Myocardial Protection in Neonates and Infants: What have we Learnt? Where do we Go?

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Abstract

Myocardial protection in neonates and infants during heart surgery is still a matter of considerable debate. Multiple centers around the world have devised their own methods. Despite multiple claims of superiority of one method over another, there is no firm evidence in favor of one method over another and considerable research work is required in this field. This review summarizes the past, present and future of myocardial protection in children.

Keywords: Myocardial protection; Cardioplegia; Cardiopulmonary bypass; Open-heart surgery; Immature myocardium

Introduction

Surgical management of cardiac defects had remained a great challenge to the surgeons for the greater part of the twentieth century. End of the Second World War saw the diaspora of cardiac surgery as a separate specialty, and the early pioneering works of such giants like Lillehei, Gibbon, Bigelow and Kirklin, to name a few, resulted in open cardiac surgical procedures becoming an acceptable and safe management modality. Over the following decades, with further refinement in the techniques, and development of newer concepts, greater and greater number of open heart surgeries is being performed with greater ease and dexterity. At the same time, the importance of early corrective surgery for congenital heart diseases is increasingly identified [1], and an increasing number of cardiac defects are being corrected surgically in the neonatal period or in infancy. Myocardial protection is central to these developments that have allowed safe cardiac surgery to be performed at a progressively earlier age. Though the term myocardial protection is sometimes, albeit erroneously, treated synonymous to cardioplegia, this is not a fact. The term myocardial protection is more holistic and includes pre-operative management of patients with medical treatment or support devices, better anesthetic agents, better strategy of cardiopulmonary bypass, better surgical procedure and better hemodynamic management. All of these components collectively count for the success of cardiac surgery. Further, structural, anatomical, physiological and functional dissimilarity of the immature myocardium to the adult myocardium mandates a differential approach towards myocardial protection in neonates and infants making it an even greater challenge. In this review, the various aspects of myocardial protection are discussed with emphasis to that in the immature heart.

Need

As many as 90% of patients who die in the peri-operative period following open heart surgery show varying combinations of gross, microscopic, or histochemical myocardial necrosis which is most severe in the subendocardium of the chamber affected by the basic cardiac lesion. This necrosis occurs in the absence of coronary artery obstruction [2]. Among the surviving patients too, late cardiac dysfunction occurs as a result of endocardial fibrosis despite a so called successful surgical outcome [3]. Protection of the neonatal heart during open cardiac procedures is thus very important. Since the peri-operative insult in the neonates is poorly tolerated and is more difficult to treat, adequate myocardial protection during surgical procedures becomes a paramount factor deciding surgical outcomes.

Historical Aspects

Cardiac surgical procedures in early surgical era were essentially the closed heart operations like ligation of patent ductus by Gross and palliation of tetralogy of Fallot by Blalock – Taussig. Hypothermia as a method of protection during cardiac surgery was first proposed by Bigelow [4]. First intracardiac repair of ASD using surface cooling and inflow occlusion was subsequently reported by Lewis and Tauffic. Development of the “heart-lung machine” by Gibbon was the crucial event which heralded the era of open heart surgery in 1953. In 1954, Lillehei, Varco and colleagues reported correction of intracardiac defects using normothermic, low flow, controlled cross circulation based on azygous flow principle and human adult as an oxygenator. A major factor in the success of this group was lack of cardiac ischemia (as aorta was not clamped) and quality of their oxygenator (which was a human adult). The first use of “elective cardiac arrest” was by Melrose in 1955, who also coined the term “cardioplegia” for the technique [5]. Gott et al. used retrograde perfusion of the heart via the coronary sinus using warm blood with Melrose solution [6]. Lillehei’s group also used retrograde perfusion of the coronary sinus with blood during aortic valve surgery [7]. However, surgeons soon found that there was vascular and myocardial injury with use of Melrose solution. [8,9]. As a result, this technique was abandoned. In the late 1950s and early 1960’s subsequent to the work of Shumway and Lower [10] on hypothermic methods to protect the heart, the use of hypothermia combined with intermittent ischemia became the dominant method of myocardial management during cardiac surgery. Along with others, Bretschneider continued to develop the methods of cardioplegia based on an “intracellular” electrolyte solution that reduced trans-membrane gradients, and arrested the heart [11]. He also developed the idea of buffering of the cardioplegic solution as an important principle of myocardial protection [12]. With continuing work on cardioplegia, investigators identified the problems with Melrose solution as toxicity due to inappropriately high ionic concentrations. As the research progressed further St Thomas’ solution was introduced for clinical use as cardioplegic solution for the first time in 1976 [13]. At present, cardioplegia remains the standard practice of myocardial protection. Buckberg’s group introduced use of blood cardioplegia the late 1970s [14]. They reported the use of warm blood cardioplegia given to induce cardiac arrest and replenish high energy phosphates in energy-depleted hearts before giving cold cardioplegia [15]. Buckberg’s group also reported the use of amino acids in the cardioplegia to...
provide substrates for Kreb’s cycle [16] that suggested substrate enhancement as factor in myocardial protection.

### Differences between Immature and Mature Heart

An understanding of the differences between the mature adult heart and immature heart of a neonate and infant is critical to the understanding of myocardial protection in this subset of patients.

#### Structural differences

The pediatric heart is smaller in size and the interstitial tissue contains more water and collagen when compared to the adult heart. This makes the absolute contractile mass of pediatric heart small [17,18]. At the cellular level, pediatric myocardial cells have a larger mass of non contractile elements and poorly developed sarcoplasmic reticulum and mitochondria that are fewer in number but have a higher cytochrome c activity [17,18]. Reduced amount of contractile elements and increased water and collagen contents partially explains the poor contractile response of the immature hearts to isotopes, their poor preload reserve and poor tolerance to afterload. However, the patients in the pediatric age group have normal coronary arteries and healthy myocardium as compared to adults who may have atherosclerotic coronary artery disease and subsequent myocardial scarring and dysfunction. This allows for relatively uniform distribution of cardioplegia by antegrade routes. Due to smaller body size, smaller hardware and prime solution volumes are required. There is relative abundance of PUFA (poly unsaturated fatty acids) in membranes of cellular and sub cellular organelles, providing additional sites of oxidative damage [19,20] and making the immature cyanotic heart more vulnerable to oxidative insult.

#### Metabolic differences

The neonatal myocyte utilizes glucose, ketone, glycogen, amino acids and fatty acids equally well. It has a very high glycogen content and very high glycolytic capacity. Thus, a pediatric heart is a very efficient energy handler, but at the same time it most preferentially utilizes glucose as its principle metabolic fuel for energy production. The immature heart has greater capacity for anaerobic metabolism and hence greater dependence on glycolysis with glucose as substrate [21]. Due to its efficient energy utilization, the pediatric heart is more resistant to ischemia. With substrate enhancement of cardioplegia with amino acids the protective effects of cardioplegia can be further enhanced.

#### Calcium handling

The pediatric heart has poorly developed sarcoplasmic reticulum which is the main sources of intracellular calcium required for myocardial contraction [22]. They have poor release of calcium from and reuptake into the sarcoplasmic reticulum which translates into poor excitation contraction coupling. Thus the pediatric heart is more dependent on the extracellular calcium for proper functioning which forms the basis for maintaining low levels of calcium in the cardioplegia and also accounts for enhanced susceptibility of pediatric heart to calcium channel blockers.

#### Enzymatic activity

The enzymes of free radical scavenging system namely superoxide dismutase, catalase and glutathione reductase are deficient in the pediatric myocardium particularly in those with cyanotic congenital heart disease [23]. In the immature particularly cyanotic heart there is also an overproduction of oxygen free radical upon re-oxygenation. The implication of these differences is that a cyanotic heart is more prone to reperfusion injury not only after the release of aortic cross clamp but also on institution of cardiopulmonary bypass if hyperoxygen bypass strategy is used [19,20,24-26]. At the same time, there was also decreased 5’ nucleotidase activity in the pediatric heart which results in a maintained nucleic acid pool which is essential for the recovery of energy debt when perfusion is resumed. However, this only partially offsets the susceptibility to reperfusion [27].

#### Catecholamine sensitivity

At birth, although the c-AMP functions normally, there is reduced coupling of myocardial beta-receptors to the adenyly cyclase. The catecholamines thus have a poorer effect on the immature myocardium as compared to adults, whereas, response to PDE III inhibitors like milrinone is normal. Adrenaline and nor adrenaline as inotropes are thus less effective in the children as compared to adults and milrinone has a better response [28].

#### Functional and physiological differences

Compared to an adult, a pediatric heart has a poor diastolic reserve, tolerates afterload poorly and has a poor inotropic reserve but has an equivalent ventricular mass [18]. The pulmonary vasculature is more reactive in children and there are some intra or extra cardiac shunts which are active or patent in the neonatal heart [26]. The pediatric heart therefore tolerates ventricular distension and residual lesions poorly and exhibits a greater negative inotropic response to anesthetic drugs and poor response to inotropes. There is more interventricular interdependence and the pediatric heart is more rate dependent for cardiac output than the adult. Due to the presence of shunt lesions there might be diastolic steal of blood during cardiopulmonary bypass which further affects myocardial perfusion and protection [18-30].

#### Ischemic preconditioning

Ischemic preconditioning is a well established defense mechanism against ischemia in adults but in most of the neonatal animal models it has been found to be deficient. A proposed explanation of this difference is that, the mechanisms responsible for ischemic preconditioning may already be active in the immature heart [20,21-34].

#### General Principles

The components to the myocardial protection, in general, are cardioplegia, hypothermia, adequate venting of heart to prevent distension, adequate venous drainage and precise surgical correction.

#### Cardioplegia

Requirement of still and bloodless field during open heart surgery requires that the aorta is to be cross clamped, essentially resulting in period without myocardial blood supply. Role of cardioplegia is to prevent detrimental effects of short periods of ischemia on myocardium. Essential characteristics of ideal cardioplegia must be rapid onset of cardiac arrest, cessation of electromechanical activity, suppression of myocardial energy demands, and maintenance of the intracellular elements during the arrest period and rapid reversal of effect without any residual detrimental effect. An ideal cardioplegia strategy should further be able to replenish the energy stores of the myocardium, wash away the products of metabolism from the myocardium, provide uniform degree of protection though out the period of cross clamp and prevent the adverse effect of reperfusion upon release of the aortic cross clamp. Though earlier in use, the techniques of empty beating heart and fibrillatory arrest are not as popular because the energy requirement of empty beating heart and fibrillating heart is considerably higher than the cardioplegic heart.
The chief constituents of cardioplegia solution are a membrane stabilizing agent, substrates, buffers, osmolar agents and additives. Their functions are discussed in brief.

**Membrane stabilizers:** Lidocaine and procaine are the membrane stabilizers used most commonly in the cardioplegia. They prevent dysrhythmias in the post clamp period. Lidocaine also acts by blocking the sodium channels thus preventing influx of detrimental amounts of sodium across the cell membrane damaged by the potassium in cardioplegia solution.

**Buffers:** There is some amount of metabolism still occurring in the cell even at very low temperature. Buffers provide adequate pH for this metabolism to continue and maintain the pH. Bicarbonates are the most commonly used buffers. Other widely used buffers in cardioplegic solutions include tromethamine (THAM) and histidine.

**Substrates:** Substrates are used in the cardioplegia solution to support the basal metabolism that occurs in the myocytes even at very low temperatures. The most preferred substrate for the myocytes is glucose. However, the use of glucose in cardioplegia solutions results in increased oncotic pressure and increased levels of lactate which is the metabolic end product of glucose in anaerobic conditions. To wash away the lactate the cardioplegia infusions are required to be repeated at small intervals. Newer concepts in cardioplegia have explored the non-glycolytic pathways of generation of ATPs. Amino acids aspartate and glutamate enter the tri carboxylic acid cycle and have been shown to be promising substrates [29]. Glutamate has been found to have a protective effect on endothelial injury caused by hyperosmolar cardioplegia solutions [30]. There is evidence that addition of adenosine to cardioplegia solutions, or its administration during reperfusion results in better recovery of ATP levels and contributes to overall improved function during the post ischemic recovery period [31-33]. Adenosine also has coronary vasodilator and oxygen free radical scavenging properties which afford cardioprotection [34].

**Osmolar agents:** Myocardial ischemia during the cross clamp damages the cell membranes that is further aggravated by high content of potassium in the cardioplegia solutions. This membrane injury results in cellular edema. Repeated doses of cardioplegia aggravate the cellular edema. To counteract this, oncotic substances are required in the cardioplegia solutions. However, too high an oncotic pressure may result in cellular dehydration. Therefore, an optimal osmolality of 370 mOsm/L considered adequate by most of investigators [1]. Mannitol is the most commonly used oncotic substrate in cardioplegia solutions. Other agents that have important oncotic effects are glucose and albumin when used in conjunction with other additives like insulin and corticosteroids. An important advantage of adding mannitol is that it also has free radical scavenging action which is useful during the reperfusion period. However, higher levels of mannitol may cause im paired uptake and utilization of glucose [35].

**Special additives:** Their use varies from centre to centre and among surgeon to surgeon.

a. **Potassium:** Potassium is the main constituent of many of the cardioplegia solutions. It brings about diastolic arrest by depolarizing the myocytes membrane. Effects of potassium on myocardium have been widely studied. High levels of potassium have been associated with many detrimental effects like myocardial ionic and metabolic imbalances, myocardial stunning, tissue edema, endothelial damage, free radical production and functional loss during reperfusion [36]. Hyperkalemia is also associated with direct endothelial toxicity and may be responsible for “stone heart” contracture seen during reperfusion due to sudden calcium influx. Recently it has been reported that low potassium (10 mmol/L) cold blood cardioplegia formula is associated with better myocardial protective effects when compared with conventional high potassium cardioplegia in paediatric patients [37].

b. **Calcium:** The calcium handling capacity of immature heart is relatively less well developed. In acyanotic hearts, comparable outcomes are observed with both hypocalcemic as well as with normocalcemic cardioplegia strategies. However, when a stressed, hypoxic/cyanotic heart is exposed to normocalcemic solutions there is an increased cellular injury, manifested by depression in post bypass myocardial and endothelial cell function [38].

c. **Magnesium:** Magnesium antagonizes the effects of calcium. When a hypocalcemic cardioplegia solution is used in hypoxic hearts, complete preservation of mycardial function may be possible even in absence of magnesium supplementation. However, when a hypoxic neonatal heart is protected with a normocalcemic cardioplegia solution, instead of a significant cellular injury, magnesium enrichment protects the heart from further damage, resulting in complete preservation of myocardial and vascular endothelial cell function [38]. Magnesium helps to provide equivalent myocardial protection with lesser doses of potassium thereby alleviating unwanted effects of hyperkalemia.

d. **Pharmacological agents:** Calcium channel blockers such as verapamil, nifedipine and diltiazem have been used in adults as adjuncts to cardioplegia to enhance myocardial protection [39]. However, in pediatric population, calcium channel blockers are not as effective as in adults. Calcium channel blockers, also have a prolonged effect, which may depress postoperative myocardial function, making them a less attractive cardioplegic additive in pediatric population. Hyperpolarizing agents are an attractive option for addition to cardioplegia solutions as hyper-polarization arrest keeps the cell membranes close to resting membrane potential. Cardioplegia enrichment with K$_{ATP}$ channel opener, Pinacidil [40] can improve left ventricular performance and coronary blood flow following ischemic arrest. Cohen et al compared hyper polarization with K$^+$- ATP channel blocking agent versus traditional potassium depolarization in rabbits and found improved functional outcome in the former; Jaywant et al [41] also concluded that Pinacidil alone provided superior myocardial protection than St Thomas solution as evidenced by decreased myocardial stunning without any significant changes in cellular metabolism.

e. **Antioxidants:** Neonates and infants are considered more prone to reperfusion injury. Supplementation with exogenous antioxidants such as iron chelators (desferoxamine) [42], catalase [43] and coenzyme Q10 [44] is useful in prevention of reperfusion injury. Use of xanthine oxidase inhibitors like allopurinol reduces oxygen free radical production [45].

**Crystalloid cardioplegia versus blood cardioplegia**

Two types of cardioplegia solutions are used in paediatric population, each with its own merits and demerits. Which one is the better of two is a matter of debate and of personal preferences.

**Crystalloid cardioplegia:** Most of them act by depolarizing the cell membrane due to high content of potassium (10-20 mmol/L), thus providing electromechanical arrest. They are of two types

a. **Extracellular:** These have higher levels of sodium, calcium and magnesium. Examples include Saint Thomas I and Saint Thomas II (Plegisol®). St. Thomas II is more common in use. It contains lower amount of potassium, calcium and sodium and has more physiological pH (7.8) as compared to acidic pH (5.5 - 7.0) of St. Thomas I.

b. **Intracellular:** They have no or low calcium and sodium.
E.g. Bretschneider –HTK (Custodiol®). Custodiol® cardioplegia is commonly used intracellular cardioplegia solution. It contains reduced amounts of sodium, potassium and calcium. It has magnesium as membrane stabilizing agent and is enriched with histidine, tryptophan and ketoglutarate. It has a pH of 7.02 – 7.20. Single dose of Custodial® cardioplegia delivered through the antegrade route give good protection for up to 2 hours duration.

The advantages of crystalloid cardioplegia include rapidity of induction, uniform distribution and rapidity of reversal of effects of cardioplegia. However, their use is associated with lower hematocrit and lower oxygen carrying capacity of the cardioplegia solution.

**Blood cardioplegia:** Globally blood cardioplegia is the most commonly used cardioplegia. Depending on institutional preferences and the type, it is prepared by mixing varying parts of blood and cardioplegia solution. Its temperature can be varied to warm, tepid or cold.

Blood cardioplegia is associated with multiple advantages. Owing to the presence of formed cellular elements in the solution, blood cardioplegia has higher oxygen carrying capacity and higher concentration of natural substrates. Thus, in the immediate post clamp period when the coronary blood supply is cut off but the heart is still beating, blood cardioplegia ensures that the heart is arrested in an oxygen rich environment with minimal loss of high energy phosphate bonds. Due to presence of naturally occurring buffers in the blood, a less acidic environment is available for cellular function. Presence of natural free radical scavengers in the blood helps in preventing reperfusion injury, to which the immature heart is particularly sensitive. Warm blood compared to cold crystalloid cardioplegia has two other theoretical advantages. Hypothermia causes hemoglobin-oxygen dissociation curve to shift to left and this may hamper oxygen delivery to the tissues. Also, hypothermia causes vasoconstriction of coronary bed which shifts to left and this may hamper oxygen delivery to the tissues. Blood cardioplegia provides superior myocardial protection. In a randomized controlled trial comparing cold crystalloid cardioplegia with cold blood cardioplegia, cold blood cardioplegia and hot shot, Modi et al [46] reported that, for cyanotic patients (younger, with longer cross clamp times), cold blood cardioplegia with a hot shot is the best method of myocardial protection. For acyanotic patients (older, with shorter cross clamp times), cardioplegia technique is not critical. In a randomized controlled trial examining the superiority of blood cardioplegia over crystalloid cardioplegia by Young et al [47], no differences were found in the clinical outcomes, and duration of aortic cross clamp was found to be the most important factor for clinical outcome. In a study comparing the outcomes with St Thomas II and Bretschneider –HTK cardioplegia solutions, Wang et al [48] have reported superior myocardial protection in infants with cyanotic congenital heart disease in the Bretschneider group. Jacoba et al [49] in a meta-analysis of 18 randomized controlled trials reporting more than 50 patients each, reported that at least 10 studies showed statistically significant clinical outcomes in favour of blood cardioplegia and 5 studies showed a statistically significantly less CK-MB enzyme release following blood cardioplegia. Another meta-analysis by Guru et al [50] concluded that in adult hearts blood cardioplegia provided superior myocardial protection compared to crystalloid cardioplegia.

**Warm induction**

In some centers practice is to start myocardial protection with delivery of warm antegrade cardioplegia followed by cold cardioplegia especially in patients with strained myocardium, reduced ventricular function, associated coronary artery disease. This is described as warm induction. Kronen et al [51] have reported that in non-hypoxic (normal) hearts the temperature of cardioplegic induction was not important. But, in hearts subjected to stress of hypoxia, providing a warm cardioplegic induction for 3-5 min facilitates repair of the hypoxic re-oxygenation injury resulting in complete preservation of myocardial function. Cold induction in such patients prevents further damage, but does not improve the injury caused by re-oxygenation. The use of warm induction in conjunction with substrate enhancement is associated with better ventricular function, fewer peri-operative myocardial infarcts, greater postoperative cardiac output, reduction in low cardiac output syndrome, particularly in energy depleted cyanotic paediatric hearts because it may help in replenishment of their stores of high-energy molecules.

**Routes of cardioplegia delivery**

Cardioplegia may be delivered in any of the three ways, namely antegrade - through the aortic root or coronary ostia, retrograde – through the coronary sinus and a combined approach. Since in paediatric population native coronary arteries are seldom diseased, retrograde cardioplegia is uncommonly used in this group of patients. Their use may be indicated in patients with severe aortic regurgitation. Retrograde route may also be used if a strategy of continuous warm infusion is desired.

**Multi dose versus single dose cardioplegia**

In the paediatric population, presence of intracardiac shunts and multiple aorto-pulmonary collateral arteries cause high amount of non coronary cardiac return which washes away the cardioplegia and re-warms the heart. A strategy of periodic replenishment of cardioplegia in such patients, though cumbersome at times, would maintain arrest, maintain uniformity of myocardial hypothermia, buffer acidosis, wash away metabolic end products, replenish high energy phosphates and restore depleted substrates. However, some studies point out that repeated multi-dose infusions with topical cooling may cause more harm than good in paediatric population, even when high energy phosphate bonds are adequately preserved [52]. This might be attributed to the high content of potassium in the cardioplegia and resultant myocardial edema. Esmolol based multi dosing cardioplegia strategy has been reported as an acceptable and safe alternative to depolarizing hyperkalemic cardioplegic solutions [52].

**Hot shot versus cold reperfusion**

A hot shot is warm, K+ containing cardioplegia solution enriched with substrates like histidine, glutathione aspartate which is given prior to releasing the aortic cross clamp and provides to heart along with oxygen and substrates for myocardial recovery. The immature heart is less tolerant to reperfusion injury compared to adult heart [53]. Use of warm substrate-enhanced reperfusion (hot shot) in conjunction with leukocyte depletion and filtration has been useful in preventing reperfusion injury in children [53].

**Del-Nido cardioplegia**

In the recent times, del-Nido cardioplegia [54] is being used...
Hypothermia is associated with coagulopathy, bleeding and enzyme, resulting in poor oxygen utilization by the tissues. Decreasing the release of oxygen to tissues, the tissue uptake of cardioplegia and uneven myocardial protection [34]. With fall in coronary microcirculation leasing to uneven distribution of results in myocardial & tissue edema. There is roleaux formation of hypothermia too. With hypothermia there is shift of pH towards cardioplegia solution. However, there are certain adverse effects bypass flow rates, decrease in dose of potassium in cardioplegia. Use of hypothermia allows for reduction in the cardiopulmonary when the temperature increases (above 15°C) minor at low temperatures (below 15°C), but becomes substantial. Experimental studies have shown that the benefit of adding bypass, prevention of calcium accumulation in the mitochondria and decrease in sarcolemmal membrane permeability with reperfusion. It is mainly used as an adjunct to chemical cardioplegia. Experimental studies have shown that the benefit of adding cardioplegia solution to hypothermia alone is minor at low temperatures (below 15°C), but becomes substantial when the temperature increases (above 15°C) [56]. It has also been shown that electromechanical arrest of the heart by itself decreases the myocardial oxygen demand by 90 %, and there is only slight 5% further reduction by decreasing the temperature to 11°C. Use of hypothermia allows for reduction in the cardiopulmonary bypass flow rates, decrease in dose of potassium in cardioplegia and prolongation of periods of cardiac arrest attained with any cardioplegia solution. However, there are certain adverse effects of hypothermia too. With hypothermia there is shift of pH towards alkalinity which impairs enzyme function. In the cardiac myocytes there is enzyme disruption and impaired ischemic anerobiosis that results in poor glucose utilization. Impaired osmotic homeostasis results in myocardial & tissue edema. There is roleaux formation in coronary microcirculation leading to uneven distribution of cardioplegia and uneven myocardial protection [34]. With fall in temperature, the hemoglobin- dissociation curve shifts to left decreasing the release of oxygen to tissues, the tissue uptake of oxygen decreases and there is decreased function of membrane enzyme, resulting in poor oxygen utilization by the tissues. Hypothermia is associated with coagulopathy, bleeding and increased infections. Topical hypothermia using ice slush or cold saline at 4°C also contributes to myocardial cooling. However, it can lead to uneven cooling especially in the presence of ventricular hypertrophy.

**Special circumstances**

**Arterial switch operation:** Usually a single dose of a long acting cardioplegia such as the del-Nido cardioplegia is preferred by the authors. However, many groups repeat the cardioplegia frequently into the coronary ostia.

**Anomalous origin of left coronary artery from pulmonary artery (ALCAPA):** In patients with ALCAPA the myocardial function is profoundly compromised in the preoperative period in a substantial number of patients. Prior to commencing cardiopulmonary bypass the pulmonary arteries must be dissected and looped. Immediately upon commencing bypass the tourniquets on the pulmonary arteries must be tightened. Both the coronary arteries are presumably perfused due to collaterals between the right and the left coronary systems. An alternative method of providing cardioplegia is by way of inserting two different cardioplegia cannulae, one in the aortic root and other in the pulmonary artery for perfusion of both of the coronaries. This method is less commonly followed. Another method is delivering the cardioplegia to the left coronary ostium upon opening the pulmonary artery.

**Aortopulmonary Window:** Similar to the patients with ALCAPA, the pulmonary arteries of these patients must be occluded with tourniquets passed around them immediately upon commencing cardiopulmonary bypass and prior to administration of cardioplegia.

**Future Trends**

**Insulin Cardioplegia**

There has been some interest in the cardioprotective effects of insulin glucose solutions following reports of protective effects in patients with acute myocardial infarction. Mechanism of action of insulin remains unclear but presumably it stimulates lactate dehydrogenase, an enzyme that converts lactate to pyruvate which is further metabolized through the tri carboxylic acid cycle. This mechanism prevents accumulation of detrimental levels of lactate in the myocytes. In patients undergoing CABG, Rao et al [57] showed that addition of glucose in cardioplegia resulted in better metabolic recovery irrespective of glucose concentration in the cardioplegia. In isolated working rat hearts, addition of both glucose and insulin cardioplegia resulted in better preservation of myocardial function [58].

**Cardioplegia enrichment with L-arginine**

Cardioplegic arrest of heart and reperfusion may lead to ischemia reperfusion injury which promotes release of endothelin-a highly potent vasoconstrictor. Along with platelet aggregation and leukocyte degranulation, endothelin-induced vasoconstriction may lead to significant impairment of microcirculatory flow. This has been termed the no-reflow phenomenon. No reflow phenomenon has been attributed to poor myocardial protection in many studies. L-arginine, an amino acid precursor for nitric oxide has been shown in studies have to protect the arrested heart from reperfusion injury [59]. This action is possible due to its vasodilator effects which counters the no reflow phenomenon. However, convincing clinical studies are required to establish it as routine strategy.

**Use of polarizing agents as cardioplegia**

Depolarising cardioplegia agents like potassium based
cardioplegia solutions have been reported to cause leakage in the capillaries due to trans-membrane ionic changes. Polarizing agents like Pinacidil, a potassium channel opener has been shown to provide good myocardial protection in immature rabbit heart [60] and adult pigs [28] in experimental models. Their use in clinical practise awaits further investigation.

Conclusion

It is apparent from the above discussion, that even though there have been rapid strides in the field of pediatric cardiac surgery, there is yet no consensus on the best available strategy of myocardial management. Newer forms of cardioplegia solutions continue to evolve despite the fact that those who are still using the older solutions report excellent results. Therefore, it is more than likely that strict adherence to one particular method of myocardial protection along with a precise surgical repair seems to provide best outcomes. We believe that large multi-institutional prospective randomized trials are required to elucidate what is the best myocardial protection strategy. Whether such trials will be ethically justifiable and permissible is not known.

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