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Evolution of Paediatric Myocardial Protection

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Review Article

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Abstract

Myocardial protection is cynosure of cardiac surgery. It has evolved over a period of 100 years but still is an enigma. From the basic understanding of cardiac physiology to advancement in cardiac surgery all have contributed to formation of principles of myocardial protection. With the progress in cardiac surgery and increasing complexity in paediatric cardiac surgery, the requirement of myocardial protection is paramount. In our review we talk about the historical aspects and future perspectives of paediatric myocardial protection.

Keywords: Paediatric Myocardial; Cardiac Surgery; Air-Embolism; Cardioplegic Myocardial

Introduction

A new development or contribution opens new vistas for further study and uncovers hitherto unrealized problems that had not existed previously. With the advent of cardiac surgery, arose a requirement for myocardial protection. Myocardial protection though imperceptible is an indispensable component of safe cardiac surgery Origin of myocardial protection was not an intentional process. It originated from the need of an arrested heart to attain a bloodless, motionless and air-embolism free environment. As Braimbridge quoted "our whole edifice of cardioplegic myocardial protection has been built on serendipity" [1]. Myocardial protection in cardiac surgery is a dynamic evolving field, which still might be in its infancy. It took birth from the need for better management of the myocardium as we advanced in pediatric cardiac surgery, tackling with tedious and challenging procedures. In their zeal to master operative procedures, most surgeons were unable to comprehend the cause of significant perioperative mortality and were obviously unaware of the need for adequate intraoperative myocardial protection during the procedure which was a significant factor in a patient's demise. The need arose in the late 1960s from the observation of acute subendocardial myocardial infarction in patients undergoing cardiac surgery, and this was contributed to improper management of the myocardium during surgery [2].

From there on trial and error have been the route by which we have achieved the current knowledge that we have of myocardial protection, with great contributions from a plethora of great and distinguished minds. Genesis of main stream open heart surgery was with paediatric cardiac surgery in the hands of Dr Clarenece W. Lillihei, Dr F john Lewis, Dr Mansur Taufic, Dr John H Gibbon, Dr John W.Kirklin, just to name a few of the many [3]. The basic physiology involved in the development of myocardial protection dates back to more than a century.

The Early Days

Sydney Ringer from the university college in London, reported that incremental increase of potassium resulted in weaker and weaker beats until cardiac asystole developed. Sydney quoted "If too much potassium is present, or too little lime salts, then the contraction of the ventricle is imperfect, and by increasing the quantity of potassium salt the beat becomes weaker and weaker till it stops" [4] After 50 years, in 1931, A.M. Baetjer and C.H McDonald, emphasized upon the cardiac function of sodium, potassium and calcium.

They concluded that calcium was determined to be essential for the production of strong, mechanical contractions of the myocytes. Sodium is responsible for the initiation and maintenance of spontaneous rhythmic contractions of the heart Lastly potassium had an antagonistic effect on sodium and calcium and appeared to regulate the interactions between sodium and calcium [5]. In 1935 George H. Zwitster and T.E. Boyd reported that the ventricles ceased contractile activity when soaked for 1 to 2 hours in Ringers solution modified to contain 0.2 % to 0.4% potassium chloride [6]. During this era, cardiac surgery was still an experimental branch and open heart surgery was still decades away. These concepts of action of ions on cardiac musculature would invariably form the basis of myocardial protection in future. Hypothermia which has an eminent place in myocardial protection as well as cardiovascular surgery has its humble beginning in ancient Greece, where it was used for treatment for tetanus by Hippocrates [7].

Era of Open-Heart Surgery

Theodor Billroth, one of the pioneers of modern abdominal surgery once stated: "A surgeon who tries to suture a heart wound deserves to lose the esteem of his colleagues" in 1896 [8]. The success of Prof Alfred Blalock, Dr Robert Gross, Dr Clarence Crafoord had proved the feasibility of cardiac surgery contrary to the earlier believes [9-11]. In 1950s Wilfred G Bigelows was investigating general hypothermia for reducing the oxygen requirements of the body in order to allow exclusion of the heart from the circulation, thus allowing surgeries on the heart [12]. In 1952 John F Lewis and Mansur Tauffic using Wilfred G Bigelows hypothermic principles successfully closed an Atrial septal defect under direct vision with inflow occlusion [13]. Their intention for using hypothermia was not myocardial protection, rather to achieve a blood less field and a still heart to work upon. Later on in 1953 Dr John H. Gibbon Jr used his cardiopulmonary bypass machine to successfully close an atrial septal defect [14]. This being a landmark in cardiac surgery, as it gave the control in hand of the surgeon to peacefully work on the heart. In 1954 C.W. Lillehei used his concept of cross circulation to perform a number of open heart surgeries, establishing its feasibility [15]. Though such a huge stride had taken place over a period of couple of years, the concept of myocardial protection was still nowhere in picture. After the development of heart lung machine, open heart surgery took off; a partly unforeseen challenge was the requirement to arrest the heart for adequate anatomic repair. Soon thereafter a further discovery was that surgical needs conflicted with myocardial demands. Surgeons require rapid induction, maintenance and easy reversal of cardiac arrest.

Myocardium requires that the cell machinery remains intact with rapid restoration of metabolism and function after cardiac arrest. With the advent of open heart surgery came in the problems of air -embolism, dynamic and blood pooled operative fields. To overcome the above mentioned problems, surgeons devised the method of elective cardiac arrest. Elective cardiac arrest itself subjected the heart to ischemic insult, thus there was a requirement of a balance between an acceptable operative field and a preserved myocardium. This requirement paved the way for development of methods for myocardial protection.

The Hyperkalemic Arrest

In 1955 came the study of Denis Melrose, born out of inadequate operative conditions during repair of mitral valve in the presence of aortic regurgitation. Denis Melrose emphasized on the need of unhurried correction of cardiac abnormalities under direct vision with a blood less field and no fear of air embolism.

Melrose advocated the use of potassium citrate to voluntarily arrest the heart and re-start the heart voluntarily [16]. In 1958, Melrose and Frank Gerbode published their work with potassium citrate arrest in 34 clinical cases of open heart surgery at Stanford university hospital [17]. After gaining experience in dogs they applied aortic root injections of potassium citrate for arrest of the human heart. The potassium citrate, maintained highly concentrated in glass vials prior to use, was dissolved in 30 ml batches of blood giving an injectate concentration in excess of 200 mM. The injection provided immediate cardiac arrest and conditions for short-lasting anatomic repair. Melrose's report in 1955 led to international recognition and adoption of his technique. Denis Melrose with his studies was successful in initiating the concept of elective cardiac arrest in order to aid cardiac surgery.

Will Sealy and colleagues report their modification of Melrose method with the use of potassium citrate, magnesium sulfate and neostigmine they achieved ischemic periods as long as 52 minutes [18]. Will Sealy and colleagues are credited with coining the term "cardioplegia". Like any other procedure soon the pitfalls of potassium citrate were evident. It was seen that use of potassium citrate caused myocardial damage, myocardial necrosis and sometimes irreversible ventricular fibrillation. These findings were well documented un 1959 by James A. Helmsworth, 1960, McFarland and coworkers [19,20]. These reports lead to a search for other methods for safer elective cardiac arrest to perform cardiac surgery and abandoning Melrose's method. After Melrose era, the concept of myocardial protection was sought after.

Myocardial protection is not merely arresting the heart to achieve an ideal operative field It deals with preserving

the myocardium while it is being worked upon and has many components. By 1960s we had come across two methods of effective myocardial protection. Hypothermia which decreased the metabolic activity as well as requirement of the myocardium and potassium induced arrest of the heart, again decreasing the metabolic requirement of the myocardium [21,22]. In the view of myocardial toxicity of potassium citrate, there was a search of alternate methods to achieve arrest. These methods were direct coronary perfusion, intermittent occlusion, topical hypothermia or normothermic ischemia. During 1960s and early 1970s direct coronary perfusion with intermittent aortic occlusion becomes the preferred method for myocardial protection [23]. This method had its drawback of flooding the operative field with blood, coronary embolism and coronary damage. In 1972 Gerald Buckberg from the University of California found that non-physiological coronary perfusion lead to sub-endocardial ischemia and necrosis [24].

Topical Hypothermia

In 1961 Hufnagel and colleagues introduced profound cardiac cooling using ice slush [25]. Norman Shumway and associates introduced selective hypothermia in anoxic cardiac arrest. They produced local hypothermia of the heart by simple perfusion of the suspended pericardial sac with a 4 deg Celsius solution of isotonic saline [26]. Selective hypothermia showed excellent result as shown by Paul W sanger and associates and Norman Shumway [27]. The greatest limitations of topical cardiac hypothermia were the short duration of safe ischemic arrest as short as 70 minutes. Normothermic ischemic arrest was adopted by Denton A. Cooley in 1964 for a period of time; IT gained popularity soon to be discarded as other method s in the view of sub-endocardial necrosis, “stone heart “phenomenon [28]. Depletion of myocardial ATP was proposed as the cause. By this time chemical cardioplegia was resurfacing with modifications in its constituents.

Resurrection of Chemical Cardioplegia

B.Hoelscher and colleagues in their study on potassium citrate cardioplegia concluded that magnesium and calcium chelating effect of citrate, which caused myocardial edema and was responsible for the ill effects of the solution [29]. In 1975 Hans J Bretschneider invented an intracellular cardioplegic solution, with intracellular concentration of sodium, a calcium free environment. Procaine was added to the solution to provide membrane stabilization and mannitol maintained ideal osmolarit [30]. T. Sondergaard and colleagues applied Bretschneider solution in clinical practice with good results [31]. David Hearse from St. Thomas’s Hospital in London published a landmark study on the isolated rat heart. Hearse created and explained the basic components of the dominant form of crystalloid cardioplegic solution currently in practice. David hearse credited Braimbridge, T.Sondergaard and Bretschneider for heavily inspiring his research. After recruiting St. Thomas’s Hospital, Braimbridge suggested to him to study on the effects of potassium, magnesium, and procaine should be Hearse proposed an “extracellular” cardioplegic solution that comprised Krebs Henseleit bicarbonate buffer at pH 7.4, 12 mM potassium, 16 mM magnesium, 10 mM ATP, 10 mM creatine phosphate, and 1 mM procaine.

Hearse went on to postulate that the topical hypothermia often used in clinical surgery might extend the protective capabilities of his solution. On the basis of Hearse’s work, Braimbridge instituted cold cardioplegia with St. Thomas’s Hospital Solution No. 1 in 1975 [32]. In1981 ST Thomas solution No 2 was introduced with a significant difference from St Thomas No1 in view of decreased calcium concentration, besides other differences [33]. Now cardioplegia was back as on of the preferred method of myocardial protection. Myocardial protection was also now an accepted phenomenon, and considered as an important factor for early and late outcomes after surgery.

Blood Cardioplegia

Gerald Buckberg of the University of California advised the supremacy of blood cardioplegia blood delivery of cardioplegia solution offered a number of advantages to the surgeon. These included augmented oxygen delivery, effective buffering by carbonic anhydrase, free radical scavenging by red blood cells and plasma constituents , ideal oncotic pressures and limitation or reversal of ischemic or reperfusion injury [34]. Buckberg also emphasized on the importance of intermittent reinfusion of cardioplegic solution because of washout from non-coronary collateral perfusion [35]. In 1970s and 1980s there was no clear division between adult and paediatric myocardial protection. In late 1980s and early 1990 s there was a surge in research about the differences in the paediatric myocardium. Over the years it was found that paediatric myocardium is quite different from its adult counterpart and required a peculiar and a divergent approach in view of protection of the myocardium. The Paediatric myocardium has smaller cells with decrease in volume of contractile elements per cell , fewer mitochondria and poorly developed sarcoplasmic reticulum and T-tubules thereby making the cell more vulnerable to calcium influx mediated injury , preferential utilization of glucose over free fatty acids for energy needs under aerobic and anerobic conditions Increased susceptibility to intracellular lactate accumulation due to decreased coronary washout and poorly developed non-coronary collaterals [36]. Paediatric myocardium also has suboptimal function of dismutase and catalase enzymes that degrades reactive oxygen species.

These all differences made it mandatory to devise a specific plan for myocardial protection in paediatric population. 1990s there was advent of specific cardioplegia catering to the need of paediatric myocardium this was del nido cardioplegia being used in Boston's children hospital Massachusetts. This solution was made keeping in mind the requirements of paediatric myocardium. The del nido cardioplegia solution is an extracellular solution mixed with autologous blood obtained from the extracorporeal circuit. It is crystalloid: blood ratio of 4: 1. One dose of 20 ml/kg is calculated to obtain optimal myocardial protection for 90 min. The potassium concentration is > 25 mEq/l. The achieved myocardial temperature is < 15°C. The crystalloid solution includes Plasma-Lyte A as a basic solution, mannitol, magnesium sulfate, bicarbonate, potassium and lidocaine. Each constituent of this solution is meticulously chosen to cater to the nedds of paediatric myocardium. The del Nido cardioplegia contains a base solution of Plasma-Lyte A, which has an electrolyte composition similar to the extracellular fluid. It is important to note that there is no calcium in the base solution. The final calcium concentration of this cardioplegia can be described as trace because 20% of the delivered volume contains patient blood. Hyperosmotic mannitol has both properties to scavenge free radicals and reduce myocardial cell swelling.

Magnesium has been shown to be a natural calcium channel blocker. Due to this effect magnesium has been shown to improve ventricular recovery in hypothermic cardioplegia solutions when coupled with a low calcium level The del Nido cardioplegia mix uses sodium bicarbonate as a buffering agent to scavenge excessive hydrogen ions which assist in maintaining intracellular pH. For arresting the myocardium, del nido mix uses potassium as hyperkalemia provides rapid arrest and reliable recovery. Lidocaine a sodium channel blocker is also a component of del-nido solution, Sodium channel blockade increases the refractory period of the cardiac myocyte. When cardioplegia is given in an ideal environment without washout, this action is prolonged because the lidocaine remains in adequate concentrations to continually affect the myocardium. The del nido cardioplegia is delivered with 20 % by volume of blood, which provides a conducive environment for a finite period of aerobic metabolism following which it provides buffering properties to promote anaerobic glycolysis [37]. Presence of oxygenated patient's blood in the solution adds the benefits of blood cardioplegia to the solution. Such as a superior oxygen-carrying capacity, better osmotic properties and antioxidant capability and many more beneficial properties.

The Current Scenario

From past we acquired many methods to arrest and/or protect the heart.

We came across the following method

- Hypothermia, systemic and/or supplied by topical cooling [26].
- Global ischemia with continuous or intermittent aortic occlusion [38].
- Aortic root or intracoronary perfusion with blood [23] and, when needed, electively induced ventricular fibrillation [39].

These modalities have been tried, tested, rejected and then again resurfaced and still are used in combination with each other till this date with cardioplegia playing the pivotal role. Over the years we have acquired immense knowledge about the paediatric myocardium, components and basics of myocardial protection have also been elucidated.

Myocardial protection is a meticulous amalgamation of the following components:

- Hypothermia
- Cardioplegia
- Avoidance of left ventricular distension
- Maintaining good venous drainage

Hypothermia

Hypothermia is used an adjunct to other methods for myocardial protection. Use of hypothermia allow reduction in the effective dose of potassium in cardioplegia solutions and thereby alleviate side effects of systemic hyperkalemia. Cold cardioplegia administration also assures longer period of cardiac arrest. How hypothermia exactly protects against ischemic damage is not precisely known but it has been shown to decrease metabolic needs of the cell, prevent calcium accumulation in the mitochondria and decrease sarcolemmal membrane permeability with reperfusion [39] It has been shown that the benefit of cardioplegia over hypothermia alone is minor at low temperatures (below 15°C), but becomes substantial when the temperature increases. Other workers have concluded 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 [40]. Cardioplegia Cardioplegia is defined as a technique involving single or repeated injections, infusions or perfusions into the aortic root or into the coronary vasculature of a hypo- or normothermic solution with intent to cause cardiac arrest and to protect the myocardium during aortic cross-clamping with global ischemia. The method by which cardioplegia provides myocardial protection is complex and many explanations are present.

Three Additive Components of Cold Chemical Cardioplegia are [40]

- Chemical arrest or the sparing of cell energy through rapid induction of arrest in diastole.

- Hypothermia or slowing the rate of cellular reactions thereby delaying energy decay and other deleterious processes during ischemia.
- Additional protection related to protective agents that prevent or reverse unfavourable ischemia-induced cellular changes.

Myocardial oxygen consumption decreases from 8 to 10 ml/100 g/min to 1 ml/100 g/min on induction of diastolic arrest at normothermia. It decreases further to 0.3ml/100 g/min with hypothermia [36].

General Constituents of Cardioplegia Solutions

- Substrate: Even under arrested and hypothermic conditions some energy is needed to keep metabolic processes on for which metabolic substrates are required.
- Buffers: These provide appropriate pH for continued myocardial metabolism irrespective of temperature.
- Membrane stabilization: The cell membrane is the myocardial subcellular structure at maximal risk of irreversible damage during aortic cross clamping.
- Osmolar agents: To minimize myocardial edema as a consequence of ischaemia, it is essential to ensure that cardioplegic perfusate has sufficient oncotic pressure to keep fluid in the intravascular space.

Types of Cardioplegia used in Paediatric Patients:

- Crystalloid cardioplegia
- Blood Cardioplegia

Crystalloid Cardioplegia

Most of these have potassium levels between 10 mmol/L and 20 mmol/L. They protect the heart by ensuring electromechanical quiescence. Special additives include lidocaine, procaine, buffers and substrate. They can be broadly subclassified into two types:

- Intracellular: These have no or low calcium and sodium. e.g. Bretschneider-HTK solution (Custodiol®).
- Extracellular- These have higher levels of sodium, calcium and magnesium. e.g. St Thomas II (Plegisol ®).

Conclusion

We have come a long way from the past in order of our understanding in how to deal with the myocardium, specifically the paediatric myocardium. Through the shoulders of the giants we have decreased our morbidity and achieved superior results but we still have a long way to go There are a still a lot of questions unanswered and from our past experiences we can say how unpredictable the future can be we evolved from an era of exclusive potassium-based arrest to completely out-throwing the concept, wandered around with many methods later on ending up accepting the hyperkalemic arrest. during the evolution we came across many innovative methods dealing with hypothermia (systemic as well as topical), inflow occlusion techniques, normothermic arrest without cardioplegia, electric shock fibrillatory arrest, use of acetyl cysteine to arrest the heart, potassium free cardioplegia, crude crystalloid cardioplegia, cardioplegia solutions containing various components catering to the various need of the arrested myocardium from substrates to membrane stabilizers, blood cardioplegia and most recently a cardioplegia specifically to cater to the need of the paediatric myocardium with all this history of about a century, it won't be an exaggeration to say that over the coming time our concepts will further change and the field shall keep on evolving. As said by T.S. Elliot "Time present and time past Are both perhaps present in time future, And time future contained in time past." Perhaps these words hold truth for myocardial protection as well. Though we need to have more customized approach and there is also presence of a solution tailored to the need of pediatric myocardium, the uniformity of distribution of the solution in the context of its worldwide use is still limited. There is further requirement of an acceptance of the fact of difference between the pediatric and adult myocardium and a requirement of an exclusive method to protect the unique myocardium in order to achieve superior results as compared to the past cardiac surgery is an ever-evolving field and there is no doubt that in the near future there will be better and focused pediatric myocardial protection, which shall lead to better patient management and decrease the morbidity as well as mortality associated with an improper myocardial protection.

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