with potassium. Adenosine's inclusion has been demonstrated to reduce arrest time and to be more effective than hyperkalemic arrest alone, resulting in decreased calcium overload in isolated myocytes. Recent clinical studies have tested the beneficial effect of adenosine in cardioplegia with hyperkalemia, showing it to be safe and effective in reducing postoperative complications. Furthermore, the combination of adenosine and lidocaine, both of which induce hyperpolarised arrest, has been found to provide adequate myocardial protection for ischemic periods exceeding 4 hours [22].

3. **Hypocalcemia:** The absence of intracellular calcium leads to cardiac arrest in diastole by inhibiting the excitation-contraction coupling process. This characteristic has been leveraged in cardioplegic

solutions in Germany for some time. Combined with hyponatremia, it further reduces sodium channel function, helping maintain the membrane potential close to the resting potential. However, the absence of calcium also increases the risk of inducing the "calcium paradox." This phenomenon occurs when reintroducing calcium to the myocardium after a period of calcium-free arrest, potentially leading to myocardial injury or dysfunction [23].

4. **Hypermagnesemia:** is effective in cardioplegic solutions. It is utilised in the St. Thomas solution at a concentration of 16 mmol/L [24].

Cardioplegia Solutions

In cardioplegia, the history of myocardial protection during cardiac surgery is closely intertwined with the development and evolution of cardioplegia solutions. Cardioplegia is the deliberate induction of cardiac arrest and myocardial protection during cardiac surgery by delivering a specialised solution directly to the heart [25]. Cardioplegia originated in the mid-20th century as surgeons sought methods to arrest the heart to facilitate complex surgical procedures temporarily. Early cardioplegia solutions primarily consisted of high-potassium solutions, which induced myocardium depolarisation, leading to the cessation of contraction and subsequent cardiac arrest. Although these solutions were effective in achieving cardiac arrest, they posed challenges related to myocardial oedema and cellular injury due to excessive potassium concentrations [26].

Over time, researchers and clinicians recognised the need for more advanced cardioplegia solutions, leading to the development of blood-based solutions that mimic physiological blood composition. Refinement continues into the 21st century, tailoring solutions to specific patient needs and procedures through variations in temperature, composition, and delivery methods. Pharmacological agents like adenosine and magnesium are also being explored to enhance myocardial protection and reduce ischemiareperfusion injury [27]. While no universally accepted "ideal" cardioplegic solution exists, formulations such as del Nido, Custodiol (HTK), and modified St. Thomas solutions have demonstrated efficacy and safety in clinical practice. The choice of cardioplegic solution often depends on surgeon preference, institutional protocols, and patientspecific factors to optimise myocardial protection and patient outcomes during cardiac surgery [28].

Cardioplegia Different Classification Systems

A. **According to ion composition**

1. **Extracellular solutions:** containing high levels of potassium, magnesium, and sodium prevent the repolarisation of myocytes. The potassium-rich perfusate in the extracellular space reduces the membrane voltage difference, leading to depolarisation. Intracellular calcium sequestration occurs via active transport across an ATP-dependent pump, allowing the myocardium to relax in diastole. However, the high potassium concentration of the cardioplegic solution prevents repolarization [29].

2. **Intracellular solutions:** typically contain low electrolyte levels. They mimic the high potassium/low sodium conditions found intracellularly, thereby reducing potential concentration gradients across the plasma membrane and halting potassium efflux. This reduction in membrane potential prevents the generation of action potentials. Additionally, the function of the Na+/K+ ATPase channel is reduced in hypothermic conditions, allowing the intracellular concentrations to persist [30].

B. **According to temperature**

1. **Warm cardioplegia:** Most investigators utilise warm cardioplegia at 37°C, although some use temperatures above 35°C. The rationale for using warm blood is that Blood cardioplegic solution, when cooled to 20°C, releases only 50% of its total oxygen content. When cooled to 10°C, it releases only 37% to 38% due to the leftward shift of the oxyhemoglobin dissociation curve with hypothermia. Normothermic cardioplegic arrest results in an oxygen requirement of 1.1 ml oxygen/100 g/min, representing a greater than 90%

reduction from baseline values. Warm cardioplegia can meet oxygen demand if oxygenated blood can reach the arrested myocardium, reduced to less than 0.3 ml/100 g/min at 20°C. However, despite these reductions in oxygen demand, anaerobic metabolism may not fully meet the substantially reduced metabolic needs of the arrested hypothermic heart. Extremely low myocardial temperatures (<10°C) may inhibit energy-generating processes like glycolysis more than they inhibit energy consumption. Hypothermia can also destabilise cell membranes, inhibit sodium-channel pumps, and cause calcium sequestration, leading to oedema, reperfusion injury, and impaired sarcoplasmic reticulum function [31].

2. **Cold cardioplegia:** Crystalloid cardioplegia solutions are typically delivered at four °C, while cold blood solutions are administered at temperatures ranging from 10 to 16°C. During cardioplegiainduced cardiac arrest, the goal is for all electrical activity to cease ideally. Hypothermia, which inherently reduces the basal metabolic rate and thus helps to decrease myocardial electrical activity, was utilised in numerous operations in the early days of cardiac surgery. Subsequently, the preferred method for cooling the heart involves infusing cold cardioplegia solutions directly into the myocardium. This approach rapidly stops electromechanical activity and reduces temperature in all myocardial layers, providing more effective myocardial protection [32].

C. **According to the approach of delivery**

1. Anterograde cardioplegia refers to the method in which the cardioplegia solution is delivered down the right and left coronary arteries, supplying the myocardium in a distribution similar to that of blood flow under normal conditions. In this technique, the anterograde cardioplegia is introduced into the proximal aorta through a catheter with three lumens: one for administering the cardioplegia, another for suctioning, and the third for measuring intraluminal pressure. It's essential to monitor the barometric pressure during cardioplegia administration to prevent

potential damage to endothelial cells and reperfusion injury caused by elevated infusion pressures [33].

2. **Retrograde cardioplegia approach:** a cardioplegia catheter is inserted through an atriotomy in the right atrium into the coronary sinus, and flow is retrograde. Intraoperative transesophageal echocardiography (TEE) is used to confirm the position of the coronary sinus cannula. This method may not provide adequate myocardial protection to the right ventricle, as the anterior cardiac veins drain directly into the right atrium, not the coronary sinus. Cannulating the coronary sinus carries a risk of perforation, which, while rare, can lead to significant morbidity and mortality. Repairing such perforations is technically challenging due to the posterior location of the coronary sinus [34].

D. Classification according to carrying vehicle

1. **Crystalloid cardioplegia:** offers several advantages, including inducing mild-to-moderate hypothermia, reducing oxygen consumption, and improving visibility during coronary artery anastomoses. However, it can lead to myocardial oedema, potentially resulting in low cardiac output syndrome (LCOS) [35].

2. **Blood cardioplegia:** provides nourishment to the endothelium and myocardium, efficient oxygen and nutrient transport, increased buffering capacity, and reduced cellular damage due to oncotic variations and decreased free radicals [36].

Cardioplegic Solutions and Strategies

Melrose Solution: During the 1950s, British physician Dennis Melrose proposed a solution to the perceived issue with potassium chloride cardioplegia by creating a cardioplegic solution using potassium citrate. Testing this solution on a canine model of cardiopulmonary bypass, known as the "Melrose solution," involved injecting potassium citrate and warm oxygenated whole blood in a 9:1 blood-to-potassium ratio into the aortic roots of hypothermic dogs. This procedure induced near-immediate cardiac arrest, and subsequent reperfusion and washout

of the solution restored heart function to pre-procedure levels [37]. The success in canine models prompted the Melrose group to apply potassium citrate cardioplegia in humans within a few years. However, subsequent studies revealed that the potassium citrate solution still led to post-cardioplegia ventricular fibrillation and myocardial dysfunction in many cases. This setback resulted in a general cessation of clinical application of potassium cardioplegia between the 1960s and early 1980s [38].

Optimum potassium concentration: Potassium-induced cardioplegia is a beneficial method for reducing myocardial injury during periods of cardiac arrest, with an optimal concentration range of potassium identified for myocardial protection in this rat model. Histological analysis of transverse sections of the left ventricular myocardium revealed that potassium-induced cardioplegia effectively reduced cell injury resulting from anoxia, with hearts exposed to cardioplegia containing potassium concentrations of 25 and 30 mEq/L exhibiting the least severe anoxic injury. However, very high doses of potassium (100-200 mEq/L) led to contracture and extensive myocardial cell injury (Gharagozloo et al., 1979).

Birmingham Solution: The Birmingham Solution, developed by Conti and colleagues, represented a significant advancement in extracellular solutions used for cardiac surgery. Its effectiveness was primarily demonstrated through the publications of Kirklin and colleagues [39]. One notable aspect of the Birmingham Solution was the inclusion of glucose as a substrate for the myocardium. This addition addressed the heart's metabolic needs during cardiac arrest and surgical procedures, providing essential energy for myocardial function. The development of the Birmingham Solution paved the way for the creation of numerous other formulations that incorporated similar essential components, including glucose, potassium, and insulin. These formulations aimed to optimise myocardial protection and metabolic support during cardiac surgery, ultimately improving patient outcomes [40].

GIK (glucose-insulin-potassium) solution/ University of Minnesota Solution: More than forty years ago, Research on glucose-insulin-potassium (GIK) solutions,

primarily conducted in the United States, has led to the development of various formulations using these essential components over the past three decades. Hewitt et al. and later Lolley et al. demonstrated the efficacy of continuous infusion of a solution containing glucose, potassium, insulin, and mannitol in significantly improving myocardial protection [41]. The combination of glucose, insulin, and potassium enhanced anaerobic glycolysis and the removal of toxic substances, thereby improving myocardial function. A modified version of this solution, incorporating albumin to increase osmolality, was extensively utilised at the University of Minnesota for many years. However, a limitation of GIK solutions is insulin degradation over time, necessitating fresh preparation for each use. Numerous investigators, including Follete and coworkers and Todd and Tyers, contributed to developing GIK solutions, often utilising dextrose as the primary vehicle. While GIK solutions demonstrate protective effects, they may offer insufficient protection during prolonged ischemia or when left ventricular function is compromised [40].

St. Thomas Solution and Plegisol: St. Thomas I cardioplegic solution, introduced globally in 1975, comprises a mixture of potassium chloride (16 mmol/L), magnesium chloride (16 mmol/L), and procaine (1 mmol/L) added to 1 L of Ringer's solution. This formulation was a foundation for several years of cardiac surgical procedures [42]. In 1981, St. Thomas II emerged as a refined version, notably reducing calcium levels by 50%, eliminating procaine, incorporating bicarbonate, and adjusting sodium and potassium concentrations while achieving a pH of 7.8. It has since become a standard worldwide, even serving as the base for cold blood cardioplegia solutions pioneered by Buckberg and colleagues [43]. St. Thomas II is administered at temperatures of 4-6°C, typically initiating with a 1000 ml infusion for a 70-kg adult, followed by intermittent 100 ml infusions every 15 to 20 minutes, supplemented by topical hypothermia to maintain the myocardial temperature below 15°C throughout the procedure. Since 1976, St. Thomas Hospital in London has been using cardioplegic solutions developed by David Hearse, a biochemist, and Mark Braimbridge, a cardiac surgeon. These solutions, initially known as "St. Thomas solution," changed electrolyte concentration

over time. In 1981, an enhanced formula, referred to as "St. Thomas no. 2" or Plegisol, was introduced by Abbott Laboratories in North Chicago [44]. The St. Thomas solution was combined with autologous blood at a ratio of 1:4. This mixture was prepared in two concentrations: one for induction and one for maintenance, with total and half potassium concentrations, respectively. The initial induction dose was administered at 20 ml/kg. Subsequent maintenance doses were given at a volume of 10 ml/kg, with re-dosing occurring at 30-minute intervals [45] and can last up to 90 minutes (Table 1).

Del Nido cardioplegia: The del Nido cardioplegia solution developed by researchers at the University of Pittsburgh in the early 1990s marked a significant advancement in myocardial protection during cardiac surgery. Patented initially, the solution is now commonly referred to as del Nido cardioplegia. Over time, modifications have been made to the original formulation, enhancing its efficacy and safety. With the expiration of the University of Pittsburgh patent, the solution is available from various compounding companies in the United States. Additionally, hospitals and healthcare facilities have the option to prepare it in-house. Over the past few years, the increased inquiries regarding del Nido cardioplegia reflect its growing recognition and adoption nationally and internationally [46]. The delivery ratio mentioned is 1:4 with oxygenated patient's blood to crystalloid [47]. A single administration of del Nido cardioplegia typically dosed at 20 ml/kg, offers sufficient protection to the myocardium for approximately 90 minutes. It achieves this by lowering the myocardial temperature to less than 15°C, effectively minimising oxygen consumption [48].

	Birmingham solution	GIK (University of Minnesota) Solution	St Thomas 1	St Thomas 2 "Plegisol"	Del Nido	Buckberg
Na (mmol/L)	100	3.5	140	110	153	152
Cl (mmol/L)	84	30		160	132	126
K (mmol/L)	30	30	20	16	26	18
Ca (mmol/L)	0.7	-	2.2	2.4	0.4	1.4
Mg (mmol/L)	-	-	16	32	6.2	4.6
HCO3 (mmol/L)	-	3.5	24	10	13	
Osmolarity (mOsm/L)	300	364	310	300		
pH			5.5-7.0	7.8		
Additives	Mannitol 5 gm/L	Mannitol 12.5 gm/L	Procaine		Lidocaine 130 mg	
		Regular ten insulin Units/L				
	Dextrose 5 gm/L	Dextrose 50 gm/L				
	Albumin 50 gm/L	Albumin 5 gm/L			Mannitol 3.2 gm /L	

Table 1. Composition Of Extracellular Cardioplegic Solution Solutions

Cold Blood Cardioplegia: Buckberg Solution: In the late 1970s, Buckberg's contribution, particularly with the introduction of plegia containing a patient's blood from the cardiopulmonary bypass (CPB) circuit, revolutionised cardiac surgical practice. (DAS, 2022a). Combining blood with crystalloid cardioplegia has emerged as the preferred formulation among cardiac surgeons worldwide, surpassing any other cardioplegic solution alone. The standard ratio of blood to the crystalloid solution, typically at 4:1 (4 parts blood to 1part crystalloid cardioplegia), has been consistently favoured. However, the specific formulation of the crystalloid portion may vary between institutions. The administration of cold blood cardioplegia, following Buckberg's proposed proportions, can be efficiently carried out using specialised equipment provided in a kit. This kit includes calibrated tubing connected to a roller pump, which facilitates the automatic mixing of blood with the clear solution before injection into the aortic root. A heat exchanger is also incorporated into the kit to maintain the solution's temperature between 4 and 6°C, decreasing myocardial temperature even below 15°C [49].

It consists of several components: Base Solution: A dextrose-based solution in normal saline. Potassium Chloride: Used as the depolarising agent to induce cardiac arrest at a dose of 80 mmol/L, which is diluted after mixing with blood to be around 20 mmol/L as the blood crystalloid ratio is 4:1. Tromethamine: Acts as a buffer to maintain the pH of the solution, and Citrate Phosphate Double Dextrose: Functions as a calcium chelator to prevent calciummediated myocardial injury.

The cardioplegia solution is administered in three phases

- **Induction:** The initial dose given to arrest the heart. This solution is typically delivered at 4°C. Potassium (K+): 18 to 20 mEq/L, pH: 7.7, Calcium (Ca++): 0.5 to 0.6 mmol/L, Osmolarity: 340 to 360 mOsm/L, Temperature: 4° to 9°C.

- **Maintenance:** Administered every 15–20 minutes during the surgery to maintain cardiac arrest and replenish oxygen and nutrients to the heart muscle. Also delivered at 4°C. Potassium (K+): 8 to 10 mEq/L [50].

- **Reperfusion:** Known as the "hot shot," delivered at 37°C just before removing the aortic crossclamp. This solution contains glutamate and aspartate, sugar substrates providing nutrients to the heart muscle before it is expected to resume beating.

Mixing oxygenated patient's blood to crystalloid at a ratio 4:1 by a particular circuit with Y- a connection mounted on a small cardioplegia heat exchanger to achieve this low temperature. [51].

Low-Volume, Single-Shot Crystalloid Cardioplegia (Cardioplexol): Cardioplexol (Bichsel, Interlaken, Switzerland) is a single-shot cardioplegia solution designed to induce cardiac arrest during surgeries such as aortic valve replacement (AVR) for severe aortic valve stenosis. It is administered directly via the aortic root and contains a specific composition of ingredients, including potassium, magnesium, procaine, and xylitol. This solution ensures controlled cardiac arrest for approximately 45 minutes per 100 ml shot, and it can be repetitively administered up to four times with a maximum dosage of 500 ml. The composition of Cardioplexol® per 100 ml includes: Potassium: 10 mmol, Magnesium: 16.2 mmol, Procaine: 1.1 mmol, Xylitol: 29.6 mmol [52]. Cardioplexol®, as a low-volume, single-shot cardioplegic strategy, appears safe for patients undergoing isolated AVR with extracorporeal circulation (ECC). This method allows for effective cardiac arrest induction while minimising the volume of cardioplegic solution required. By conducting additional research, including randomised controlled trials and observational studies, researchers can gather more comprehensive data on the performance of Cardioplexol® across various cardiac surgeries and patient profiles. This will help better understand its potential benefits and limitations in different clinical scenarios, ultimately guiding clinicians in optimising its use for improved patient outcomes [53].

Antegrade intermittent warm cardioplegia of Calafiore: Physiologic basis: When blood cardioplegic solution is cooled to 20°C, only 50% of its total oxygen content is released, decreasing to 37-38% at 10 °C due to the leftward shift of the oxyhemoglobin dissociation curve caused by hypothermia. Normothermic cardioplegic arrest drastically reduces oxygen demand to 1.1 ml oxygen/100 g/min,

representing over a 90% reduction from baseline values. Warm cardioplegia can partially meet oxygen demand, but hypothermic cardioplegia, despite reducing oxygen demand further, leads to suboptimal recovery of function and reduced intracellular metabolites. Extremely low myocardial temperatures (<10°C) inhibit energy production more than consumption. Hypothermia also destabilises cell membranes, inhibits pumps, and causes calcium sequestration, resulting in oedema, reperfusion injury, and impaired function—blood Source: Normothermic (37°C) blood collected from the oxygenator [54].

In 1994, Calafiore et al. introduced antegrade intermittent warm blood cardioplegia based on potassium, finding it superior to cold crystalloid cardioplegia, especially in high-risk patients. They described a setup in 1995 involving normothermic blood delivery with potassium addition using a perfusion syringe. In 1998, Caputo et al. modified this technique by adding magnesium, suggesting its role in inhibiting calcium channels during ischemia. The perfusion syringe contained potassium chloride and magnesium sulfate. Calafiore's protocol included normothermic blood perfusion combined with a cardioplegia solution bolus followed by reperfusions at intervals during ischemia, with decreasing potassium and magnesium concentrations see Table 2 [55]. Using Tubing Size ¼ inch, Blood is infused through the aortic root cannula or directly in the coronary ostia using a roller pump at a temperature of 37°C "actively warmed during bypass" [56] (Table 2).

Dose	Flow Rate (mL/min)	Syringe pump (mL/h)	Duration (min)	$[K^+]$ (mEq/L)
First	300	18-20	2	18-20
Second	200	120	2	20
Third	200	90	2	15
Fourth	200	60	3	10
Fifth	200	40	4	6.3
Sixth	200	40	5	6.3

Table 2. Delivery Protocol For Antegrade Intermittent Warm Cardioplegia Of Calafiore. [56]

Modified Basal Protocol

- **Magnesium Addition:** Mg++ bolus was added at the dose end for membrane stabilisation, an adjustable dosage.

- **Retrograde Route Integration:** A new section for retrograde cardioplegia at a fixed flow rate of 150 mL/minute, not replacing the antegrade route but delaying it during valvular surgery.

- **Potassium Management:** The K+ concentration was fixed at 12 mEq/L from the second dose, adjusted based on the patient's measured [K+] after 5 minutes.

- **Flexibility:** Adaptable CPL delivery to surgical rhythm, including K+ concentration reduction, additional Mg++ for waveform activity, extra K+ shots for heart beating, temperature adjustments, and optional retrograde route without replacing antegrade, allowing for extended ischemic intervals if needed [57].

Microplegia: The micro plegia technique, also known as all-blood, K+ -enriched cardioplegia or mini plegia, was initially introduced by Menasche et al. in 1996 as a safe and efficient alternative to conventional blood or crystalloid cardioplegia. It allows for the delivery of large volumes of blood cardioplegia while minimising the use of crystalloid solutions. This method involves mixing blood from the cardiopulmonary bypass circuit with small quantities of concentrated additives (in a ratio of 66:1), including a potassium-rich solution see Table 3. Precision pumps are utilised to accurately deliver these additives, thereby minimising the amount of crystalloid in the cardioplegia solution. This approach enables the administration of substantial quantities of cardioplegia without the drawbacks associated with large volumes of crystalloid infusion into the patient [58].

It is just the concept of using whole blood to reduce crystalloid as much as possible without specific composition or temperature. We can consider Calafiore cardioplegia as a mode of microplegia even though no data in the literature mentions this. Still, microplegia can be delivered as warm, tepid or even cold, whatever the composition, antegrade or retrograde, continuous or intermittent (Table 3).

	Time (min)	Potassium (mmol/L)	Magnesium (g/L)	Lidocaine (mg/L)	Flow (mL/min)
Induction	2	20	1.6	40	300
	2	13	1.6	40	300
Repetition dose	2	6	1.6	40	300
Hotshot	1		1.6	40	300

Table 3. Below is the composition of the microplegia according to (Basel Microplegia Protocol). [58]

Microplegia, termed pure blood cardioplegia with reduced volume and intermittent delivery, offers an alternative strategy. Its benefits include decreased hemodilution, less myocardial oedema, and prompt recovery of ventricular function. Furthermore, the intermittent administration of microplegia may better regulate harmful inflammatory reactions to global ischemia and regional reperfusion than the less controlled single-dose approach of diluted cardioplegia [59].

Histidine-Tryptophan-Ketoglutarate (HTK) Solution (Custodiol): Custodiol is a widely used intracellular crystalloid cardioplegic solution for myocardial protection in complex cardiac surgery and organ preservation in transplant surgery. It is favoured by cardiac surgeons for its convenience. It can be administered as a single dose and offers myocardial protection for up to three hours, allowing uninterrupted complex procedures [60]. HTK, also known as Bretschneider's solution, was developed in the 1970s. Classified as an intracellular crystalloid cardioplegia, HTK has low sodium and calcium content. Sodium depletion in the extracellular space leads to myocyte plasma membrane hyperpolarisation, inducing diastole cardiac arrest. This mechanism differs from conventional extracellular cardioplegic solutions, which cause arrest through membrane depolarisation by high potassium content [61].

Custodial contains several components (see Table 4) that contribute to its effectiveness. Its high histidine content buffers acidosis resulting from anaerobic metabolite accumulation during ischemia. Ketoglutarate enhances ATP production during reperfusion, while tryptophan stabilises cell membranes, and mannitol reduces cellular oedema and acts as a free-radical scavenger. These combined features make Custodial a valuable option

for myocardial protection and organ preservation during surgical procedures [62]. Reichenspurner et al. conducted a study to assess the impact of histidine-tryptophan-ketoglutarate (HTK) solution in 600 patients undergoing heart transplantation between 1981 and 1991. The study cohort consisted of 524 male and 76 female patients. Their findings revealed favourable outcomes with HTK solution, mainly when the ischemic times were under 4 hours. This suggests that the HTK solution effectively preserves heart function during transplantation procedures, especially within a limited ischemic time frame [63].

Bretschneider or HTK solution necessitates infusion of 2 to 4 litres (commonly used dose in adults 20 ml/kg) at 3-4 Degrees Celsius, over 7 to 9 minutes at a line pressure of approximately 125 mmHg until achieving electrical arrest, then reduced to approximately 75 mmHg for the remaining dose. They typically require only a single infusion regardless of the duration of the ischemia. However, other protocols recommend an additional dose of 10 ml/kg if the electrical activity is present or before 120 minutes of myocardial ischemia has elapsed [64].

Donor Heart Preservation

Reducing the occurrence of ischemia-reperfusion injury (IRI) in the donor's heart is the cornerstone of practical preservation. The practice of heart preservation is Ex Vivo Machine Perfusion or static cold storage (SCS) in heart preservative solutions (HPSs) following cardioplegia. There is a wide gamut of HPSs currently in use. At least 167 different solutions are used, and all of them are classified according to the sodium and potassium anion concentrations as extracellular and intracellular. Intracellular solutions contain high sodium, potassium, and magnesium levels, whereas extracellular solutions contain low electrolyte levels [29]. The most frequently

Component	HTK	STF	UW	UW-1	Celsior
Cations					
Component	HTK	STF	UW	UW-1	Celsior
Na^+	15	20	30	125	100
K^+	10	27	125	30	20
Mg^{2+}	4	–	5	5	13
Ca^{2+}	0.015	–	–	–	0.25
Anions					
Cl^-	50	27	–	–	41.5
HPO_4^{2-}	–	–	–	–	–
$H_2PO_4^-$	–	–	25	25	–
HCO_3^-	–	20	–	–	–
SO_4^{2-}	–	–	5	5	–
Substrates and Metabolites					
Glucose	–	250	–	–	–
Glutamate	–	–	20	–	–
Ketoglutarate	1	–	–	–	–
Tryptophan	2	–	–	–	–
Adenosine	–	–	5	5	–
Metabolically Inactive Osmotic Agents					
Mannitol	30	60	–	–	60
D-Raffinose	–	–	35.4	35.4	–
HES (g/l)	–	–	50	50	–
Antioxidants					
Lactobionate	–	–	100	100	80
Allopurinol	–	–	1	1	–
Glutathione	–	–	3	3	3
Organic Buffers					
Histidine	180	–	30	–	–
Histidine-HCl	18	–	–	–	–
Others					
Osmolarity	310	409	320	320	360

Table 4. Composition of Different Heart Preservative Solutions. [37]

used intracellular solutions are the histidine–tryptophan–ketoglutarate (HTK), University of Wisconsin (UW), Euro-Collins, and Stanford (SFT) solutions. On the other hand, Celsior is the most common extracellular one. Differences in their composition are reflected in their practical and preservation properties. For example, just a single administration of HTK provides two hours of IRI protection. Celsior contains antioxidants, lactobionate, and glutathione, which protect against oxidative stress during reperfusion [65].

Static Cold Storage: Static cold storage is the predominant method of heart preservation worldwide, utilised for adult and pediatric hearts. This approach involves rapid removal of blood from the organ, thorough flushing of the vascular bed with a heart preservation solution and maintaining the organ in a state of hypothermia until it can be transported to the recipient hospital for transplantation. During the donor cardioectomy procedure, the superior vena cava is ligated, and the inferior vena cava is incised to drain blood from the patient. The left heart is then vented, often through an incision of the left atrial appendage or a pulmonary vein. Subsequently, the aorta is cross-clamped, and the heart is flushed with cold preservation solution via an aortic root cannula and cooled externally with ice. Once cooled and flushed, the heart is explanted and typically placed in a sterile bag filled with preservation solution, then double-bagged and transported in an ice-filled cooler. These steps aim to induce diastolic arrest, reduce metabolic demands, and minimise ischemic injury during transport.

Hypothermia slows cellular metabolism and reduces the degradation of compounds vital for cell viability. It also decreases lysosomal lysis, preventing the release of autolytic enzymes and cell death. According to Vant Hoff's rule, metabolic activity decreases by 50% for every ten °C reduction in temperature [66], with metabolic activity at four °C being approximately 10–12% of normothermic conditions [67]. Prolonged ischemia and hypothermia can lead to cellular oedema, acidosis, and the generation of reactive oxygen species upon reperfusion. Various heart preservation solutions have been developed to mitigate these effects, each with unique compositions

of cellular nutrients, electrolytes, buffering agents, and antioxidants. Euro Collins solution was the first available solution for approximately 15 years until the introduction of the University of Wisconsin (UW) solution in 1988. Subsequently, numerous new and modified solutions have been developed, with histidine-tryptophan-ketoglutarate (HTK), UW, and Celsior being the most used solutions today [68].

Celsior Solution: Celsior® is a specialised solid-organ preservation solution primarily used for transplantation procedures, particularly heart transplantation, and it has gained popularity worldwide. Both experimental and clinical data support its safety and efficacy compared to other commonly used organ preservation solutions such as HTK-Bretschneider's (Custodiol®) or University of Wisconsin (ViaSpan®) [69].

Composition: It is an extracellular-type solution with low potassium and low viscosity. Its composition includes various solutes aimed at advanced organ preservation, tailored explicitly for heart transplantation, Glutamate: A precursor of Krebs cycle intermediates, it enhances myocardial performance after ischemia by promoting energy production and preventing contracture lesions, Reduced Glutathione: Acts as a coronary endothelial protector and scavenges oxygen free radicals, thereby limiting oxidative stress, Mannitol and Lactobionate: Included to prevent cell swelling, Magnesium: Helps limit calcium overload in cells, Buffer: Histidine serves as the primary buffer, ensuring reasonable pH control, particularly at temperatures under 10°C.

Administration: Celsior® is administered at 4 °C with a calculated dose of 10 to 15 ml/kg. Additional doses, termed diplegia, may be administered after 70-90 minutes at a dosage of 5-7 ml/kg if the remaining ischemia time is expected to be prolonged [70].

Eurocollins solution: Collins's solution, introduced in 1969, marked the first preservation solution to enter the commercial market. Initially utilised for preserving kidney, heart, liver, and lung grafts, it underwent modification in 1980 to enhance its impermeant composition and chemical

stability. This updated formulation, known as EuroCollins solution, offered improved protection during prolonged cold ischemia and gained widespread usage [71]. Collins's solution initially included a high potassium content and relied on glucose as an osmotic barrier. While it achieved satisfactory storage times for abdominal organs, hearts proved more susceptible to ischemic injury. Glucose's low protective properties, coupled with the acidotic conditions resulting from glucose conversion to lactate, necessitated the substitution of mannitol or sucrose for glucose as the impermeant agent [72].

The University of Wisconsin Solution (UW): (Viaspan®): Developed in the 1980s at the University of Wisconsin-Madison for organ preservation, it was later adapted for cardiac surgery. The University of Wisconsin (UW) solution is one of the most commonly utilised preservation solutions, renowned for its efficacy in experimental and clinical transplantations. Numerous investigators have attested to its effectiveness in providing myocardial protection. However, despite its widespread use, the UW solution has been noted for a drawback: it can induce endothelial dysfunction [73].

The UW solution is an intracellular solution designed to counteract the escape of intracellular potassium. It contains a significant potassium concentration for this purpose. Potassium lactate and raffinose are included to prevent cellular oedema. Glutathione neutralises free oxygen radicals and maintains cell membrane integrity. Adenosine is added to stimulate ATP resynthesis, while allopurinol, a xanthine oxidase inhibitor, provides protective effects during ischemia. These components work synergistically to preserve and protect tissues during transplantation effectively.

UW solution quickly became the "gold standard" of preservation fluids, notably highlighting the inadequacy of Na+/K+ ratios achieved during cold preservation. It contains lactobionate and raffinose, metabolically inert substances that prevent organ oedema, making it suitable for multiorgan usage. Adenosine in UW provides a precursor for ATP, while allopurinol and glutathione act as antioxidants. UW solution has been shown to limit ischemic damage from prolonged storage and improve myocardial function in the early posttransplant period, enabling transplantation of organs with ischemic times exceeding 300 minutes [74].

Summary of the Novel Formulations of Heart Preservation Solutions Mentioned in the Text

Somah: An extracellular solution containing energy substrates, metabolic modulators, antioxidants, Larginine, and phosphate and bicarbonate buffers. Preclinical testing demonstrated better cardiac myocytes and endothelial cell viability than controls. It also showed better cardioprotection compared to Celsior and UW solutions [75].

CRMB solution: Based on Celsior, this solution has a decreased potassium concentration to prevent potassium-mediated injury. Histidine was excluded, and adenosine, L-arginine, and allopurinol were added. Preclinical testing showed improved LV function, tissue high-energy phosphate level, and nitrogen oxide production compared to Celsior [76].

Krebs–Henseleit buffer-based (KHB) solution: Developed for myocardial protection, it showed better protection in isolated rat hearts than STH2, particularly at normothermia. Its composition includes glucose, phosphate and bicarbonate buffer systems, decreased Ca2+ concentration, and mild hyperosmolarity [77].

Dsol: Based on a UW solution with high sodium and low potassium content, Dsol lacks HES and uses sucrose and mannitol instead of raffinose. It also includes deuterium oxide, which is known for its antiischemic effects. Preclinical testing showed increased graft survival and lower graft injury extent in a rat heart transplantation model [78].

Custodiol-N is a typical intracellular-type HPS with a lower histidine concentration, added amino acids and iron chelators, and replaced mannitol with sucrose. It demonstrated superiority over HTK in a rat heart transplantation model [79].

2019 Eacts/Eacta/Ebcp Guidelines on Cardiopulmonary Bypass in Adult Cardiac Surgery: Cardioplegia

Numerous experimental studies have favoured blood cardioplegia over crystalloid solutions to reduce cardiac enzyme release and metabolic response. However, large clinical trials have shown no significant differences in major or minor postoperative outcomes between crystalloid and blood cardioplegia in patients undergoing coronary artery bypass grafting (CABG) or aortic valve replacement. Meta-analyses have also failed to demonstrate consistent superiority of one type of cardioplegia over the other in terms of perioperative myocardial infarction (MI) or mortality rates. Nonetheless, blood cardioplegia has been associated with a lower incidence of low cardiac output syndrome (LCOS) immediately upon reperfusion [80].

While the outcomes of crystalloid versus blood cardioplegia have been extensively studied, data on bleeding complications and transfusion rates are limited. Some studies suggest that crystalloid cardioplegia may lead to higher intraoperative hemodilution, increased blood loss, and a greater need for packed red blood cell (PRBC) transfusions than cardiople. Consequently, blood cardioplegia solutions are recommended to minimise hemodilution-related complications, especially in patients with specific risk factors such as anaemia, low body surface area (BSA), chronic kidney disease, or those undergoing complex procedures [80]. Cardioplegia can be administered using antegrade or retrograde techniques, with antegrade delivery more common. Though slower to induce cardiac arrest, retrograde cardioplegia may not adequately protect the right ventricle due to insufficient flow to its microvasculature. Antegrade and retrograde cardioplegia may be employed in complex cases to ensure uniform distribution [81].

While cardioplegia is typically administered cold and intermittently to maintain cardiac arrest and hypothermia, a single-shot approach may be used in low-risk cases with short aortic clamp times. Warm or tepid blood cardioplegia has been developed to enhance myocardial recovery in patients with acute myocardial infarction (MI). It has shown benefits regarding postoperative cardiac index and lower cardiac enzyme release compared to cold cardioplegia. However, challenges such as poor distribution and interruption of normothermic cardioplegia limit its widespread use, necessitating further research to validate its efficacy. Additionally, warm blood-controlled reperfusion ('hot-shot) at the end of complex procedures has shown promise in mitigating myocardial metabolic derangements but requires further investigation.

Conclusion

In conclusion, myocardial protection during cardiac surgery minimises the risk of myocardial damage. Cardioplegia and other myocardial protection strategies have evolved, with newer techniques more effective in reducing myocardial injury. Understanding the pathophysiology of myocardial ischemia and the metabolic landscape of the myocardium is critical in developing effective myocardial protection strategies. While myocardial injury can occur during cardiac surgery, the incidence of frank myocardial infarction is relatively low. Nevertheless, it is essential to continue exploring and refining myocardial protection strategies to ensure the best possible outcomes for cardiac surgery patients.

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