Chapter

# Potassium and Cardiac Surgery

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## Abstract

Potassium homeostasis affects cardiac rhythm and contractility, along with vascular reactivity and vascular smooth muscle proliferation. This chapter will focus on potassium dynamics during and after cardiac surgery involving cardioplegic arrest and cardiopulmonary bypass (CPB). Hyperkalemic, hypothermic solutions are frequently used to induce cardioplegic arrest and protect the heart during cardiac surgery involving CPB. Common consequences of hyperkalemic cardioplegic arrest and reperfusion include microvascular dysfunction involving several organ systems and myocardial dysfunction. Immediately after CPB, blood potassium levels often drop precipitously due to a variety of factors, including CPB -induced electrolyte depletion and frequent, long-term administration of insulin during and after surgery. Meanwhile, some patients with pre-existing kidney dysfunction may experience postoperative hyperkalemia following cardioplegia. Any degree of postoperative hyper/hypokalemia significantly elevates the risk of cardiac arrythmias and subsequent myocardial failure. Therefore, proper management of blood potassium levels during and after cardioplegia/CPB is crucial for optimizing patient outcomes following cardiac surgery.

**Keywords:** potassium, hypokalemia, hyperkalemia, low potassium, high potassium, hyperkalemic cardioplegia, cardiopulmonary bypass, cardiac surgery, open heart surgery, postoperative arrhythmias, perioperative arrhythmias

## 1. Introduction

Intracellular and blood potassium levels have crucial effects on cardiovascular system homeostasis. At the most fundamental level, the potassium concentration gradient across cardiac muscle cell (cardiomyocyte) cell membranes is a chief determinant of cardiomyocyte resting membrane potentials. Indeed, disruptions to this concentration gradient (e.g. via increasing or decreasing extracellular blood potassium levels) can lead to altered cardiomyocyte contractility and excitability. Potassium is also vasoactive, with different effects at different extracellular concentrations. At low (5-8 mM) to moderate (8-16 mM) extracellular levels, potassium relaxes the smooth muscle in blood vessel walls by promoting hyperpolarization of vascular smooth muscle. However, at higher levels (16-25 mM and above) (e.g. cardioplegic concentrations), potassium promotes vasoconstriction by facilitating depolarization. Moreover, potassium is released by vascular endothelial cells in response to various chemical mediators and shear stress, thereby contributing to the action of endothelium-derived hyperpolarizing factor [1]. For all of these reasons and more, keeping track of daily

potassium intake is often recommended as a lifestyle modification for chronic cardiovascular diseases such as hypertension.

Harnessing the pivotal role of potassium in cardiovascular physiology has proved quite useful for cardiovascular surgery, namely in the form of hyperkalemic (high potassium) cardioplegia. Indeed, throughout the past several decades, a large body of research has testified to the ability of externally administered hyperkalemic solutions to arrest cardiac contractility [2]. This, in conjunction with the development of cardiopulmonary bypass (CPB, also known as the "heart-lung machine"), revolutionized cardiac surgery [3]. These days, many highly invasive procedures like coronary artery bypass grafting are routine with minimal risk of postoperative mortality.

However, hyperkalemic cardioplegia is not without its consequences. Hyperkalemic cardioplegia and reperfusion following CPB have been associated with perioperative and postoperative tissue damage and microvascular dysfunction across several different vascular beds. Moreover, hyperkalemic cardioplegia is also associated with postoperative myocardial dysfunction and reduced cardiac output. Furthermore, blood potassium abnormalities after hyperkalemic cardioplegia-reperfusion, chiefly hypokalemia (but also hyperkalemia, to a lesser degree) are common postoperative challenges in the cardiac ICU. Both abnormalities significantly elevate the risk of arrythmias and, if not managed properly, cardiac arrest and sudden death.

This chapter will discuss the basics of potassium cardioplegia with an emphasis on clinical relevance, beginning with a brief history. Subsequent sections will elaborate on the basic physiology, before considering several perioperative and postoperative adverse effects of hyperkalemic cardioplegia. When possible, information about treatment and clinical management is included. The chapter will conclude with a brief mention of up-and-coming alternatives to hyperkalemic cardioplegia.

## 2. Potassium and cardiac surgery

### 2.1 Brief history of potassium cardioplegia

As early as the late 1800s, physiologists were starting to become aware of the ability of potassium compounds to arrest cardiac contractility, beginning with individuals like Sidney Ringer who observed that potassium chloride froze the heart in diastole and calcium stimulated the heart during systole [2]. Moving into the start of the 20th century, further investigations revealed associations between high serum potassium and cardiac arrest following ventricular fibrillation; studies also revealed associations between cardioplegia and restoration of sinus rhythm following coronary artery administration of potassium chloride solution and subsequent washout [2]. However, in most of these cardioplegic experiments (often conducted in dogs), refractory ventricular fibrillation and post-procedure reperfusion damage to the myocardium limited discussion of the clinical usefulness of these findings.

During the 1950s, British physician Dennis Melrose hypothesized that the problem with potassium chloride cardioplegia was chloride; therefore, he created a cardioplegic solution using potassium citrate, and tested it on a canine model of cardiopulmonary bypass [4]. Injection of the "Melrose solution", of potassium citrate plus warm oxygenated whole blood in a 9:1 blood:potassium ratio, into the aortic roots of hypothermic dogs, produced near-immediate cardiac arrest. Reperfusion and washout of cardioplegic solution resulted in restoration of heart function to pre-procedure

levels [2]. Within a few years, the Melrose group successfully induced potassium citrate cardioplegia in humans.

Unfortunately, future studies would reveal that in many cases, the Melrose potassium citrate solution still produced post-cardioplegia ventricular fibrillation and myocardial dysfunction [5]. This led to a general pause in clinical application of potassium cardioplegia between the 1960s and early 1980s, in favor of other options mostly involving induction of hypothermic cardiac arrest, which turned out to be no better with respect to postoperative damage than the Melrose solution.

Eventually, research into techniques for potassium cardioplegia would pick up again, and the result would be development of novel solutions for cardioplegia and intraoperative organ preservation. Numerous studies in animal models have validated the principles of diastolic cardiac arrest due to depolarizing potassium cardioplegia [2, 3, 6–10]. In addition, invention and refinement of heart-lung machines to accompany cardioplegia in the operative room (CPB) opened many new possibilities for cardiac surgery. Today, potassium cardioplegia is an integral tool for cardiac surgeons performing a variety of highly invasive procedures such as coronary artery bypass grafting and aortic valve replacements.

## 2.2 Types and techniques of potassium cardioplegia

Despite variability in composition, delivery, and temperature, most cardioplegic solutions in use today involve some level of potassium chloride as the main inducer of cardiac arrest, along with ions such as magnesium, low-dose calcium and bicarbonate, the latter of which is particularly important for controlling solution pH [6]. The "original" hyperkalemic cardioplegic solution was the Melrose formula of the 1950s that was discussed earlier, consisting of potassium citrate and warm blood in a 9:1 blood:potassium ratio. However, due to the high incidence of postoperative complications including ventricular fibrillation, this solution is no longer in major clinical use.

### *2.2.1 Crystalloid vs. blood*

In general, cardioplegic solutions fall under two broad umbrellas: crystalloid vs. blood, and warm vs. cold (**Table 1**). Two crystalloid cardioplegic solutions worth noting are the Custodiol (also known as Bretschneider) and St. Thomas solutions [7]. The St. Thomas solution, introduced first by Hearse and colleagues in 1975, is an example of a short acting cardioplegic solution involving potassium chloride concentrations between 10 and 30 mM [8]. In general, the St. Thomas solution requires repeat dosing, roughly every 20 minutes, to sustain cardioplegia for long durations [7, 9]. Furthermore, myocardial acidosis has been noted between doses of St. Thomas solution [10].

In contrast, the Custodiol solution is a form of long acting, single dose cardioplegia consisting primarily of potassium chloride, sodium chloride, and magnesium sulfate as the chief electrolytes [11]. Additional components of the Custodiol solution include tryptophan (membrane stabilization) and histidine buffer (to maintain pH and buffer against byproducts of anaerobic glycolysis that build up during cardioplegia). Curiously, the relatively low levels of potassium (9 mM) and sodium (15 mM) in Custodiol appear to induce cardioplegia through a form of hyperpolarized arrest as opposed to depolarized arrest, unlike most other potassium cardioplegic solutions that have potassium concentrations in the range of 16-36 mM and sodium concentrations in the range of 10-110 mM (see **Table 1** for detailed solution ion concentrations).

| | St. Thomas Cardioplegia | Custodiol Cardioplegia | Del Nido Cardioplegia | Buckberg Cardioplegia | Warm Calafiore Cardioplegia (one variant) |
|---|---|---|---|---|---|
| K+ | 16 mM | 9 mM | 26 mM | Cold induction: 36 mM Maintenance: 36 mM<br>Reperfusion: 15 mM | 18–20 mM for inducing arrest, repeat delivery every 20 min with decreasing K concentrations |
| Ca | 1.2 mM | 0.015 mM | | | 1.3 mM |
| Mg | 16 mM | 4 mM | 2 g of 50% magnesium sulfate | | 15.5 mM |
| Na | 110 mM | 15 mM | | | |
| NaHCO3 | 10 mM | | 13 mM | | |
| Other Components | | 18 mM Histidine hydrochloride<br>18 mM histidine<br>2 mM tryptophan<br>30 mM mannitol<br>1 mM potassium hydrogen 2-ketoglutarate | 13 mL of 1% lidocaine<br>3.2 g/L of 20% mannitol | *Cold Induction:* 392 mL 5% dextrose, 50 mL 0.3 M tromethamine, 30 mL citrate–phosphate-2-dextrose<br>*Maintenance*: 798 mL 5% dextrose, 123 mL 0.3 M tromethamine, 61 mL citrate–phosphate-2-dextrose<br>*Reperfusion*: 26 mL 50% dextrose; 56 mL 0.3 M tromethamine; 113 mL citrate–phosphate-2-dextrose<br>62.5 mL glutamate/aspartate | 500 mL 5% dextrose<br>4 mM tris(hydroxymethyl) aminomethane<br>Core body temperature maintained at 37 degrees Celsius |
| Blood vs. Crystalloid | Crystalloid | Crystalloid | 4:1 crystalloid: blood ratio | 4:1 crystalloid: blood ratio | Normothermic blood |

**Table 1.**
*Composition of common potassium-based cardioplegic solutions.*

The general rationale for blood-based cardioplegia has centered on the theory that cardioplegic solutions containing blood are more "physiologic" than crystalloid solutions. For example, blood can support aerobic respiration and may be able to preserve normal myocardial metabolism during surgery. Therefore, blood cardioplegia may reduce the negative consequences of prolonged ischemia during CPB [11]. However, insufficient evidence exists currently to verify that hypothesis, and so any purported advantages of blood over crystalloid cardioplegia are for the time being mainly speculative.

Three hyperkalemic cardioplegic solutions in clinical use that contain blood are the Del Nido, Buckberg, and Calafiore solutions. The Del Nido solution uses a crystalloid:blood ratio of 4:1, and like the Custodiol solution is a long-acting cardioplegic solution, with one dose of 20 ml/kg providing myocardial protection for up to 60–90 minutes [7, 12]. Chief ionic ingredients include potassium chloride for rapid depolarized arrest, sodium bicarbonate to scavenge protons and buffer intracellular pH, and magnesium to block calcium channels and prevent intracellular calcium accumulation during cardioplegic arrest, thereby promoting postoperative myocardial recovery [12, 13]. Lidocaine in the Del Nido solution acts as a sodium channel blocker to mitigate against the sodium "window current" and reduce intracellular sodium accumulation [14].

Buckberg's cardioplegia is a dextrose and saline-based solution that, similar to the Del Nido solution, consists of a crystalloid:blood ratio of 4:1 [15]. Other components include potassium chloride as the primary depolarizing agent, a tromethamine buffer, and citrate phosphate double dextrose to serve as a calcium chelator. However, unlike the Del Nido solution, Buckberg cardioplegia must be given as three separate formulations, some of which must be administered in multiple doses [15]. First, an induction solution stops the heart, and additional infusions of induction solution must be given every 15 to 20 minutes throughout the procedure. Second, a maintenance solution must be administered to sustain cardiac arrest and provide oxygen and nutrients to the cardiomyocytes. Finally, a reperfusion solution containing glutamate and aspartate is administered prior to removal of the aortic cross clamp to provide the heart with nutrients prior to restarting myocardial contractions.

Calafiore cardioplegia differs from Buckberg and Del Nido in that blood forms the sole foundation of Calafiore cardioplegic solution [16]. Indeed, the original rational proposed by Calafiore et al. was that blood alone, without any crystalloid component, contained everything necessary to prevent ischemia–reperfusion damage. Therefore, simply administering a cardioplegic solution consisting of blood plus extra potassium would be enough to safely stop and later, restart the heart [16]. Moreover, unlike most other forms of cardioplegia in use, the original Calafiore solution was normothermic throughout administration; however, some subsequent variations of Calafiore cardioplegia have used cold blood [16, 17].

### *2.2.2 Warm vs. cold*

Most current methods for administering cardioplegic solutions involve cold cardioplegia, most often cold crystalloid solutions delivered after reducing core body temperature to hypothermic levels [18]. For example, the induction and maintenance solutions for Buckberg cardioplegia are delivered at 4 degrees Celsius after cooling core temperature to below 30 degrees Celsius, with reperfusion solution delivered at 37 degrees Celsius [15]. Similarly, del Nido and Custodiol cardioplegia are often given at 4 degrees Celsius after induction of systemic hypothermia [15, 19].

This practice stems from experimental evidence suggesting that mild hypothermia can protect the myocardium from ischemic damage during cardioplegia [20]. Hypothermia reduces the basal metabolic rate of the heart, which in turn reduces oxygen consumption—an effect augmented by potassium-induced arrest during hyperkalemic cardioplegia [21]. A variety of potential mechanisms may be at play. In animal models of cardiac arrest, mild hypothermia (32–35 degrees Celsius) has been shown to reduce post-arrest infarct size, possibly through various signal transduction pathways, such as Akt and mTOR signaling, both of which are altered during the course of hypothermia [20]. Another potential cardioprotective mechanism of hypothermia may be reduced phosphorylation of various mitogen activated protein kinases (MAPK) like ERK1/2 that normally activate pro-inflammatory mediators like COX-2 (arachidonic acid metabolism) [18]. In general, many details concerning mechanisms of hypothermic myocardial protection during cardioplegia remain to be elucidated.

However, cold hyperkalemic cardioplegia may also inhibit myocardial enzymes that are important for the metabolic and functional recovery of the heart after surgery [22, 23]. Moreover, sustained systemic hypothermia (especially at temperatures below 20 degrees Celsius) during cardiac surgery has also been associated with ventricular fibrillation after rewarming [21]. Given these negative consequences, an increasing amount of attention has been given to the possibility of warm hyperkalemic cardioplegia, primarily warm blood hyperkalemic cardioplegia. Unlike cold hyperkalemic cardioplegic solutions, warm cardioplegic solution is typically administered at between 30 and 35 degrees Celsius under normothermic, as opposed to hypothermic, CPB [24]. Potential advantages of warm blood hyperkalemic cardioplegia over cold crystalloid may include improved myocardial restoration, reduced intracellular swelling, improved membrane stabilization, and reduced hypoxic red blood cell deformation [25].

Of course, warm hyperkalemic cardioplegia is not without its own consequences. Some studies have reported increased likelihoods of perioperative strokes and encephalopathy [26]. Moreover, warm hyperkalemic cardioplegia may contribute to vasodilation during cardiopulmonary bypass, requiring increased use of alpha agonists during operation to maintain stable arterial perfusion pressures [25]. There are also several variations of warm cardioplegia; one common technical variant is "hot shot" cardioplegia, which involves warm induction and subsequent cold cardioplegia, followed by a warm reperfusion [27].

Comparing the effectiveness of warm vs. cold hyperkalemic cardioplegia remains an inconclusive subject of intense debate. A meta-analysis by Fan et al., reported no differences between length of stay, stroke incidence, and atrial fibrillation between patients undergoing warm vs. cold cardioplegia [28]. However, warm cardioplegia correlated with better postoperative cardiac indices and lower peak creatine kinase MB concentrations than cold cardioplegia [28]. The latter findings, along with reduced postoperative cardiac troponin levels, have been replicated in other studies [29, 30]. Meanwhile, other studies comparing warm blood and cold crystalloid hyperkalemic cardioplegia do not show significant differences with respect to perioperative myocardial infarction and low cardiac output syndrome [31].

### *2.2.3 Anterograde vs. retrograde*

In general, administration of hyperkalemic cardioplegic solution can be done in either retrograde or anterograde fashion. Prior to both, IV heparin is administered,

and the patient's core body temperature is lowered to hypothermic levels, after which the aortic cross-clamp is placed and cardiopulmonary bypass is initiated [7]. Anterograde cardioplegia refers to delivering cardioplegic solution through a cannula inserted just proximal to the aortic cross-clamp. From there, the solution can flow into the left and right coronary arteries that supply the myocardium [32]. With anterograde cardioplegia, arrest usually occurs within 30 to 60 seconds. Retrograde cardioplegia may be considered in patients with complications such as severe coronary artery damage (e.g. severe stenosis) or aortic valve damage. Unlike anterograde administration, in retrograde administration the cardioplegia catheter is inserted into the coronary sinus from the right atrium, and solution is injected at a lower pressure (given the lower tolerance of the coronary sinus walls to turbulent flow) to avoid coronary sinus perforation [32].

## 2.3 Physiology of potassium cardioplegia during cardiac surgery

### *2.3.1 Physiology of cardiac muscle contraction*

Under physiological circumstances, the cardiomyocyte resting membrane potential is largely determined by two key factors: action of the sodium-potassium ATPase, and the high resting permeability of cardiomyocyte cell membranes to potassium [33]. First, the sodium-potassium ATPase hydrolyzes ATP to continuously pump potassium into the cell and sodium out of the cell, with a relative ratio of 3Na out/2 K in per molecule of ATP. Because it is the primary ion pump active while the cell is at rest, the sodium-potassium ATPase plays a critical role in generating the characteristic sodium and potassium electrochemical gradients across the cardiomyocyte cell membrane (high potassium and low sodium inside the cell relative to out). Second, at rest the cardiomyocyte cell membrane is most permeable to potassium while being relatively impermeable to other ions. This results in a resting membrane potential for cardiomyocytes that is close to the Nernst equilibrium potential for potassium, roughly −85 to -90 mV.

During cardiac muscle contraction, sinoatrial node stimulation induces a transient increase in the resting membrane potential of cardiomyocytes, which in turn opens voltage-gated sodium channels once the membrane potential surmounts -65 mV. Due to the high inward ion driving force on sodium (based on the considerable difference between the Nernst potential for sodium and the resting membrane potential), sodium ions flow through the sodium channels into the cardiomyocyte and further depolarize the cell until it reaches about 20 mV. At this point, sodium channels inactivate and L-type voltage gated calcium channels take over the maintenance of the action potential, allowing influx of calcium ions and producing the classic plateau depolarization of cardiac ventricular action potentials. Eventually, as calcium channels close and membrane potential begins to dip, delayed rectifier potassium channels open and restore membrane potential to the resting state. By this point, enough calcium has entered the cardiomyocyte to promote calcium-induced calcium release from intracellular calcium stores in the cardiomyocyte sarcoplasmic reticula, allowing muscle contraction to occur.

### *2.3.2 Physiology of potassium cardioplegia*

Extracellular hyperkalemia is the core principle underpinning most warm blood and cold crystalloid cardioplegic solutions. Essentially, administration of hyperkalemic solution takes advantage of the pivotal role of the potassium electrochemical

gradient in determining cardiomyocyte resting membrane potential in order to elevate the resting membrane potential to a less negative value than typical baseline level. For example, physiologic extracellular potassium levels are often in the range of 3.5–5 mM, producing a resting membrane potential around -85 mV. During cardiac surgery involving cardioplegia, hyperkalemic solutions often raise extracellular potassium to the range of 10-40 mM (often midway in this range, around the 25 mM level), elevating cardiomyocyte resting membrane potentials to anywhere between −65 to -40 mV [34]. Arresting cardiomyocytes at this new range of elevated membrane potentials promotes fast sodium channel inactivation, thereby blocking myocardial action potential conduction. It also blocks repolarization, which is why hyperkalemic cardioplegia induces what is called "depolarized arrest." Finally, it is important to note that cardioplegic arrest also significantly reduces cardiomyocyte oxygen consumption in a manner reminiscent of how severe ischemia depletes cellular ATP reserves [33].

## 2.4 Side effects of high potassium cardioplegia

### *2.4.1 Myocardial calcium loading*

Despite its clinical usefulness in reversibly arresting the heart during cardiac surgery, sustained depolarized hyperkalemic cardioplegia is not without some negative perioperative consequences. First, while most voltage-gated "fast" sodium channels are inactivated at membrane potentials above -50 mV (a frequent target cardiomyocyte membrane potential for potassium cardioplegia), resulting in generally poor membrane sodium conductance, not *all* sodium channels are inactivated. Moreover, during hyperkalemic cardioplegia the ion driving force on sodium is still quite high, even at the new depolarized cell membrane potentials. Ultimately, this situation produces a small but significant sodium influx into cardiomyocytes through the small fraction of sodium channels that remain open during potassium cardioplegia, a phenomenon known as the sodium "window current" [35].

Similarly, ATP depletion and reduced myocardial oxygen consumption during hyperkalemic cardioplegia leads to myocardial ischemia. Ischemia forces myocardial cells to resort to anaerobic glycolysis for energy production, which generates lactate as a byproduct. Increasing lactate levels in cardiomyocytes produces a metabolic acidosis and promotes increased activity of the H+/Na antiporter to move protons out of the cells at the expense of bringing in more sodium [36]. Finally, the combination of high extracellular potassium, intracellular acidosis, and hypothermia due to cold cardioplegic solution inhibits action of the sodium-potassium ATPase, which further facilitates the buildup of intracellular sodium [34].

Note that -50 mV is also in the vicinity of the reversal potential of the sodium/calcium exchanger [37, 38]. Under normal circumstances, the sodium/calcium exchanger moves 3 Na in for every 1 Ca moved out of the cell. However, due to the sodium window current and depolarized arrest in hyperkalemic cardioplegia, the sodium/calcium exchanger eventually begins operating in reverse, moving 3 Na out for every 1 Ca in, producing a so-called calcium "window current." Moreover, if the hyperkalemic cardioplegic solution holds cardiomyocyte membrane potentials above -50 mV, e.g. at around -40 mV, then voltage-gated slow calcium channels will begin to activate, causing further calcium influx [39]. All of these reasons help explain why many hyperkalemic cardioplegic solutions in clinical practice are also hypocalcemic relative to physiological extracellular calcium levels (or contain calcium channel blockers), to attempt to mitigate the severity of myocardial calcium loading [34].

Cytosolic calcium loading during hyperkalemic cardioplegia contributes to cardiomyocyte damage through several mechanisms [40]. Enhanced activation of calcium dependent proteases and lipases (e.g. phospholipases) contributes to plasma membrane phospholipid degradation, ultrastructural changes in the sarcolemmal membrane, and accumulation of pathological catabolic byproducts. Enhanced activation of calcium-dependent ATPases accelerates depletion of intracellular ATP stores that have already been lowered following hypothermic arrest. This further perturbs cardiomyocyte sarcolemmal calcium transport channels that rely on ATP to maintain intracellular calcium homeostasis. Moreover, hypoxia during hyperkalemic cardioplegia increases mitochondrial calcium uptake via reversal of mitochondrial sodium/calcium exchangers in a manner akin to reversal of cardiomyocyte cell membrane sodium/calcium exchangers [41].

Mitochondria can only endure so much calcium uptake before the onset of irreversible damage. Indeed, following reperfusion after hyperkalemic cardioplegia arrest, mitochondria exhibit increased oxygen free radical production and reduced superoxide dismutase activity, indicative of heightened oxidative stress [41]. Sustained oxidative stress can lead to opening of mitochondrial permeability transition pores (MPTP), which promote mitochondrial swelling and mitochondrial membrane rupture. An assortment of mitochondrial enyzmes and molecules, such as cytochrome c, leak out into the cytosol through the MPTPs [41]. Cytochrome c is implicated in intrinsic apoptotic pathways through activation of cytosolic caspases and subsequent formation of myocardial apoptosomes [41].

### *2.4.2 Myocardial apoptosis*

Myocardial apoptosis during hyperkalemic cardioplegic ischemia–reperfusion merits further consideration for two major reasons. First, several studies have shown associations between hyperkalemic cardioplegic arrest and endothelial cell and cardiomyocyte apoptosis [42–44]. Second, several independent pathways of myocardial cell injury converge on apoptosis. Examples include mitochondrial oxidative stress and activation of an intrinsic apoptotic pathway (introduced earlier), or an extrinsic pathway driven by elevated humoral factors such as Fas or TNF-alpha acting on pro-apoptosis cell membrane receptors [44, 45]. Both intrinsic and extrinsic pathways converge upon a similar final common pathway that is chiefly regulated by two key protein groups: the Bcl-2 and cysteine protease caspase families [46, 47].

Within the Bcl-2 family, two proteins are particularly significant: Bcl-2 itself, and Bad. The former is anti-apoptotic while the latter is pro-apoptotic. Phosphorylation inhibits Bad, blocking it from inactivating Bcl-2 [48]. Farther downstream in apoptotic signaling, cleavage of caspase 3 and poly ADP-ribose polymerase (PARP) is essential for ensuring final progression towards apoptosis. Meanwhile, apoptosis may also proceed via a caspase-independent pathway involving release of the mitochondrial flavoprotein apoptosis-inducing factor (AIF) from the mitochondria into the cytosol through MPTPs [49, 50].

A possible framework for understanding myocardial apoptosis after hyperkalemic CPB is as follows [48]. Activation of the intrinsic (mitochondrial) pathway leads to increased Bad activation/decreased Bcl-2 activation, which initiates the caspase cascade. Activation of the extrinsic pathway bypasses Bcl-2/Bad to directly activate the caspase cascade. As more and more caspases become activated, eventually terminal caspases, such as caspase 3, will be cleaved, leading to PARP cleavage. By this point, apoptosis has been irreversibly induced; DNA fragmentation and cell death

quickly follow. In contrast, AIF translocation from the mitochondria to the cytosol may directly activate downstream/terminal caspases, bypassing initial/intermediary constituents of the caspase cascade.

Studies have shown that caspase 3 cleavage and Bcl-2/Bad phosphorylation are significantly increased in myocardial tissue following hyperkalemic cold-blood cardioplegia and reperfusion, even as total protein levels do not change [48]. Meanwhile, myocardial AIF levels increase slightly, accompanied by a trend towards nuclear translocation, consistent with a model of AIF induced chromatin condensation and DNA fragmentation as a mechanism of cell injury [48]. Note that both pro-apoptotic (e.g. caspase 3) and anti-apoptotic (e.g. phosphorylated Bad) mediators are activated—nevertheless, given the downstream terminal position of caspase 3, the overall balance in myocardial cells appears to be tipped in favor of pro-apoptotic signaling.

Different formulations of hyperkalemic cardioplegia (e.g. cold crystalloid, warm blood, etc.) may exhibit differing degrees of myocardial protection and prevention of apoptosis. Indeed, evidence exists suggesting that cold blood hyperkalemic cardioplegia is superior to warm blood, warm crystalloid, and cold crystalloid cardioplegia, in terms of increased Bad phosphorylation and decreased caspase 3 activation [51]. Taken together, this combination of events appears to result in less apoptosis. In addition, these effects are associated with improved left ventricular function following cardioplegic arrest. However, this is not a universal finding in the literature. More work must be done to verify these conclusions and confirm if there truly is a definitive benefit to any one technique of hyperkalemic cardioplegia with respect to prevention of apoptosis.

### *2.4.3 Coronary vasomotor dysfunction*

An extensive body of research has established that hyperkalemic solutions induce significant vasoconstriction when experimentally applied to coronary artery and aortic ring preparations [2]. Thus, it is no surprise that hyperkalemic cardioplegia induces significant functional changes to the microcirculation, especially the coronary circulation [52]. For example, a sizeable number of patients undergoing hyperkalemic cardioplegia experience coronary artery spasm [52].

Potassium can influence coronary vasoconstriction in several ways. Holding coronary vascular smooth muscle membrane potentials at sustained depolarization during hyperkalemic cardioplegia increases the likelihood of generating contractions [53]. Potassium may also act indirectly to cause vasospasm through action on the coronary endothelium. Indeed, endothelial vasoconstrictive and vasorelaxant factors govern homeostatic regulation of coronary vasomotor tone. These factors influence vascular smooth muscle through modulation of various cell membrane potassium channels, including calcium-activated potassium channels and ATP-activated potassium channels [54, 55]. Important endothelial-derived relaxing factors include nitric oxide, endothelial-derived hyperpolarizing factor (EDHF), and cyclooxygenase enzymes. Important endothelial-derived constricting factors include endothelin-1 and thromboxane A2.

Porcine models of hyperkalemic cardioplegia showed that hyperkalemia significantly attenuated EDHF-mediated relaxation in coronary artery preparations [56, 57]. Moreover, hyperkalemic vasoconstriction has also been linked with impaired nitric oxide release [58] and impaired acetylcholine-dependent vascular relaxation [59, 60]. Potential mechanisms at play may involve potassium-induced inhibition of G protein and non-G protein signal transduction pathways, increased reactive oxygen and

nitrogen species generation, decreased activity of endothelial nitric oxide synthase, and increased arachidonic acid metabolism [2]. Curiously, hyperkalemic cardioplegia has also been associated with decreased responsiveness of human coronary arterioles to the endothelial vasoconstrictors endothelin-1 and thromboxane A2 [61, 62]. These findings testify to the complexity of mechanisms underpinning coronary vasomotor dysfunction following hyperkalemic cardioplegia, most of which remain to be elaborated.

### *2.4.4 Myocardial and coronary endothelial dysfunction*

Despite its cardioprotective effects, hyperkalemic cardioplegia-reperfusion can exert detrimental effects on the myocardial and coronary endothelium, promoting endothelial dysfunction [63, 64]. One aspect of endothelial dysfunction—production of various endothelium-derived relaxing and contracting factors—was discussed earlier due to its relevance in coronary vasospasm. Other important features of endothelial dysfunction during hyperkalemic cardioplegic arrest include endothelial injury, inflammation, reactive oxygen species production, coagulation cascade dysfunction, and endothelial tight junction degradation [52, 65–67]. All these adverse effects may occur with potassium levels as low as 10 mM, well within the realm of most hyperkalemic cardioplegic solutions [2]. To elaborate, potassium concentrations of 30 mM in St. Thomas and Custodiol cardioplegic solutions proved considerably more damaging to the vascular endothelium than potassium concentrations of 20 mM, demonstrating the importance of strict potassium limits in hyperkalemic cardioplegic solutions [6].

A variety of structural changes to the vascular endothelium have been observed in experimental models of hyperkalemic cardioplegia. Key examples include endothelial intracellular vacuolization, membrane blebbing, adventitial fibrosis, and overall reduced viability [68, 69]. Furthermore, hyperkalemic cardioplegia promotes increased lipid uptake and cholesterol deposition in vascular intimae in primate models of post-graft venous atherosclerosis [70]. In addition, compromised endothelial adherens junctions during hyperkalemic cardioplegia mediate increased vascular permeability and tissue edema [67]. Indeed, animal models of cardioplegia/CPB show increased post-procedure VE cadherin, beta-catenin, and gamma-catenin fragments, all of which are important structural components of adherens junctions [71]. In humans, increased endothelial cadherin phosphorylation, and decreased overall beta-catenin levels, have been observed in atrial tissue following hyperkalemic cardioplegia/CPB [72].

Details of specific mechanisms underlying these endothelial disturbances remain largely unclear; however, many possibilities exist. For example, it is generally agreed that depolarization induced by hyperkalemic cardioplegia is a critical initiating step of the underlying pathophysiology [2]. Endothelial depolarization increases activation of neutrophils, inflammation, voltage sensitive NAPDH oxidases, and platelets [62, 63, 73, 74]. Inflammation and neutrophil activation often reinforce each other, as pro-inflammatory cytokines like IL-1, IL-6, and TNF-alpha further stimulate endothelial changes that promote neutrophil extravasation. NADPH oxidase catalyzes formation of important reactive oxygen species such as superoxide anions, which if left unchecked are severely cytotoxic. The amount of superoxide production during hyperkalemic cardioplegia has been linked to the extent of endothelial depolarization and translocation of the small G protein Rac from the cytosol to plasma membrane [75].

With respect to coagulation, potassium depolarization appears to have a direct stimulatory effect via enhancing ADP and collagen-induced platelet aggregation, along with an indirect effect through increased superoxide production [76, 77]. The latter appears to act through inhibition of endothelial NTPDases [78]. Membrane hyperpolarization reverses all these actions.

When left unchecked, sustained myocardial dysfunction following hyperkalemic cardioplegia-reperfusion may lead to myocardial stunning, a form of postoperative left ventricular dysfunction [1]. Myocardial stunning often manifests as markedly reduced cardiac output without obvious evidence of infarction or injury (e.g. no signs of elevated troponin or CKMB in blood). Like myocardial apoptosis, myocardial stunning represents another final common pathway of convergence for several different pathophysiological mechanisms of hyperkalemic cardioplegia, chiefly dysregulated free radical production, coagulation imbalances, and excessive catecholamine release [1]. However, unlike with apoptosis, in this scenario injury results from abnormal myocardial contractility as opposed to myocardial cell death.

### 2.5 Postoperative potassium abnormalities: physiology and management

Postoperative imbalances in a variety of different electrolytes, including calcium, magnesium, potassium, and phosphate, have been observed following cardioplegia/CPB. Here, we will focus on potassium, beginning with hypokalemia. Hypokalemia can be defined as a serum potassium level that is less than 3.5 mEq/L [78]. Postoperative hypokalemia is a common finding after cardiac surgery involving hyperkalemic cardioplegia and CPB, and manifests almost immediately after the patient is weaned off the bypass circuitry [79]. Hence IV potassium supplementation during cardioplegia is extremely important to mitigate against the most severe manifestations [80].

However, even with electrolyte supplementation in the operating room, CPB poses a high risk of post-procedure electrolyte depletion [81]. The pivotal role of potassium in normal cardiac contractility means that disturbances in potassium homeostasis significantly increase the risk of arrythmias and, in severe cases, sudden cardiac arrest. Indeed, arrythmias, especially atrial tachyarrhythmias (e.g. atrial fibrillation, atrial flutter) and, less frequently, ventricular arrhythmias, are a major source of morbidity and mortality following cardiac surgery [82, 83].

Specific mechanisms underpinning this phenomenon remain largely unclear; however, a variety of possibilities exist [78]. For example, poor oral intake of potassium-rich foods prior to cardiac surgery may contribute to enhanced depletion during surgery. In addition, prolonged preoperative use of digoxin, along with thiazide and loop diuretics may play a role. These agents may cause hypomagnesemia (low magnesium levels), which can contribute to extracellular potassium depletion. Under normal circumstances, intracellular magnesium binds to and blocks the pores of renal outer medullary potassium (ROMK) channels in the distal nephron, preventing outward flux of potassium into the renal tubular network [78]. Thus hypomagnesemia may remove this physiologic limiter, leading to increased renal clearance of potassium.

A hyperactive aldosterone response to stress may also be implicated, particularly in the context of congestive heart failure [78, 80]. Moreover, increased catecholamine (norepinephrine and epinephrine) release during cardiopulmonary bypass may facilitate hypokalemia given the influence of catecholamines on plasma potassium [84, 85]. Animal models have shown that elevated catecholamine levels can produce first,

a transient hyperkalemia due to activation of hepatic calcium-dependent potassium channels by alpha adrenergic stimulation and second, a sustained hypokalemia by stimulation of skeletal muscle Na-K ATPase [86]. Such studies need to be replicated in humans undergoing cardiopulmonary bypass-hyperkalemic cardioplegia in order to verify the applicability of these putative mechanisms.

Because glucose is often given during cardioplegia, insulin may also be administered to minimize the chances of hyperglycemia. However, given that insulin acts as a regulator of potassium distribution between intracellular and extracellular fluid compartments by stimulating Na-K ATPase activity, it is possible that insulin administration during and after cardioplegia may contribute to potassium depletion [87]. Next, given that many cardioplegic solutions in current practice are cold hyperkalemic solutions, any potential impact of hypothermia on potassium homeostasis during cardiac surgery cannot be ignored. As with insulin, hypothermia has been linked to an intracellular shift of potassium away from the extracellular space through as-yet unelaborated mechanisms [88]. Finally, the CPB circuit itself has been shown to significantly dilute overall blood plasma protein concentrations, which may also affect plasma ion homeostasis [89].

In general, treatment of postoperative hypokalemia largely centers on administration of potassium chloride (KCl) solution to elevate extracellular potassium concentrations to physiologic levels. Indeed, in the case of pediatric cardiac ICU patients for whom enteral potassium supplementation is contraindicated, IV KCl administration is one of the only available tools for correcting hypokalemia [90]. For most patients, this proves sufficient to correct the imbalance and stave off the development of hypokalemia-induced arrhythmias. However, in a small minority, external KCl solution does not reverse the hypokalemia—and so in these patients, the chances of arrhythmias increase exponentially.

Although hypokalemia is the most common potassium electrolyte abnormality following hyperkalemic cardioplegia-CPB, postoperative hyperkalemia may occur under certain, albeit rarer, circumstances. In general, postoperative hyperkalemia is a concern mainly in patients with renal failure undergoing CPB, most likely due to renal tubular dysfunction [91]. Severe hyperkalemia may be treated with IV calcium gluconate, an insulin-dextrose regimen, and diuretics [92]. If a patient has end-stage renal disease, dialysis may be the best option to treat hyperkalemia, along with IV calcium to stabilize the myocardium and IV insulin to shift potassium into cells [93].

### 2.6 Alternatives to hyperkalemic cardioplegia

Hyperkalemic cardioplegia is by far the most widely used method of cardioplegia in current clinical practice. However, because of the numerous perioperative repercussions of hyperkalemic cardioplegia, a variety of attempts have been made to explore alternative approaches. Given that many adverse effects of hyperkalemic cardioplegia stem from its induction of depolarized arrest, one popular avenue of investigation has been the possibility of hyperpolarized arrest. Hyperpolarization is the natural resting state of cardiomyocytes, so in theory, arresting the heart at its baseline hyperpolarized state may better preserve physiological integrity. In isolated animal heart models, hyperpolarized arrest has been achieved via pharmacologic activation of ATP-sensitive potassium channels [94, 95]. Following reperfusion, this form of hyperpolarized arrest appeared to lead to improved postischemic functional recovery when compared to hearts protected with depolarized arrest.

Meanwhile, so-called "polarized arrest" has been proposed as another alternative to hyperkalemic cardioplegia. The core principle behind this concept is administration of sodium channel blockers, such as procaine in humans or tetrodotoxin in animal models [96]. Sodium channel blockade prevents depolarization-induced activation of calcium currents, which normally carry out the bulk of the cardiomyocyte action potential. Overall, in animal models, tetrodotoxin-induced polarized arrest reduces metabolic demands during ischemia, including myocardial oxygen consumption, more so than hyperkalemic cardioplegia [96]. Furthermore, polarized arrest may produce less significant postoperative ionic imbalances, with further protection provided by coincident administration of sodium/potassium/chloride transporter and sodium/proton exchanger inhibitors [96]. Nonetheless, more work needs to be done to verify the broader clinical applicability of these alternatives to hyperkalemic cardioplegia.

## 3. Conclusions

By taking advantage of the pivotal role of potassium in cardiomyocyte physiology, hyperkalemic cardioplegia has become an integral tool for cardiac surgery. From the early days of Dennis Melrose's simple potassium citrate solution to complex modern-day formulations such as the Del Nido and Buckberg media, approaches to developing and administering hyperkalemic cardioplegic solutions have evolved considerably, with a continuing focus on developing the most cardioprotective and least damaging solutions possible. While initial approaches to hyperkalemic cardioplegia revolved around hypothermic solutions, normothermic/"warm" solutions, along with blood as opposed to crystalloid-based solutions, are gaining momentum as potential alternatives to mitigate adverse perioperative consequences of cold hyperkalemic cardioplegia. Some of those consequences include myocardial calcium loading, myocardial apoptosis, coronary vasomotor dysfunction, myocardial endothelial dysfunction, and myocardial stunning. With any form of hyperkalemic cardioplegia, plasma potassium abnormalities following reperfusion, mainly postoperative hypokalemia, remain a persistent clinical concern. And while most patients respond well to IV KCl supplementation, some do not and proceed to develop fatal arrythmias, underscoring the need for further research to understand the mechanisms at play and develop new treatments. In the future, it is possible that other approaches such as hyperpolarized or polarized arrest may challenge the widespread use of depolarized hyperkalemic cardioplegic arrest. Nevertheless, for the time being, hyperkalemic cardioplegia remains dominant in cardiac surgery, and will likely continue to be so for some time to come.

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