DOES THE USE OF MICROPLEGIA SIGNIFICANTLY IMPROVE OUTCOMES IN CONGENITAL HEART SURGERY?

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfillment of the requirements for the Degree of Master of Medicine in Cardiothoracic Surgery.

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DECLARATION

I, Sharmel Bhika, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in Cardiothoracic Surgery at the University of the Witwatersrand, Johannesburg. It has not been submitted for any degree or examination at this or any other University.

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Sharmel Bhika
04th April 2019

DEDICATION

To my family for their unconditional support.

To my mentor, Dr K. Naidoo, for his incredible surgical knowledge and clinical guidance.

To my supervisor, Prof G. Candy, for his selfless guidance and priceless research knowledge.

To the patients and their families, for being agreeable to partake in the study, without their permission my research would not be possible.

PRESENTATION FROM THE STUDY

Wits Faculty of Health Sciences Research Day & Postgraduate Expo:
Prize winner: Best student poster presentation in the category of
Clinical Sciences and Therapeutics for Health – September 2018

Bert Myburgh Research Forum 2018, Wits, faculty of Health Sciences, Department of Surgery:
Prize winner: 1st Prize - Best Student presentation.
3rd Prize – Best Oral presentation.

ABSTRACT

Introduction: In cardiac surgery requiring cardiopulmonary bypass myocardial protection is of paramount importance and cardioplegia aims to optimize the ischaemic period. The aim of this study is to compare short-term postoperative outcomes of elective congenital cardiac patients undergoing corrective cardiac surgery using two different cardioplegia solutions. A comparison of clinical and biochemical findings were assessed between two cardiac arresting agents, namely all-blood Microplegia and crystalloid St Thomas' Hospital II Cardioplegic solution.

Methods: Forty-two paediatric patients were prospectively randomised prior to corrective cardiac surgery to two techniques of myocardial protection; group I tepid (28°C) Microplegia (MPS) and group II cold (4°C) St Thomas' Hospital Cardioplegic Solution II (STS) crystalloid cardioplegia. Perioperative data was prospectively collected. Endpoints included serial measurements of Troponin I, haemoglobin/ haematocrit and lactate; time taken for spontaneous return to normal sinus rhythm; and need for postoperative inotropic support.

Results: Surgery resulted in increased immediate post-aortic unclamping myocardial lactate and troponin I levels in both groups, however, significantly lower lactate (2.36 ± 0.76 vs 4.19 ± 1.09 mmol/l, $p<0.0001$) and troponin I levels (8.18 ± 3.68 vs 22.88 ± 13.39 ng/ml, $p<0.0001$) were observed in Group I vs Group II. Improved myocardial contractility as measured by quicker spontaneous return to normal sinus rhythm and reduced perioperative requirement for inotropic support as well as a reduced need for blood transfusion was evident in Group I.

Conclusion: Microplegia showed significantly less myocardial injury, haemodilution and reduced need for inotropic support in the first 24 hours post congenital cardiac surgery.

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LIST OF ABBREVIATIONS

ABG	Arterial blood gas
AXC	Aortic crossclamp
CPB	Cardiopulmonary bypass
ECMO	Extra-corporeal Membrane Oxygenation
EF	Ejection fraction
MPS	Microplegia solution
STS	St Thomas' Hospital Cardioplegic Solution II
SRNSR	Spontaneous return to normal sinus rhythm
TEE	Trans-oesophageal echocardiography
Trop I / cTnI	Troponin I
SEM	Standard error of the mean

CHAPTER 1 - INTRODUCTION

Myocardial protection is critical during the surgical repair of almost all congenital heart surgery requiring cardiopulmonary bypass. The goal of myocardial protection is to minimize myocardial metabolism during ischaemia thus preserving myocardial function in the relaxed arrested heart, whilst facilitating cardiac repair in a bloodless surgical field. The basic principles of myocardial preservation include: rapid diastolic cardiac arrest, hypothermia to reduce myocardial oxygen consumption, and avoidance of myocardial oedema [1].

Innovations in techniques of myocardial preservation have allowed improvements in myocardial protection and subsequent outcomes following congenital heart surgery. Low cardiac output syndrome incurred as a result of perioperative myocardial injury is still the commonest cause of morbidity and mortality following cardiac surgery [2]. Currently, many options may be considered when choosing a myocardial preservation strategy. Arresting the heart to provide myocardial preservation from ischaemia and reperfusion can be achieved using a diversity of cardioplegic solutions. Potassium (in concentrations ranging from 10 to 40mmol/L) is the most frequently used depolarizing agent to induce cardiac arrest. Cardioplegia can be divided into blood and crystalloid cardioplegia with a host of other electrolytes and pharmacological agents added at various concentrations.

Crystalloid versus Blood Cardioplegia

The advantages of crystalloid cardioplegia are the immediate cardiac arrest which ensures minimal depletion of cardiac energy reserves, and since crystalloids have no cellular elements of blood, they distribute rapidly to ensure uniform cooling. Additionally, crystalloid cardioplegia is cost effective, readily available and easily administered. The solutions are supplemented with buffering agents such as bicarbonate.

Theoretically blood cardioplegia confers improved oxygen carrying capacity and a superior buffering ability over crystalloid cardioplegia. Despite the added potassium for the induction and maintenance of cardiac arrest, blood cardioplegia shares a similar electrolyte and osmotic profile to normal coronary blood flow perfusing the myocardium. Furthermore, oxidative damage to the heart may be attenuated by the oxygen free radical scavenging properties of blood.

A cornerstone of cardiac surgical practice has been cold crystalloid potassium-based

cardioplegia which was introduced in the early 1950's. This early cardioplegic technique to initiate and maintain cardiac arrest during heart surgery was soon followed by the use of intermittent cold blood cardioplegia [3]. Subsequently, blood cardioplegia has become the most popular choice amongst surgeons in the United States of America (USA) [4] and is being used increasingly in both Europe and the United Kingdom. All-blood, potassium-enriched cardioplegia, called microplegia or miniplegia, was originally described by Menasche *et al* in 1996 as a safe and effective alternative to blood or crystalloid cardioplegia [5]. Conventionally, blood cardioplegia is composed of a blood:crystalloid mixture (commonly in the ratio of 4:1 or 8:1), additives, and a potassium-rich solution. Microplegia is reconstituted by combining small volumes of concentrated additives (66:1) to blood from the cardiopulmonary bypass circuit, including a potassium-rich solution, thereby allowing a large volume of blood cardioplegia to be delivered with relatively minimal amounts of crystalloid.

Changes in the myocardial metabolic status occur during the vulnerable ischaemic period and upon reperfusion following removal of the aortic cross-clamp. It is this metabolic status that largely determines the functional recovery of the myocardium [6]. Myocardial tissue acidosis resulting in lactate production is one of the most sensitive markers of inadequate myocardial preservation [7]. It is well established that the persistence of peripheral lactate release during cardiac reperfusion is an independent predictor of postoperative low cardiac output syndrome [8]. Further techniques that have been validated in assessing the degree of myocardial injury are measurements of specific metabolites or biochemical markers, such as cardiac troponin and serum creatine kinase MB isoenzyme (CK-MB) [9-11]. This is done by direct catheter sampling from the coronary sinus (venous drainage of the myocardium) post removal of the aortic cross-clamp. This evaluation of myocardial metabolism during cardiac surgery, therefore allows the investigator to quantify the degree of physiologic damage. Inadequate myocardial protection is also responsible for elevation of serum troponin I [7,11,12]. Troponin I has been recognised to be a highly sensitive and specific marker of myocardial injury, and thereby reflects the adequacy of intraoperative myocardial protection. Furthermore, postoperative troponin I prognosticates long-term cardiovascular events at follow-up [13,14]. Both lactate and troponin I release, can therefore explain the efficacy of myocardial preservation [7].

The goals of myocardial protection during cardiac surgery are not only to facilitate the procedure by providing a motionless (asystolic heart) bloodless field, thereby facilitating the precision of the procedure, but also to avoid iatrogenic injury induced by cardiopulmonary bypass itself or by surgically imposed ischaemia. In addition, myocardial protective strategies

are geared to preventing reperfusion injury and myocardial oedema which manifests upon the ultimate release of the aortic crossclamp.

In our practice we observed upon release of the aortic crossclamp and reperfusion of the ischaemic heart, a quicker recovery of myocardial activity and decreased requirement for post-operative inotropic support following Microplegia. This observation initiated the current investigation to formally compare these two cardioplegic solutions used routinely in our unit.

The aim of this randomised study was to determine short-term patient outcomes using two different compositions of cardioplegia used in our institution during congenital cardiac surgery. The study was to answer the question: Does myocardial protection with microplegia in paediatric congenital open heart surgery significantly reduce the perioperative myocardial insult and improve the postoperative haemodynamic (need for inotropic support) status. The objectives were to measure myocardial ischaemic injury as reflected by time taken for spontaneous return to normal sinus rhythm and the need for postoperative inotropic support and the need for postoperative blood transfusion as reflected by postoperative haemoglobin measurements.

CHAPTER 2 – MATERIALS / METHODS

Patients and Study design

The study was approved by the Human Research Ethics Committee (Medical) of the University of Witwatersrand, Johannesburg, South Africa, Protocol No.: **M160384;** dated**:** 18/05/2016. Permission to conduct the study was obtained from the Department of Cardiothoracic Surgery and the hospital authorities at the Charlotte Maxeke Johannesburg Academic Hospital in Johannesburg, South Africa. The parents / legal guardians of the patients for surgery were given a written document (Appendix C) explaining the aims and risks versus benefits of the study concomitantly with the preoperative counseling concerning the operative procedure. This consenting document was dated and signed by the surgeon and parent.

***Patients*:** Patients referred from surrounding cardiology clinics for elective corrective congenital heart surgery, participated in the study.

Inclusion criteria: Patients of either gender and of body weight 5-20kg, with one of the three of the most commonly seen congenital defects of varying complexity, lesions of either Tetralogy of Fallot, ventricular septal defect or atrioventricular septal defects were included.

Exclusion criteria: Patients with interstitial lung disease or with poor preoperative ventricular function EF < 50%, inherent bleeding disorders (eg Di George Syndrome, haemophiliacs, Von Willebrands disease), more than one cardiopulmonary bypass run, or failure to separate from cardiopulmonary bypass - ECMO, preoperative liver disease and redo surgery were excluded from the study. Neonates were also excluded from the study.

Study design:

During 2016, a pilot study of forty-two elective paediatric congenital cardiac patients were enrolled in a single-centre randomised study comparing outcomes using two different cardioplegia solutions, each administered at different temperatures. The two randomised groups of cardioplegia were as follows:

1. Microplegia (MPS); n=21, delivered to the aortic root with the Quest MPS system (Integrated Myocardial Protection System-2, Quest Medical Inc; Allen TX, US). Ratio blood to crystalloid > 60:1. Temperature: tepid, 28°C
2. St Thomas' Hospital Cardioplegic Solution II (STS); n=21, Adcock Ingram Critical Care (Pty) Ltd; Johannesburg. Crystalloid cardioplegia. Temperature: cold, 4°C.

The cardioplegia solutions are both used in our current practice in congenital cardiac surgery at Charlotte Maxeke Johannesburg Academic hospital. See Table 2.1.

Computer randomisation generated a list with the patient assignment to one of the two cardioplegia solutions (ie solution 1 or solution 2). Forty-two opaque envelopes were used, arranged in the computer generated random sequence, each containing a note indicating either solution 1 or solution 2. The sealed, non-transparent envelopes were labelled numerically according to the randomly generated sequence specified by the computer program. This was done by an unbiased person who had no involvement or interest in the outcome of the study. On the morning of surgery of the patient enrolled in the study, the next numerical opaque envelope was opened by the perfusionist preparing the cardiopulmonary bypass machine and the cardioplegia solution for the operation and in this way the patient was assigned that solution for the procedure thereby ensuring allocation concealment. One perfusion team comprised four members and only one consultant surgeon and one registrar (the investigator) operated on these cases to keep the operating technique constant. The surgeons were blinded to the cardioplegia solution used for the operation until administration of the initial dose after the aorta was cross-clamped. At this point, the different colour of the Microplegia (sanguinous) and crystalloid (asanguinous) solutions would identify the solution being used. With the exception of the Cardiopulmonary Bypass perfusion technicians, primary and registrar surgeon, all other staff (anaesthetists, biochemists, cardiologists, nursing staff, intensivists) dealing with the biological sampling, perioperative care and/or collection and analysis of data were blinded as to the randomisation assignment of the patient. Perioperative data was collected on a study datasheet (Appendix D) by a nonbiased, blinded member of the surgical team.

42 patients with congenital heart defects randomised to two different cardioplegic solutions used during corrective cardiac surgery during 2016 in a single centre study .

Inclusion criteria:

- Body weight: 5-20kg
- Congenital defects either:
  - Ventricular septal defect
  - Atrio-ventricular septal defect
  - Tetralogy of Fallot

Exclusion criteria:

- Neonates
- Interstitial lung disease
- LV dysfunction (EF < 50%)
- Inherent bleeding disorders / liver disease.
- More than 1 CPB run / failure to separate from CPB / ECMO.
- Redo surgery.

St Thomas' Cardioplegic solution (n=21)

Microplegia (n=21)

Figure 2.1. Study design.

Table 2.1. Preparation/Composition of cardioplegia solutions being compared.

		Induction dosage	**Maintenance dosage**
Administered volume	**Solution composition**	**30ml/kg bolus**	**10ml/kg given at 20min intervals**
St Thomas Solution (n=21) Temperature: 4°C			
Composition	KCl (mmol/L)	16	16
	$NaHCO_3$ (mmol/L)	10	10
	MgCl (mmol/L)	16	16
	$CaCl_2$ (mmol/L)	1,2	1,2
Microplegia (n=21) Temperature: 28°C			
Composition	KCl (mEq/L)	30	15
Additives (50ml)	(ml/L)	15	7
	$MgSO_4$	5g/10ml	5g/10ml
	Lidocaine 2%	50mg/5ml	50mg/5ml
Blood priming solution: 35ml			

Operative Technique

Both anaesthesia and surgery employed routine standard procedures to correct these defects in all cases. Surgery was performed through median sternotomy. The standard management of cardiopulmonary bypass (CPB) was used - Aorto bi-caval cannulation, systemic cooling, snaring of the cavae, aortic crossclamping followed by antegrade administration of cardioplegia. The cardiopulmonary bypass (CPB) circuit included a Medtronic phosphorylcholine-coated paediatric/infant custom pack tubing set, Terumo roller pump and a hollow fiber membrane, coated oxygenator, which incorporates a 40 micron filter. Heparin was administered at a dose of 300 IU/kg to attain a target activated clotting time of 400 seconds or above prior to initiating CPB. For this study the extracorporeal circuit was always primed with a fresh frozen plasma to leucodepleted homologous packed red cell solution reconstituted in a 1:1 ratio and 100 mg/kg IU of heparin. A non-pulsatile CPB flow was established at 2.4 L/min/m^2. Patients were systemically cooled to mild-moderate hypothermia (28-32 °C) at the time of cardioplegic arrest.

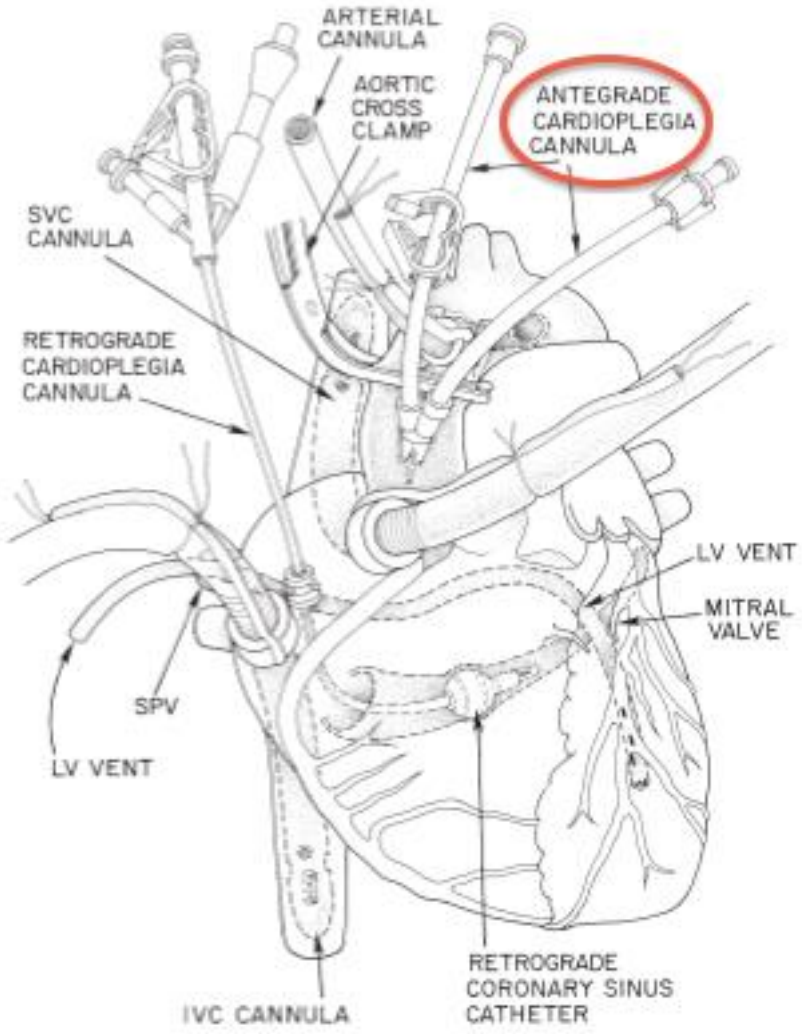

Figure 2.2. Antegrade administration route of cardioplegia solutions. Adapted from: Liao K. Surgical Treatment of Coronary Artery Disease. Ch. 22. In: Coronary Heart Disease. ed by Vlodaver Z., Wilson R., Garry D. Springer, Boston, MA, 2012 pp.405-422

Cardiac arrest was accomplished by administration of the hyperkalaemic cardioplegia solutions in an antegrade fashion via a cannula placed in the ascending aorta, proximal to both the aortic crossclamp and the aortic arterial cannula (Figure 2.2). The cardioplegia was delivered at a bolus arresting dose of 30 ml/kg and maintenance doses of 10 ml/kg given repeatedly at 20 minute intervals at an average aortic root pressure of 80-100 mmHg. The volume of the doses for both cardioplegia solutions being compared were the same, only the compositions and temperatures differed. Topical ice slush was applied around the heart repeatedly when maintenance doses of cardioplegia were given throughout the procedure.

Study End Points

End points included:

1. Serial (x5) biochemical measurements: Lactate + Troponin I + Haemoglobin level blood sampling:
    - In theatre preoperatively (T0);
    - In theatre 10 minutes post removal of aortic crossclamp (T1);
    - 6 hours post crossclamp removal (T2);
    - 12 hours post crossclamp removal (T3);
    - 24 hours post aortic unclamping (T4).

    The lactate and haemoglobin levels were measured from arterial blood gases and the troponin I levels were measured with iStat (Point of care) cartridges.
2. The time of intraoperative spontaneous recovery to normal sinus rhythm (SRNSR) after unclamping of the aorta. The perfusionists had timers running from the time of unclamping and observations for sinus rhythm were made at 60 seconds; 120 seconds; 180 seconds; 5 and 8 minutes.

3. The requirement for inotropic support was categorized as shown in Table 2.2.

Table 2.2. Scale of the need for inotropic support.

	INOTROPIC INTRAVENOUS INFUSIONS
NONE	0
LOW	Dobutamine ≤ 2,5 ug/kg/min
MEDIUM	Dobutamine > 2,5 ug/kg/min ≤ 5 ug/kg/min
HIGH	Dobutamine > 5 ug/kg/min and/or addition of adrenaline and/or phenylephrine.

The attending anaesthetists practice is to introduce inotropic support routinely post unclamping of the aorta, irrespective of whether or not the patient requires additional support of cardiac contractility. The study therefore assessed the need for inotropic support as follows:

- On admission to ICU (T1)
- At 10am the following morning (T2).

Coronary Sinus Sampling

Coronary sinus blood (venous drainage of the myocardium) sampling was done directly through the right atrium (the right atrium was routinely opened during the corrective procedures in this trial). This venous blood was aspirated 10 minutes after the aorta was unclamped, allowing the heart to eject and perfuse the coronaries with oxygenated blood while flushing residual cardioplegia from the coronary system. Aspiration was done with an Argyle Polyurethane Umbilical catheter size 5Fr and this sample specimen was analysed for lactate and troponin I levels which should reflect metabolic parameters for myocardial injury during the reperfusion state.

Data Handling and Statistical Comparison

Data was recorded in EXCEL (Microsoft) and analysed using Statistica V8. Data has been reported in tables and graphs as frequency (n) and as means (±standard deviation or standard error of the mean) or median and range. Frequencies in each group were compared with a Chi-squared test with a Fischer Exact test if $n<5$. Comparison between the groups (Microplegia vs St Thomas' Hospital Cardioplegic solution II) was made using a t-test if the data was normally distributed. Statistical differences between groups where the data was not normally distributed used a Mann Whitney test. Serial measurements were compared using repeated measures ANOVA. A p-value of <0.05 was regarded as being statistically significant.

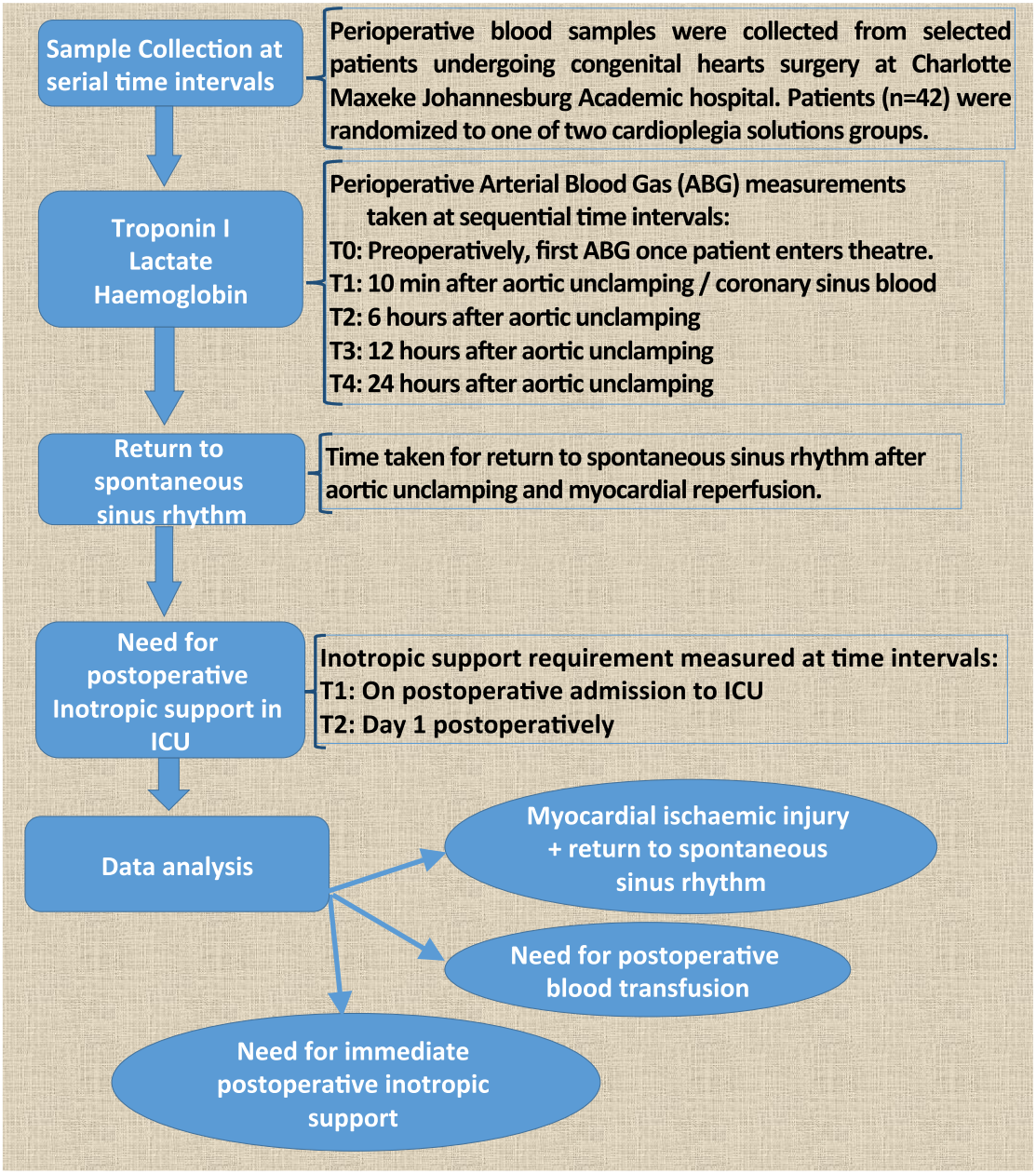

Figure 2.3. Methodology for the prospective study comparing STS to MPS in congenital cardiac surgery.

CHAPTER 3 – RESULTS

Patients

Table 3.1 shows the demographic and perioperative variables. No significant differences were observed between any of the variables. Post-randomisation, no patient was excluded from the study. All patients enrolled completed the study and there were no deaths. None of the patients had post-operative renal failure or a severe cardiac event requiring resuscitation. None of the patients had residual lesions detected after the initial repair on trans-oesophageal echocardiography in either group, and no patient required cardiopulmonary bypass to be re-instituted intraoperatively.

Biochemical results

The troponin I levels collected at several sampling times are presented in Figure 3.1. The preoperative levels were not elevated in either of the groups. Surgery was associated with significant perioperative troponin leak in both groups ($p<0.0001$ for both groups) which is reflected by increased T1 values. However, coronary sinus sampling (T1) showed significantly lower mean troponin I (±SD) values with MPS compared to STS (8.18 ± 3.68 vs 22.88 ± 13.39 ng/ml, $p<0,0001$; Fig. 3.1.). The levels remained significantly lower throughout the 24 hour postoperative time-course with a gradual reduction in troponin levels seen in both groups. Troponin I level was elevated 10 minutes (T1) and at the 6 hour measurement (T2) post aortic unclamping for both groups (Fig. 3.1.). The troponin I level for the STS group was significantly higher (highest reading for one patient was >50 ng/ml) than the MPS group (highest reading for one patient was 15.3 ng/ml) at these times ($p<0.0001$). T3 and T4 show gradual decreases in these serial troponin measurements which were not significantly different from T1 and T2.

As shown in Fig 3.2, surgery resulted in increased myocardial lactate levels (T1), as measured immediately post aortic crossclamp removal, in both groups. Furthermore, significant differences were shown in higher mean lactate levels (±SD) for the STS group (2.36 ± 0.76 vs 4.19 ± 1.09 mmol/l, $p<0.0001$). This significant difference continued during the postoperative (at 24 hours, T4) period (1.07 ± 0.56 vs 1.89 ± 0.54 mmol/l, $p<0.0001$; Fig. 3.2.).

Table 3.1 – Patient demographic and perioperative variables. Data as mean±STD and as median [range] for skewed data.

Variable	**All (n=42)**	**Group 1 Tepid MPS (n=21)**	**Group 2 Cold STS (n=21)**	**Statistical difference between groups p value**
Weight (kg)	10.1±4.0	10.0±4.0	10.1±4.0	*0.93*
Gender (male/female)	21/21 (50% female)	10/11	11/10	*0.76*
Body surface area (m^2)	0.50±0.16	0.48±0.15	0.51±0.16	*0.56*
Aortic crossclamp time (min)	72.9±46.0 60 [19-229]	69.0±44.4 57 [31-229]	76.8±48.2 65 [19-228]	*0.41*
CPB time (min)	118.6±55.1 100.5 [48.0-316]	115.3±49.4 107 [66-292]	121.9±61.4 100 [48-316]	*0.89*
Volume of cardioplegia (ml)	673±512 550 [165-3300]	613±335 520 [165 – 1790]	732±641 600 [270-3300]	0.82
Diagnosis: 1.Tetralogy of Fallot (n) 2.Ventricular septal defect (n) 3.Atrioventricular septal defect (n)	 7 31 4	 2 18 1	 5 13 3	0.21

Abbreviations: CPB - Cardiopulmonary bypass; MPS – Microplegia; STS - St Thomas' Hospital Cardioplegic Solution II

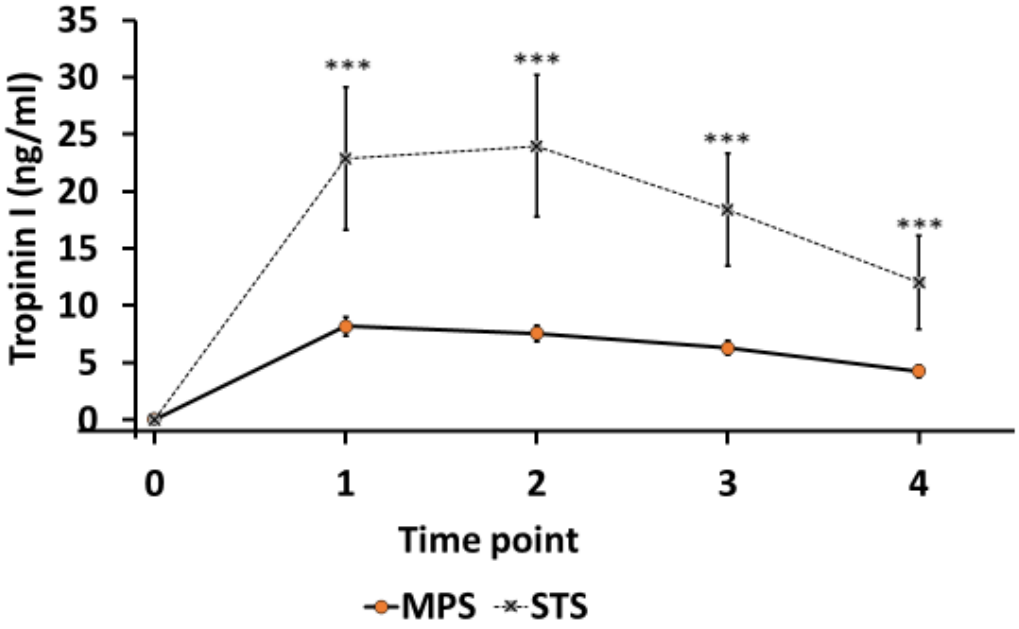

Figure 3.1. Time course of troponin I in the peri- and post-operative repair of congenital heart defects. Differences ($p<0.0001$) are between patients randomised to MPS (solid line) or STS (-------). Times T0: in theatre preoperatively (T0); T1: in theatre 10 minutes post removal of aortic crossclamp; T2: 6 hours post crossclamp removal; T3: 12 hours post crossclamp removal; T4: 24 hours post aortic unclamping. Data as means ±SEM.

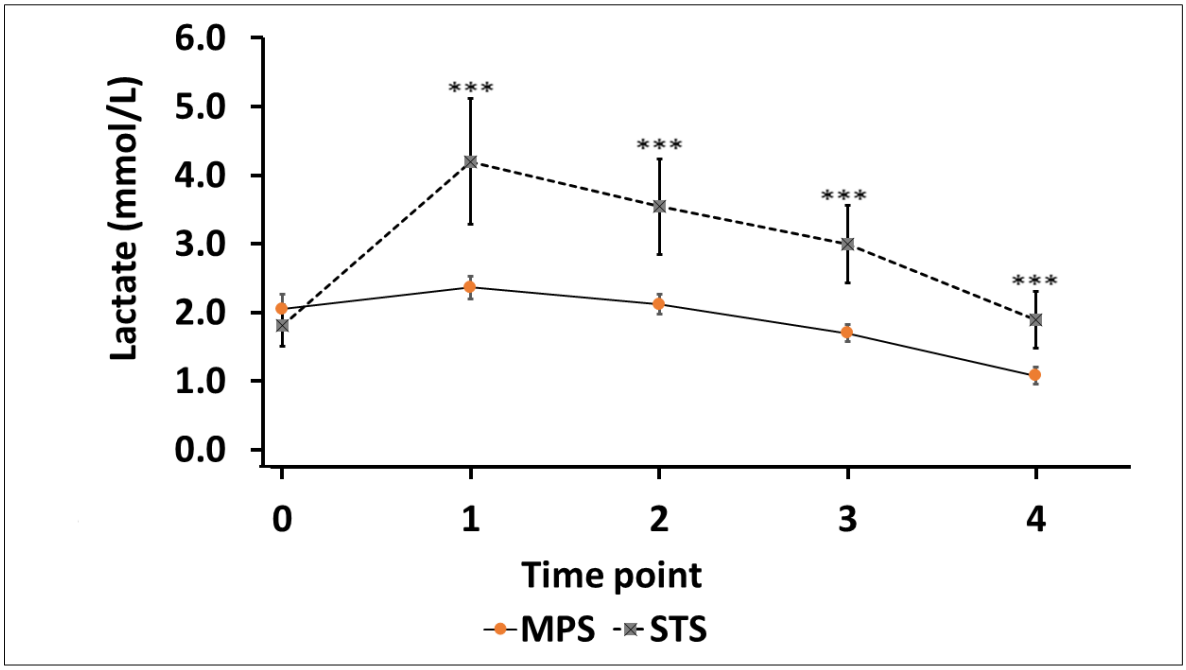

Figure 3.2. Time course of lactate in the peri- and post-operative repair of congenital heart defects. Differences ($p<0.0001$) are between patients randomized to MPS (solid line) or STS (-------). Times as given in Fig 3.1.

Preoperative haemoglobin levels readings (T0) were not significantly different (Fig. 3.3.) between the two treatment groups. Haemoglobin levels dropped significantly for both groups between preoperative haemoglobin levels and T1 readings (specimens taken 10 minutes post aortic unclamping) and in the STS group showed significantly lower haemoglobin values (9.6 ± 1.0 vs 8.2 ± 0.06 g/dl, $p<0.0001$) suggesting possible haemodilution in this group and need for blood transfusion.

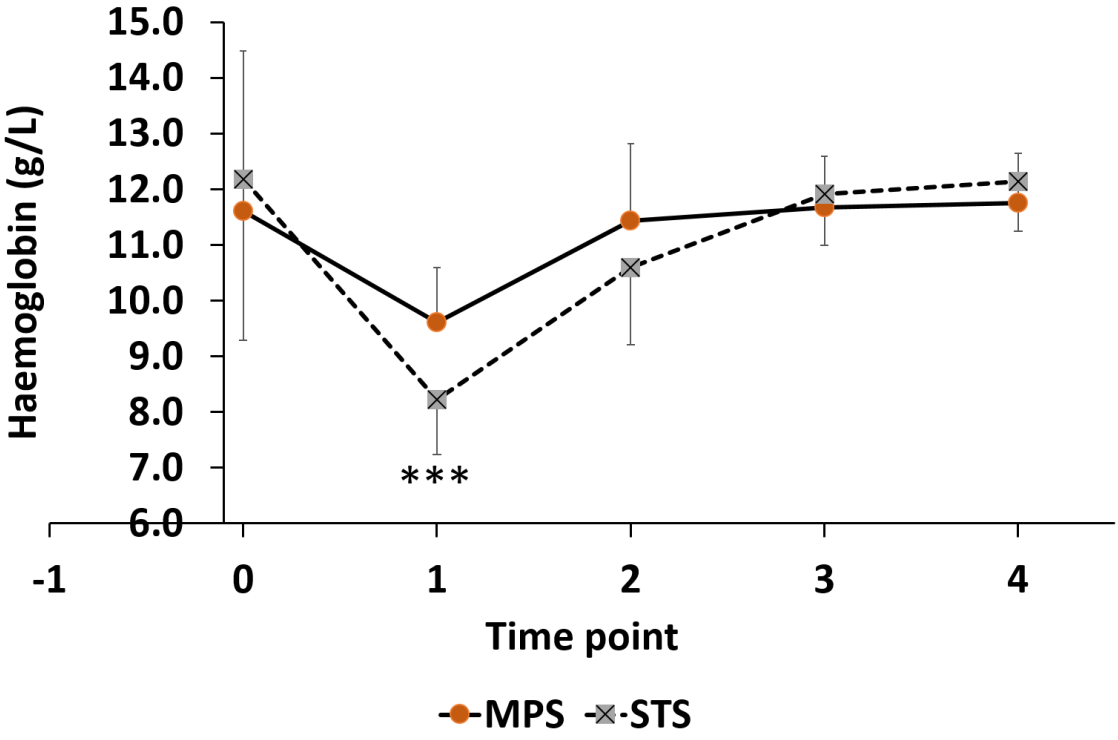

Figure 3.3. Time course of haemoglobin in the peri- and post-operative repair of congenital heart defects. Differences ($p<0.0001$) are between patients randomised to MPS (solid line) or STS (-------). Times as given in Fig 3.1.

Spontaneous return to normal sinus rhythm

Following reperfusion, the time of spontaneous return to normal sinus rhythm (SRNSR) in the MPS group was significantly quicker than those of the STS group (1.14 ± 0.35 vs 3.33 ± 0.57 seconds, p <0.0001; Fig. 3.4.). SRNSR in < 60 seconds occurred in 85% of the MPS group vs 0% of the STS group for this time interval. These results suggesting that the immediate myocardial protective effect of MPS solution is superior to that of St. Thomas crystalloid cardioplegia. Only 1 out of the 42 patients in the study was paced until day 1 postoperatively, this patient was in the STS group which contributed no statistical difference in the comparison (p=0.8).

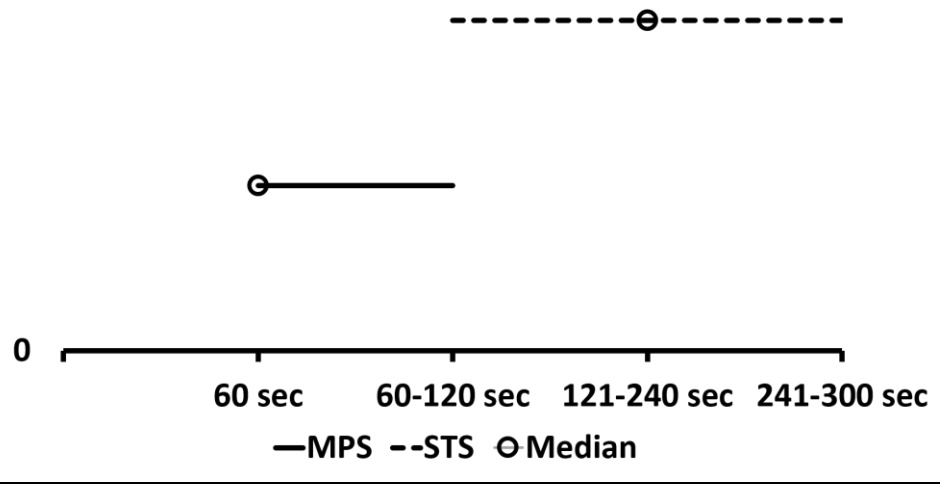

Figure 3.4. Time taken to achieve sinus rhythm following cardioplegia with MPS compared to STS solution. Median values shown as circles and the lines as the range.

Haemodynamic Results

The need for inotropic support for the first postoperative night proved to be more prevalent in the STS group (p=0.0022), with the majority of cases in the STS group showing the need for inotropic support > Dobutamine 2.5 µg/kg/min even on day 1 post op review (T2). The trend for both groups demonstrated a reduced need in inotropic support from T1 to T2.

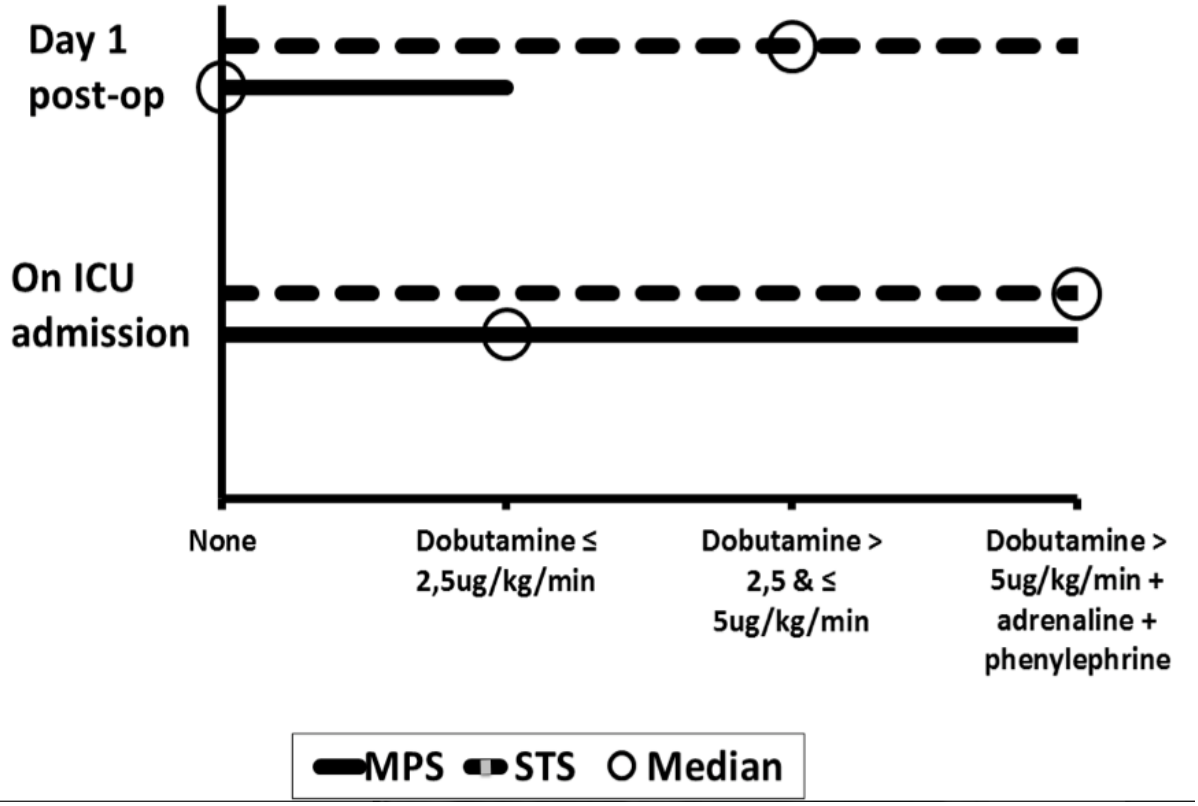

Figure 3.5. Requirement for inotropic support for the first postoperative night (T1) and day 1 post-op review (T2) following cardioplegia with MPS and STS solutions (see text for further detail). Data as median and range.

CHAPTER 4 – DISCUSSION

Currently, extrapolations from findings of comparative studies in myocardial protective strategies using different cardioplegia solutions in adult and animal population groups have erroneously been ascribed to the paediatric population. However critical differences in subcellular structural and functional organization as well as metabolic substrate utilization differentiate the adult from the paediatric models. Even today, in congenital heart surgery requiring CPB, the single most common cause of postoperative morbidity and mortality is perioperative myocardial injury [2]. To our knowledge there are no prospective clinical studies published comparing the efficacy of traditional crystalloid cardioplegia to all-blood Microplegia in paediatric congenital cardiac surgery.

In neonates, the enhanced tolerance of the immature myocardium to hypoxia is partially explained by the biochemical differences in energy production between immature and mature myocardium. As well as long chain fatty acids (predominant source), the adult heart also uses lipids, carbohydrates and amino acids to fuel metabolism, in contrast, the foetal heart relies more on anaerobic metabolism. At present, the bulk of evidence available points to the neonatal myocardium being considerably more resistant to ischaemia compared to the mature myocardium [2,15]. Neonatal patients were therefore excluded in this study.

Most European centers use crystalloid cardioplegia, while most North American surgeons use blood cardioplegia to provide additional oxygen substrate. In a North American multi-institutional survey, 86% of surgeons used blood-based cardioplegia (of which 5% used Microplegia) as their preferred cardioplegia regime in paediatric cardiac surgery, whilst only 14% of surgeons in northern USA used crystalloid cardioplegia solutions [16]. Microplegia relies on a precision pump to administer specific volumes of additives within the cardioplegia solution while minimizing the quantity of crystalloid delivered to the patient. Administration of less crystalloid should avoid volume overload and minimize haemodilution, which may lead to decreased blood product use. Additionally, the increased number of red blood cells, thus haemoglobin molecules present in MPS, should improve oxygen delivery. The combination of lower crystalloid volume and improved oxygen delivery should, in theory, lead to reduced myocardial oedema and more rapid and improved ventricular function [5]. There is clear evidence that myocardial oedema negatively impacts both systolic and diastolic

ventricular function. A previous study in Yorkshire pigs showed that the detrimental consequences of haemodilution, volume overload and blood transfusions may also be avoided with Microplegia [17]. Starr et al. [18] further showed that a lower osmolarity cardioplegia solution is associated with higher myocardial water content and impaired diastolic filling. One goal of any myocardial protection strategy should be to minimize myocardial oedema. Although interstitial myocardial water content was not measured in this study, the detrimental effects of myocardial oedema, mainly delayed intraoperative spontaneous return to normal sinus rhythm and an increased need for postoperative inotropic support showed significantly superior results in the MPS group. Intraoperative spontaneous return to normal sinus rhythm is typically considered an indicator of good myocardial preservation. Additionally, low cardiac output syndrome is frequent during the first hours post cardiac surgery, however, this occurrence reflects a relatively delayed degree of myocardial recovery. The minimization of the ischaemic insult resulted in improved 24-hour postoperative ventricular function as evidenced by the significantly lower inotropic requirement and lactate measurements in the MPS group.

Postoperative lactate levels, particularly the measurement taken ten minutes after removing the aortic crossclamp, correlates with ischaemic myocardial acidosis that occurs in the arrested heart. The significantly elevated lactate levels of the STS group in comparison with the MPS group shows clear evidence of the resulting superior myocardial preservation of the latter.

The significant difference in haemoglobin levels at T1 (10 minutes post aortic crossclamp removal) and T2 (6 hours post crossclamp removal) demonstrates that the STS group of patients likely underwent more significant perioperative haemodilution as compared with the MPS group. T3 and T4 haemoglobin levels of STS were higher than MPS and this could have either been due to excessive blood transfusion or over-diuresis of the STS group. Consequently, there may be a tendency for increased blood transfusion in the STS group owing to the immediate postoperative reduced haemoglobin levels.

Cardiac troponin I, a regulatory protein unique to myocardium, reflects the quality of perioperative myocardial preservation [19]. Mildly elevated perioperative troponin I levels are of no prognostic significance and are expected owing to intraoperative cardiac manipulation and surgical trauma to cardiac tissue. Onorati et al [20] following sampling from the coronary sinus during reperfusion, demonstrated the predictive role of troponin I on hospital outcome as well as postoperative left ventricular recovery post adult coronary

surgery. Even though this study was on patients with unstable angina, our results reflect similar findings of significantly reduced perioperative myocardial damage in patients subjected to MPS.

Hypothermia during cardiopulmonary bypass exerts its protective effect by multiple mechanisms; the most obvious mechanism being the reduction of both metabolic rate and oxygen consumption [21]. The optimal cardioplegia temperature for myocardial protection is controversial but has been previously studied. It is well established, however that crystalloid cardioplegia should be used at temperatures lower than the tepid (27- 29°C) temperature used in some studies which show inferior results. In canine models Magovern et al. [22] demonstrated equivocal outcomes in myocardial protection regardless of whether blood cardioplegia at 20°C or crystalloid cardioplegia at 4°C was administered, however, reduced recovery was observed with crystalloid at 20°C versus blood at 4°C. Comparisons between warm blood cardioplegia (37°C) against tepid blood cardioplegia show no clear advantange of the one over the other. Buckberg and colleague's results [23] suggested that there are very slight differences in oxygen consumption when the temperature is reduced from 37°C to 29°C. The relationship, however, between myocardial wall tension and myocardial oxygen consumption (MvO_2) in the context of hypothermia is considered to be optimal at 28°C [23]. Hayashida et al. [24] determined the ideal blood cardioplegia temperature and concluded that antegrade cardioplegia administered at a tepid (29°C) temperature was associated with reduced myocardial injury resulting in optimal myocardial preservation. Similarly other studies have confirmed the benefit of tepid blood cardioplegia in comparison with cold blood cardioplegia, with regard to reduced myocardial damage, a quicker recovery of left ventricular function and even improved clinical outcomes [24-28]. In our study, the MPS group which showed results of superior myocardial preservation may have confirmed or even optimized the benefits of MPS when used at a tepid temperature.

Patients with congenital heart disease often have to adapt with the effects of volume overload, cyanosis or ventricular hypertrophy. Once subjected to cardiac surgery using cardiopulmonary bypass and ischaemic cardiac arrest, these pathologies become more concerning and thus, an optimal myocardial protective strategy would need to be chosen with consideration. The conclusion that the subendocardium [29] and hypertrophied ventricles [12] may be more predisposed to ischemic injury implies that the imbalance between myocellular energy and oxygen supply relative to consumption is the predominant mechanism of post-ischaemic myocardial dysfunction. It is, therefore, imperative that especially these patients

would benefit from any refinements in myocardial preservation regarding recovery of ventricular contractility, optimal cardioplegic temperature and prevention of ischaemic injury.

Study limitations

The time of assessment and data analysis only reflects outcomes of short-term myocardial recovery. The trend of myocardial recovery after 24 hours was seen in all patients subjected to both cardioplegic solutions. A longer term analysis is required to determine conclusively if any cardioplegia solution really shows significant benefit.

The fact that two different temperatures of cardioplegia were used, may have introduced a confounding variable. It is difficult to determine if temperature or cardioplegia solution beneficially affected the study end-points.

It remains to be determined if the reduced haemodilution with MPS further translates into the reduction of myocardial oedema on coronary reperfusion.

Peri-operative echocardiography would more accurately determine left and right ventricular systolic and diastolic function.

Although blinded to the study groups, the different anaesthesiology teams varied according to their practice preference which may have introduced variation in the administration of fluid management, transfusion triggers observed and thresholds for introducing and/or escalating inotropes. These may have introduced confounding variables into the study.

In summary, all-blood MPS resulting in the administration of less crystalloid, may have decreased myocardial oedema to permit more rapid recovery of ventricular function in surgery to correct congenital heart defects in paediatric patients. The detrimental consequences of haemodilution, volume overload and potential blood transfusions may also be avoided. The key findings indicate that serum troponin, lactate and haemoglobin measurements intraoperatively, 6 hours, 12 hours and 24 hours post aortic crossclamp removal in the MPS sample group were all significantly lower than crystalloid St Thomas Hospital's Cardioplegic Solution II. Furthermore, the MPS group required less inotropic support and myocardial recovery to spontaneous normal sinus rhythm was significantly quicker. This comparative study has clearly shown significant short-term (over 24 hours) clinical and biochemical superior outcomes in our MPS group. These convincing results has

directed these investigating surgeons towards the routine use of Microplegia in their cardioplegic myocardial protection strategy in paediatric cardiac surgery.

CHAPTER 5 – REFERENCES

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CHAPTER 6 – MANUSCRIPT SUBMITTED TO EUROPEAN JOURNAL OF CARDIOTHORACIC SURGERY FOR REVIEW

APPENDIX A – APPROVED RESEARCH PROTOCOL

APPENDIX B - ETHICS CLEARANCE FOR RESEARCH PROTOCOL

APPENDIX C – INFORMED CONSENT DOCUMENT

APPENDIX D – STUDY DATASHEET

APPENDIX E – PLAGIARISM CLEARANCE

APPENDIX F – DECLARATION FOR SUBMISSION OF PUBLISHED ARTICLE