Early Outcomes of Custodiol Versus Blood Cardioplegia in Coronary Artery Bypass Graft Surgery at Ain Shams University Hospitals

Thesis

Submitted for Partial Fulfillment of the Master Degree in Cardiothoracic Surgery

By

Ahmed Hassan Mohamed

M.B.B.Ch, Faculty of Medicine, Ain Shams University

Under Supervisors

Prof. Dr. Gamal Samy Sayed

Professor of Cardiothoracic Surgery
Faculty of Medicine – Ain Shams University

Ass. Prof. Dr. Ihab Abdelrazek Ismail

Assistant Professor of Cardiothoracic Surgery
Faculty of Medicine – Ain Shams University

Dr. Ramy Mohamed Reda Khorshid

Lecturer of Cardiothoracic Surgery
Faculty of Medicine – Ain Shams University

Faculty of Medicine
Ain Shams University
2018

First of all, thanks to **Allah** whose magnificent help was the main factor in completing this work.

No words could express my deepest thanks and appreciation to **Prof. Dr. Gamal Samy,** Professor of Cardiothoracic Surgery, Faculty of Medicine, Ain Shams University, for inspiring me with the idea of this work. His patience, precious advice and guidance enlightened my way throughout this work.

I want also to express my profound gratitude to **Ass. Prof. Dr. Ihab Abdelrazek,** Assistant Professor of Cardiothoracic Surgery, Faculty of Medicine, Ain Shams University, for his patience, valuable advice and continuous help in completing this work.

I am also deeply indebted to **Dr. Ramy Khorshid,** Lecturer of Cardiothoracic Surgery, Faculty of Medicine, Ain Shams University, for his kind help, guidance, useful advices, continuous encouragement and support all through my entire work.

Finally, my deepest thanks to all my family and colleagues who helped me in the production of this work.

Introduction and Aim of Work

Inadequate myocardial protection in long ischaemic periods followed by reperfusion is an issue of concern in cardiac surgery. Cardioplegic solutions improve the tolerance to ischaemia and reperfusion by preserving myocardial energy reserves, preventing osmotic and electrolyte imbalances and buffering acidosis[1]

The cardioplegic solutions can be classified into two main groups. One is based on extracellular components with high potassium, magnesium and bicarbonate levels, while the other is based on intracellular electrolytes. Both have demonstrated beneficial effects as measured with the biochemical markers in biological models and in patients, although the latter option (intracellular composed solution) may appear more effective [2]

Histidine–tryptophan–ketoglutarate (HTK) is a solution based on the intracellular level of electrolytes, proposed by Bretschneider in the 1970s [3]

Histidine, tryptophan, ketoglutarate and manitol act as buffers and improve high energy production via adenosine triphosphate during reperfusion, stabilize cell membranes and maintain osmotic regulation of the cell membrane . Several studies have shown the efficacy of the

HTK solution based on biochemical markers or physiological evaluation in experimental models . In recent years, HTK has been used as a multi-organ preservation solution as well as cardioplegia in cardiac surgery in several countries but not universally throughout the world.[4]

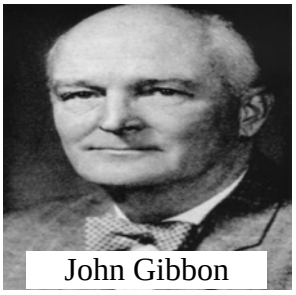
A single-dose cardioplegia may be an attractive option in more complex cardiac procedures as re-administration of cardioplegia can disturb the technical flow of the operation[5]

To our knowledge, no studies have directly compared the use of HTK and blood cardioplegia in a spectrum of complex cardiac surgical procedures. This somewhat surprising given the high number of procedures performed worldwide with this cardioplegic solution. As such, the purpose of this study was to assess the safety of the HTK solution when compared with our standard tepid blood cardioplegia coronary artery bypass graft operations.

Historical Review

Developments in a scientific field are studied historically, it becomes apparent that discoveries generally follow each other sequentially.

Frequently a new development or contribution opens new roads for further study and uncovers the unrealized problems that had not existed previously. Discoveries are frequently made in response to a need and the historic development of techniques in myocardial preservation is no exception. For example, there was no urge to concentrate on preserving myocardium prior to 1953, the year when John Gibbon first successfully closed an atrial septal defect in Philadelphia using cardiopulmonary bypass[6].


John Gibbon

The continuous activity worldwide led to rapid use of a variety of pumps and oxygenators as the era of open-heart surgery began. Surgeons soon learned that opening a chamber in a beating heart rapidly led to lethal air embolism, which could be avoided successfully only by stopping the heart. Another problem for the surgeon was poor visibility in a blood-filled operative field, making this wearisome operation even more difficult.

Both of these problems stimulated efforts to provide a quiet and dry field, which could best be achieved by arresting the heart and temporarily stopping circulation to the myocardium.

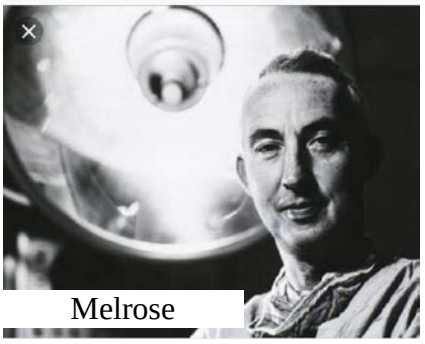
The obvious way to achieve that objective was to cross-clamp the aorta during the time required for the intracardiac repair[6].

In their attempt to master perfusion techniques and operative procedures, however, most surgeons lost sight of the cause of significant perioperative mortality and were generally unaware that inadequate intraoperative protection of the myocardium during the procedure was a significant factor in a patient's demise. Before the advent of pump oxygenators, some thoughtful investigators had begun to work with various means of inducing hypothermia to protect the myocardium.

Bigelow and associates in Canada[6,7], Lewis and colleagues in Chicago[6]. Swan and co-worker in Denver[6], and Brock and Ross in London[6], had already acquired significant clinical experience from 1950 to 1956 using total body hypothermia with transient circulatory interruption to perform cardiac operations. The concept of perfusion hypothermia stimulated Brown and colleagues in Durham NC[8] to develop a practical heat exchanger with

help from the Harrison Radiator Division of the General Motors Corporation. Such heat exchangers allowed rapid cooling and rewarming, and heat exchangers remain in use to this day. The profound hypothermic techniques of Drew and Anderson[9] in the United Kingdom also showed the importance of cold in protecting the heart as well as the body as a whole.

In England[10] Melrose and colleagues were among the first to realize the potential value of arresting the heart and restarting it at will, that value being both the prevention of air embolism and the production of a quiet operative field. Their legendary animal experiments led them to standardize potassium citrate as a method to achieve cardiac arrest. Unfortunately the high concentration of potassium produced focal areas of necrosis in the myocardium, and this finding served to slow progress in as regards of cardiac arrest infusions for 10 years. Lam's group in Detroit[11] used acetylcholine for short-lived elective cardiac arrest, but its effect proved to be too short to make it practical for regular use.


Melrose

In the mid-1950s, Sealy Young, and colleagues[12] in Durham were working with various drugs to prevent ventricular fibrillation. In the course of these studies, they developed a solution containing potassium, magnesium, and neostigmine, and used the solution for elective cardiac arrest along with hypothermia. Interestingly, they were the first to use the term "cardioplegia" in the course of these studies. Doctor Sealy recounts that they used this solution routinely until cardioplegia went out of fashion in the 1960s[6,12].

Being skeptical of potassium-containing solutions because of increasing reports that they caused myocardial damage, Shumway's group in California[13] began using topical hypothermia with simultaneous aortic cross clamping by circulating cold saline solution through the pericardial sac. This lavage technique proved to be so successful that they have used it ever since.


Denton Cooley

From 1966 to 1972, Denton Cooley and associates[14] in Houston experimented with simply cross-clamping the aorta at normo-thermic temperatures to produce arrest. To their fear, this caused ischaemic contractures and the term "stone heart" was coined. In most these cases of myocardial contractures, the patients had severe left ventricular

hypertrophy in the presence of far advanced aortic valve disease with congestive failure.

From 1961 until 1972, intensive studies were being carried out in German cardiac centers, by Holscher and associates, Bretschneider, Kirsch and colleagues, who worked with various chemical additives to cardioplegic solutions to provide safer cardiac arrest. The resulting multicomponent cardioplegic solution termed Bretschneider's solution, became the standard in many centers[6].

It is interesting that in 1970, while chemical cardioplegia and non-cardioplegic techniques were being tried Benson Roe and associates in San Francisco[15] were infusing cold Ringer's solution containing 20 mEq K/Liter to cool the myocardium to 15°C. They thought that this was a completely safe cardioplegic mixture, and Dr. Roe recounts that, at that time, it was becoming universally accepted[6].

Although there were some centers in which chemical cardioplegia was actively used, particularly in Europe there was little favorable use of this cardio-protective approach in the United States. However, credit for "second look" at potassium-


Paul A. Ebert

induced cardioplegia in the United States should go to Gay and Ebert[16]. In 1973 they undertook a series of experiments performed in New York with the initial idea that some types of chemical arresting agent, in conjunction with hypothermia, would allow rapid and safe elective arrest. This experiment resulted in a publication outlining functional, metabolic, and morphologic effects of potassium-induced cardioplegia. It was a slow process to attract surgeons back to potassium as a vehicle for achieving cardiac arrest, particularly at a time when continuous coronary perfusion and the use of ventricular fibrillation were popular. Gradually, however, the effectiveness and safety of cold potassium cardioplegia were realized, and its use continues today[6].

Hearse and colleagues[17,18] in 1976 described their development of an isolated rat heart perfusion preparation that allowed them to evaluate a multitude of cardioplegic formulations. Their studies using this preparation resulted in the development of the St. Thomas solution number-1, but what is more important, they contributed immensely to our knowledge of physiology and chemistry of myocardial cells subjected to ischemia, cardioplegia arrest, and subsequent reperfusion. Indeed, the basic principles of surgical myocardial protection had been established by this group, including the effects of and optimal levels of hypothermia, potassium, calcium, glucose and osmolality[6].

In 1978, Gerald Buckberg and his group in Los Angeles[6,19] reported reduced post ischaemic myocardial damage after modification of calcium, potassium, pH, and osmolality in a blood cardioplegic mixture. Their great studies showed the importance of blood as a cardioplegic vehicle along with the addition of glutamate, aspartate, and other additives for enrichment to energy-depleted myocardium represent major milestones in myocardial preservation.

More recently, these findings have been applied to resuscitation of cardiogenic shock after acute myocardial infarction. Along with Dr Vinten-Johansen, these investigators have evaluated different modifications of blood cardioplegia, different administration techniques, and control of the composition of blood cardioplegia with various additives to protect the myocardium during long periods of arrest. Their achievements in identifying surgical ischaemic-reperfusion injury, and their attempts to prevent and treat reperfusion injury based on the pathophysiologic mechanisms, are realy significant[6].

In contrast to the aforementioned investigations, it is of interest that Dr Akins, in Boston in 1984[20], had accumulated significant patient data using this technique of hypothermic fibrillatory arrest without cardioplegia, with very low mortality. His statistics are impressive and

exemplify an alternative method of myocardial protection.

Solarzano and colleagues[21], in Toronto gained the attention of cardiac surgeons in 1978, when they introduced the concept of retrograde coronary sinus perfusion as an adjunct to myocardial protection. Even though Gott and associates had described this technique in 1957, it had largely been unused until this group reported their experience[6] .

Menasche and colleagues[22] in Paris also reported a large experience using retrograde coronary sinus perfusion and showed its particular value in aortic valve operations. Advantages of the retrograde route in facilitating the operative procedure as well as in protecting the myocardium have attracted many cardiac surgeons, and the method has been in widespread use for the past 20 years[23].

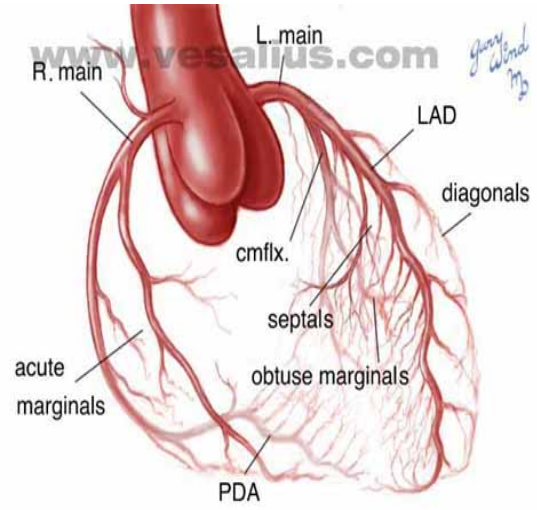
Nevertheless, research activity continues, and this approach may well emerge as a preferred one in certain clinical situations. It is apparent from this historical review that surgeons nowadays owe a great debt of gratitude to the aforementioned investigators and clinicians worldwide[24]. Their monumental contributions over the past 40 years have also demonstrated that numerous methods of myocardial protection can be used successfully in given situations. The controversies thus generated by different

cardioplegic solutions, vehicles, delivery modalities, and additives continued to stimulate further investigation and clinical trials. Application of such findings should allow safer operations and a higher recovery rate for patients around the world.

Anatomy of the Blood Supply of the Heart in Relation to Myocardial Protection

Coronary arteries:

A coronary artery is defined as any artery or arterial branch that supplies cardiac parenchyma i.e. any structure within the pericardial cavity, including the myocardium, the semilunar and atrio-ventricular valves, the great vessels and the visceral pericardium or epicardium.



The parietal pericardium should not be included, so the pericardial arteries should not be considered coronary arteries.

They are called coronary arteries because they encircle the heart in the manner of a crown. The word

"coronary" comes from the Latin word "corona" and Greek "koron" meaning crown.

Coronary artery system[25] consists of the left and right coronary arteries, which normally arise from Ostia located in the left and right sinuses of Valsalva, respectively. In about 50 percent of humans a "third coronary artery" "conus artery" arises from a separate ostium in the right sinus.

Additional smaller Ostia may be found in the right sinus, which give rise to multiple right ventricular branches. Up to five separate coronary Ostia have been described[26]