
# Impact of peak intraoperative lactate levels on post-operative outcomes in congenital cardiac surgery

**FRANS JOHANNES PRETORIUS**

Dissertation submitted in the fulfilment of the requirements of the degree

**MASTER OF HEALTH SCIENCES**

**CLINICAL TECHNOLOGY**

Department of Health Sciences
Faculty of Health and Environmental Sciences

Central University of Technology
Bloemfontein, South Africa

**Supervisor:** Dr L Botes, D-Tech, (CUT)
**Co-Supervisors:** Prof FE Smit, PhD, Assoc. FCS (Cardiothoracic Surgery SA), MBChB MMed (UFS)

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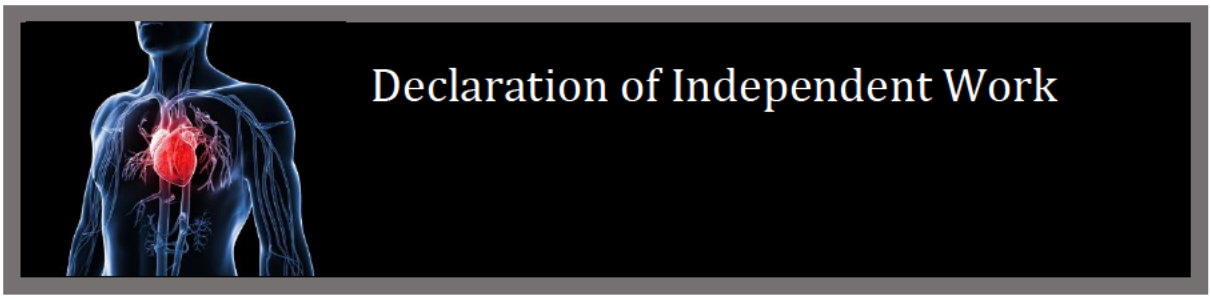


I, Frans J Pretorius, do hereby declare that this research project submitted to the Central University of Technology for the degree **MASTERS OF HEALTH SCIENCES IN CLINICAL TECHNOLOGY** is my own independent work that has not been submitted to any institution by me or any other person in fulfilment of the requirements for the attainment of any qualification.

**Signature** **Date**

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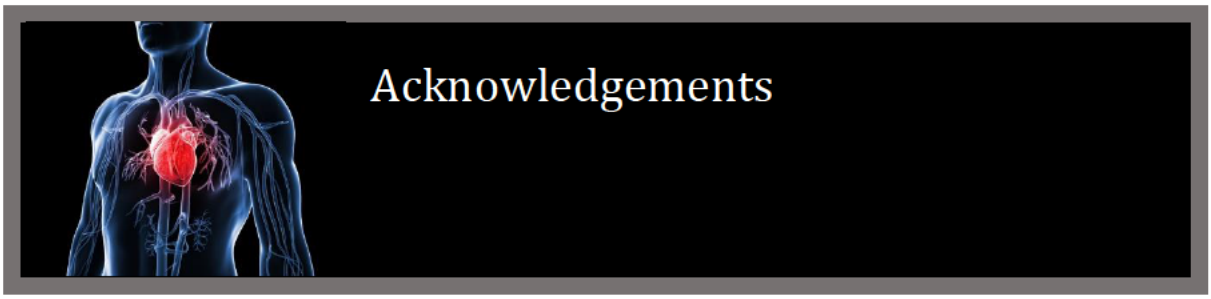

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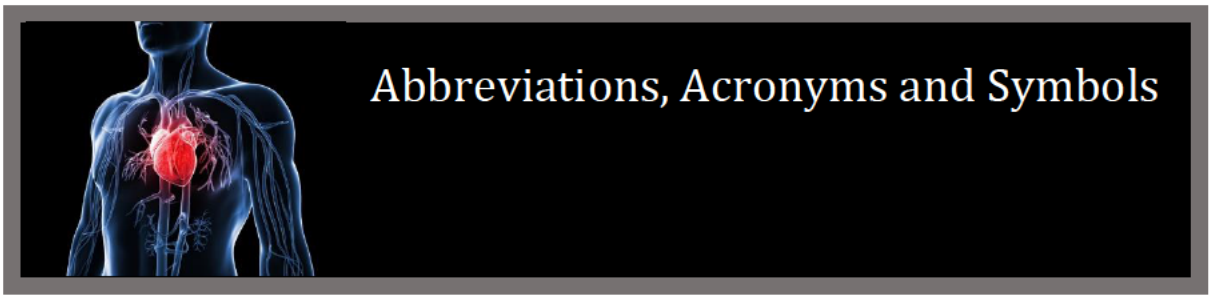


# Abbreviations, Acronyms and Symbols

| | |
|---|---|
| °C | degrees Celsius |
| > | greater than |
| ≥ | greater than or equal to |
| < | less than |
| ≤ | less than or equal to |
| % | percentage |
| ABG | arterial blood gas |
| ACT | activated clotting time |
| ALCAPA | anomalous left coronary artery from the pulmonary artery |
| ASD | atrial septal defect |
| ATP | adenosine triphosphate |
| AVSD | atrioventricular septal defect |
| BSA | body surface area |
| $Ca^{2+}$ | calcium ion |
| CAD | coronary artery disease |
| ccTGA | congenital corrected transposition of the great arteries |
| CHD | congenital heart disease |
| CI | cardiac index |
| cm | centimetre |
| CNS | central nervous system |
| CoA | coenzyme A |
| CPB | cardiopulmonary bypass |
| CPS | cardioplegic solution |
| CTS | cardiothoracic surgery |
| DHCA | deep hypothermic circulatory arrest |
| $DO_2I$ | delivery of oxygen increase |
| DORV | double outlet right ventricle |

| | |
|---|---|
| e.g. | example |
| ECG | electrocardiogram |
| FDA | food and drug administration |
| FRC | functional residual capacity |
| g | gram |
| GCP | good clinical practice |
| GIT | gastrointestinal tract |
| $H^+$ | hydrogen ion |
| $HCO^3$ | bicarbonate |
| Hct | haematocrit |
| HIV | human immunodeficiency virus |
| Hr | hours |
| i.e. | that is |
| IABP | intra-aortic balloon pump |
| ICU | intensive care unit |
| INVOS | in-vivo optical spectroscopy |
| ISBN | international standard book number |
| IV | intra-venous |
| $K^+$ | potassium ion |
| kg | kilogram |
| kPa | kilo pascal |
| L | litre |
| LDH | lactate dehydrogenase |
| LTD | limited |
| LV | left ventricle |
| LVOT | left ventricular outflow tract |
| $m^2$ | meter squared |
| Max | maximum |
| MELAS | mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes |
| mEq/L | milliequivalents of solute per litre of solvent |
| MERRF | myoclonic epilepsy with ragged red fibres |
| $Mg^{2+}$ | magnesium ion |

| | |
|---|---|
| mg/dL | milligrams per decilitre |
| min | minute |
| Min | minimum |
| ml | millilitre |
| mmol/day | millimoles per day |
| mmol/kg/day | millimoles per kilograms per day |
| mmol/kg/hour | millimoles per kilogram per hour |
| mmol/L | millimoles per litre |
| mOsmol/kg $H_2O$ | milliosmoles per kilogram of water |
| mV | millivolt |
| n | number of patients |
| $Na^+$ | sodium ion |
| $NaHCO_3$ | sodium bicarbonate |
| NIRS | near-infrared spectroscopy |
| $O_2$ | oxygen |
| PA | pulmonary artery |
| $PaO_2$ | partial pressure of oxygen |
| $PCO_2$ | partial pressure of carbon dioxide |
| PEEP | positive end-expiratory pressure |
| PTY | proprietary |
| RACHS-1 | risk-adjusted classification for congenital heart surgery |
| RSA | Republic of South Africa |
| $rSO_2$ | regional oxygen saturation |
| RV | right ventricle |
| $S_{cv}O_2$ | central venous oxygen saturation |
| SD | standard deviation |
| SIRS | systemic inflammatory response syndrome |
| STS | Society of Thoracic Surgeons |
| $SvO_2$ | mixed venous saturation of oxygen |
| TAPVC | total anomalous pulmonary venous connection |
| TGA | transposition of the great arteries |
| US | United States |
| VC | vital capacity |

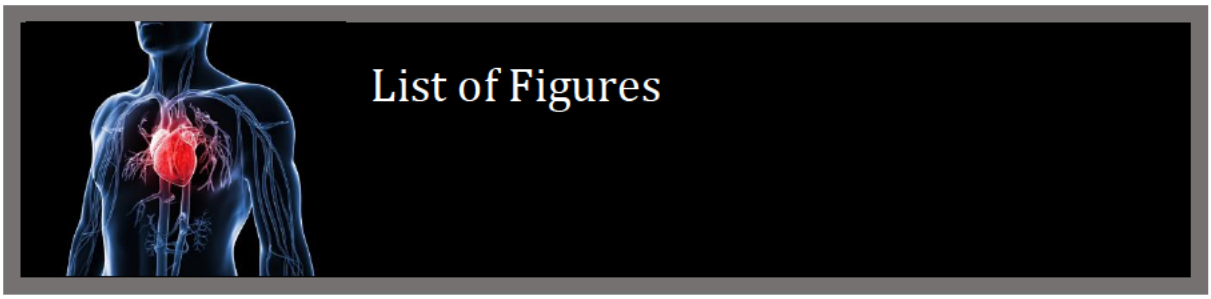
| | |
|---|---|
| $VCO_2$ | carbon dioxide elimination |
| VIS | vasoactive inotropic score |
| $VO_2$ | oxygen consumption |
| VSD | ventricular septal defect |

# Important Definitions

| | |
|---|---|
| Acidosis and Alkalosis | Too much acid in the body, a distinctly abnormal condition resulting from the accumulation of acid or from the depletion of alkaline reserves. In acidosis, the pH of the blood is abnormally low. Acidosis is associated with diabetic ketoacidosis, lung disease, and severe kidney disease. The opposite of acidosis is alkalosis in which there is too high a pH due to excess base or insufficient acid in the body (Medicinenet, 2017). |
| Adverse effects | A harmful or abnormal result. An adverse effect may be caused by administration of a medication or by exposure to a chemical and be indicated by an untoward result such as by illness or death (Medicinenet, 2017). |
| Aerobic | Oxygen-requiring. Aerobic bacteria need oxygen to grow (Medicinenet, 2017). |
| Anaerobic | Not requiring oxygen. Anaerobic bacteria, for example, don't require oxygen to grow (Medicinenet, 2017). |
| Cardiopulmonary bypass | A procedure to mechanically circulate and oxygenate the blood while surgery is performed on the heart, thus providing a motionless, bloodless operating field for the surgeon to operate. Draining oxygen poor blood from the heart through the heart-lung machine, and then returning oxygen rich blood back to the body (Medicinenet, 2017). |
| Cardioplegia | Paralysis of the heart, as may be done electively in stopping the heart during cardiac surgery. Cardioplegia may be done |

| | |
|---|---|
| | using chemical, cold (cryocardioplegia), or electrical stimulation (Medicinenet, 2017). |
| Complications | An unanticipated problem that arises following, and is result of, a procedure, treatment, or illness. A complication is so named because it complicated the situation (Medicinenet, 2017). |
| Hemodynamics | Hemodynamics is the study of all parameters influencing blood flow or circulation (Merriam-Webster, 2017). |
| Hyperlactatemia | Is a persistent, mild to moderate (2-4mmol/L) increase in blood lactate concentration without metabolic acidosis, whereas lactic acidosis is characterized by persistently increased blood lactate levels (usually >5mmol/L) in association with metabolic acidosis (Gunnerson, 2017). |
| Hypoperfusion | Decreased blood flow through an organ, consequently there is a decrease in oxygen delivery. If hypoperfusion is prolonged it may cause cellular dysfunction and even death (Merriam-Webster, 2017). |
| Inflammation | A local response to cellular injury that is marked by capillary dilatation, leukocyte infiltration, redness, heat, and pain that serves as a mechanism initiating the elimination of noxious agents and damaged tissue (Merriam-Webster, 2017). |
| Metabolic | Relating to metabolism, the whole range of biochemical processes that occur within us (or any living organism). Metabolism consists of anabolism (the build-up of substances) and catabolism (the breakdown of substances) (Medicinenet, 2017). |
| Morbidity | Loss of physical or psychological well-being, resulting from disease, illness, injury, or sickness, especially where the affected individual is aware of their own state (Merriam-Webster, 2017). |

| | |
|---|---|
| Mortality | The state or condition of being subjected to death, a fatal outcome (Merriam-Webster, 2017). |
| Neonate | A new-born baby, specifically a baby in the first 4 weeks after birth. After a month, a baby is no longer considered a neonate (Medicinenet, 2017). |
| Paediatrics | The field of medicine that is concerned with the health of infants, children, and adolescents; their growth and development; and their opportunity to achieve full potential as adults (Medicinenet, 2017). |
| Pathophysiology | The physiology of abnormal states; specifically: the functional changes that accompany a syndrome or disease (Medicinenet, 2017). |



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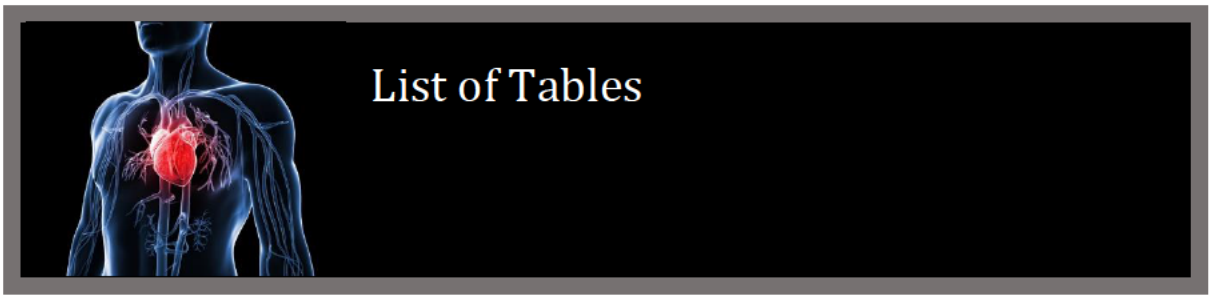

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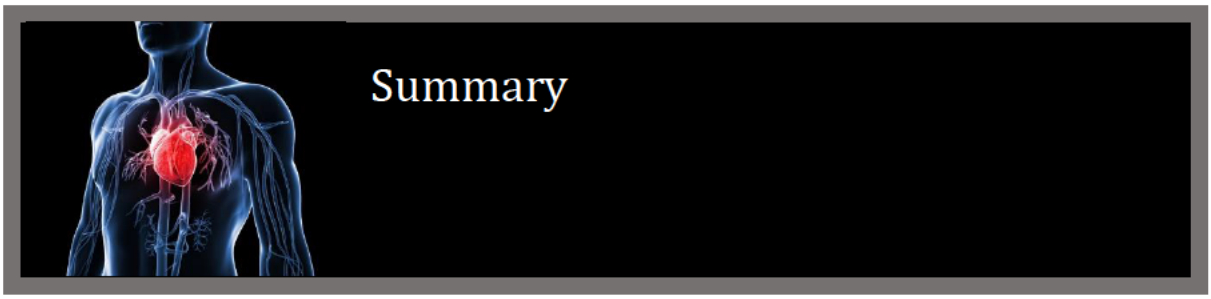




## Introduction

Hyperlactatemia, intraoperatively has been associated with the development of postoperative complications and outcomes. About 10-20% of cardiac patients develop hyperlactatemia during cardiac surgery and the severity thereof is associated with an increased morbidity and mortality. Therefore, hyperlactatemia has been used as a marker to predict postoperative outcome in children during and after cardiac surgery. However, different lactate cut-off values are assigned to different patient groups to predict adverse clinical outcomes and even death. However, the value of peak intraoperative lactate levels in cardiac surgery to predict clinical outcomes is still controversial because of discrepancies regarding reference intervals (3-6mmol/L), cut-off points, time and whether single or multiple lactate measurements should be considered. Increased (peak) lactate levels may be an indication of low cardiac output or reduced tissue oxygen extraction. In cardiac surgery, no specific lactate level has been identified as a consistent indicator for adverse clinical outcomes.

Therefore, the aim of the study was to determine whether a peak intra-operative lactate value ≥4mmol/L is associated with increased postoperative complications and outcomes and whether the use of St Thomas II cardioplegia or Bretschneider custodiol cardioplegia is associated with increase postoperative complications and outcomes in congenital heart disease (CHD) patients receiving cardiopulmonary bypass (CPB).

## Methodology

Ninety-six (96) patients with CHD that received CPB were divided into two cohorts. Group 1 consisted of patients with all peak intraoperative blood lactate values <4mmol/L and group 2, patients with at least one peak intraoperative blood lactate value ≥4mmol/L. The ninety-six (96) patients were then divided according to the cardioplegic solution received during corrective cardiac surgery. CPS 1 consisted of patients that received St

Thomas II cardioplegic solution and CPS 2 patients that received Bretschneider custodiol cardioplegic solution. For both analyses the demographic, anthropometric, clinical, intraoperative and postoperative complications and outcomes were recorded for each group and compared.

**Results**

Group 1 (n=52) and 2 (n=44) were created based on high and low lactate values, therefore, it is no surprise that statistical significance is present intraoperatively between the two (2) groups ($p<0.05$). The patients in group 2 were younger (median 2.4 months) compared to the patients in group 1 (median 14.5 months) at the time of surgery. Postoperatively, the lactate levels in group 1 was significantly lower compared to group 2, however, at 48h post-CPB both groups had normal mean lactate values of <2mmol/L. Intraoperatively, the aortic cross-clamp time and total bypass time were longer in group 2 (144.5 min; 221.4 min) compared to group 1 (125.3 min; 178.1). Postoperative complications were reported for both group 1 and 2 but only wound/sternal dehiscence ($p=0.0208$) and sternum left open ($p=0.0157$) showed statistical significant differences between the two (2) groups. No statistical significant differences were reported for mortality and postoperative outcomes between the two (2) groups.

The patients receiving CPS 2 (n=37) were younger ($p<0.0001$), weigh less ($p=0.0004$) and were shorter (0.0003) compared to the patients receiving CPS 1 (n=59). Intraoperatively, CPS 2 had higher lactate values ($p=0.0332$) lower sodium values ($p<0.0001$) and a longer total bypass time ($p=0.0328$) compared to CPS 1. Postoperatively, the only statistical significant differences between CPS 1 and CPS 2 were recorded for phrenic or recurrent laryngeal nerve (RLN) injury ($p=0.0199$) and new onset seizures ($p=0.0199$). Patients receiving CPS 2 had a higher incidence of both phrenic or recurrent laryngeal nerve injury and new onset seizures. No statistical significant differences were reported for mortality and postoperative outcomes between the two (2) groups.

**Discussion**

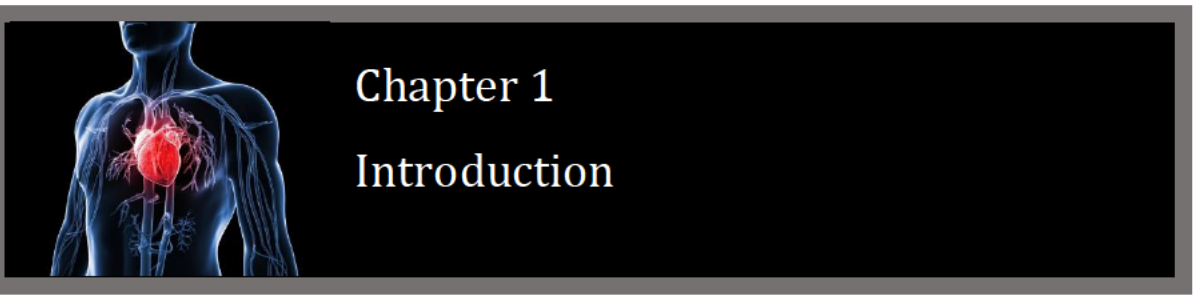
Postoperative complications were reported for both lactate groups but limited statistical significant differences were recorded between patients with peak intraoperative lactate

levels ≥4mmol/L versus those with lactate levels <4mmol/L. In this study, assessing lactate levels at a single point intraoperatively did not correlate with postoperative complications or mortality. Reason being, the absolute peak intraoperative lactate value of 4mmol/L was probably too low to demonstrate an association between hyperlactatemia as a predictor for increased postoperative clinical outcomes and complications. In addition, in our unit any intraoperative increase in lactate levels above 2.5mmol/L prompts the need for therapeutic interventions.

The only statistical difference between the two cardioplegia groups were for new onset seizures and phrenic or recurrent laryngeal nerve injury. Associations between these injuries and the use of Bretschneider custodiol cardioplegia has already been published. No substantial differences were found between St Thomas II and Bretschneider custodiol cardioplegia with regard to other postoperative complications, clinical outcomes and mortality.

**Conclusion**

Therefore, in this study increased postoperative complications and outcomes were not associated with patients with an intraoperative peak lactate value ≥4mmol/L and no clear association could be made between the use of cardioplegic solutions as a predictor of postoperative complications and outcomes.



# Chapter 1
# Introduction

Paediatric heart disease is a term used to describe various heart conditions in children. The most common type of paediatric heart disease is congenital, meaning it is present at birth. Congenital heart disease (CHD) can exist in adults but is still considered CHD if the adult was born with the disease. The incidence of congenital heart defects is approximately 7 to 10 per 1,000 live births (Dönmez and Yurdakök, 2014). About 4 out of 1000, will need surgery to treat CHD (Jacobs and Hess, 2015).

When compared to the 1940s and 50s when most CHD cases were fatal, substantial advances in the treatment of paediatric heart disease over the last 20 to 30 years led to an increase in the survival rate of children presenting with CHD (Jacobs and Hess, 2015). Both technological and improved diagnostic, surgical, anaesthetic and postoperative management led to an increase in survival rates (Dinardo and Zvara, 2008). For instance, extracorporeal support and cardiopulmonary bypass (CPB) have evolved from futuristic visions of surgical pioneers to safe and efficient means of support for infants and paediatrics undergoing complex cardiac procedures (McRobb *et al.*, 2014; Schure, 2010).

However, the management of CPB in infancy poses many challenges and has an increased risk of morbidity and mortality when compared to the adult population (Dönmez and Yurdakök, 2014). Infants are more prone to complications because of immature organ systems, and warrants a more complete understanding of anatomic, metabolic, and physiological differences between infants and adults. Furthermore, patient care must be individualized for the degree of haemodilution and hypothermia, acid-base strategies, flow rates, circuit designs, priming of the pump and the choice of cannulas (Jones and Elliot, 2006; Shen *et al.*, 2003).

Postoperative outcomes and complications can be associated with a magnitude of factors that occur intraoperatively. The complications can affect different organ systems and can

include cardiac, renal, pulmonary, neurological and infectious complications to name just a few (Vijarnsorn *et al.,* 2012; Agarwal *et al.,* 2011). Furthermore, the time spend on CPB during paediatric cardiac surgery is associated with longer Intensive Care Unit (ICU) stays, increased intubation times, and increased mortality (Agarwal *et al.,* 2014; Agarwal *et al.,* 2011).

Hyperlactatemia, intraoperatively has been associated with the development of postoperative complications and outcomes. About 10-20% of cardiac patients develop hyperlactatemia during cardiac surgery and the severity thereof is associated with an increased morbidity and mortality. Therefore, hyperlactatemia has been used as a marker to predict postoperative outcome in children during and after cardiac surgery (Siegel *et al.,* 1996).

During paediatric cardiac surgery hyperlactatemia reflects tissue malperfusion and cellular hypoxia (Siegel *et al.,* 1996). However, the aetiology of hyperlactatemia during cardiac surgery is still controversial but many authors tend to attribute hyperlactatemia to tissue hypoxia (type A hyperlactatemia) and to type B hyperlactatemia (without tissue hypoxia). Although hyperlactatemia can be used as a predictor of morbidity and mortality in cardiac surgery it is important to consider that the initial stimulus for lactate production may occur during CPB. Type A hyperlactatemia is characterized by impaired tissue oxygenation which leads to an increased anaerobic metabolism and the excessive production of pyruvate which is then converted into lactate that can result in lactic acidosis. Type B hyperlactatemia is characterized by an increased or impaired cellular metabolism that can be initiated due to the inactivation of pyruvate dehydrogenase or due to drug-induced mitochondrial dysfunction. Type B hyperlactatemia is frequently seen in the early postoperative period after cardiac surgery (Yilmaz *et al.,* 2011; Livesey, 2006; Maillet *et al.,* 2003).

An elevated serum plasma lactate level is common in paediatric CHD at the time the patient is admitted to ICU after cardiac surgery. However, the patient must reach normal lactate levels within 24 hours (Hr) after being admitted to ICU, if not it is associated with an increase in morbidity and mortality (Molina-Hazan and Paret, 2014).

The use of serum lactate levels to predict adverse outcomes in intensive care settings are well defined (Perfecto *et al.,* 2012; Shime *et al.,* 2001). Different lactate cut-off values are assigned to different patient groups to predict adverse clinical outcomes and even death (Perfecto *et al.,* 2012; Shime *et al.,* 2001). However, the value of peak intraoperative lactate levels in cardiac surgery to predict clinical outcomes is still controversial because of discrepancies regarding reference intervals (3-6mmol/L), cut-off points, time and whether single or multiple lactate measurements should be considered (Kanazawa *et al.,* 2015). Increased (peak) lactate levels may be an indication of low cardiac output or reduced tissue oxygen extraction but perhaps the change in lactate over time is a more reliable marker of a response to therapeutic interventions and subsequent clinical outcomes. In cardiac surgery, no specific lactate level has been identified as a consistent indicator of adverse clinical outcomes (Molina-Hazan and Paret, 2014; Molina-Hazan *et al.,* 2010).

Therefore, the aim of this study was to evaluate whether an association exists between peak intraoperative blood lactate levels ≥4mmol/L and increased postoperative complications and outcomes in paediatric CHD patients receiving CPB surgery.

## 1.1 Aim

To evaluate the impact of peak intra-operative lactate values on post-operative complications and outcomes in CHD patients receiving CPB.

## 1.2 Objective

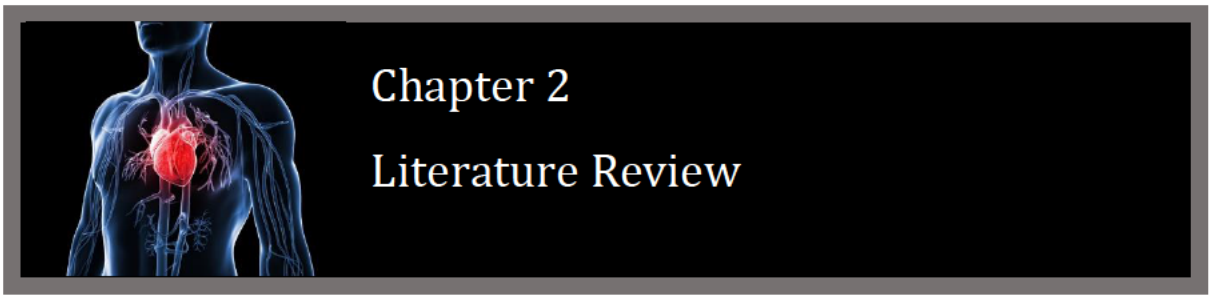
1.) To evaluate whether a peak intraoperative lactate level ≥4mmol/L is associated with increased postoperative complications [complications as listed in Society of Thoracic Surgery (STS) database].

2.) To evaluate whether a peak intraoperative lactate level ≥4mmol/L is associated with increased postoperative outcomes (length of inotropic support, ventilation time, time spend in ICU).

### 1.2.1 Sub-objective

As a sub-objective of the study the patients were divided based on the cardioplegic solution used during CPB and not divided based on peak intraoperative lactate values. Due to the fact that this was a retrospective study the variables that could influence the results with regard to the use of cardioplegia was not standardized. Hence, the reason why this analysis was only regarded as a sub-objective.

Therefore, the sub-objective was to evaluate whether the use of St Thomas hospital II cardioplegia or Bretschneider custodiol cardioplegia is associated with increase postoperative complications (STS Database) and outcomes (length of inotropic support, ventilation time, time spend in ICU) in CHD children receiving CPB.




## 2.1 Congenital heart disease (CHD)

CHD is the most frequent cause of fatal malformations among infants, occurring in approximately 8 out of 1000 live births (Wren, 2012; Bernier *et al.,* 2010; Hoffman and Kaplan, 2002; Hoffman, 1995). CHD is related to an abnormal cardio-circulatory structure or function that presents at birth. However, sometimes the disease is only discovered later in life. During embryonic development, CHD stems from an alteration in normal structural development, or failure of a structure to develop properly. The structural and functional development of the circulatory system may be significantly influenced by non-typical patterns of cardio-circulatory flow because of anatomical defects (Bernier *et al.,* 2010; Hewitson and Zilla, 2010). Furthermore, postnatal events have a noticeable impact on the clinical presentation of a specific isolated malformation (Bernier *et al.,* 2010).

Despite the continuing progress in non-surgical and surgical treatments that allows for the survival of most CHD patients, some complex heart diseases are still associated with considerable morbidity and mortality (Botto and Correa, 2003). There is a high morbidity and mortality rate among infants because of CHD, and it affects the quality of life during childhood and adulthood, depending on the progression of the disease (Majnener *et al.,* 2008). It also affects the quality of life and social interactions for the parents of children with CHD (Bertoletti *et al.,* 2014).

## 2.2 Aetiology of congenital heart disease

In vertebrates, embryonic development of the heart starts at day fifteen (15) and comprise an organized series of molecular and morphologic events that involve five (5) primary steps (Gittenberger-de Groot *et al.,* 2005; Moorman and Christoffels, 2003; McFadden and Olson, 2002):

a. Pre-cardiac cell migration from the primitive streak and assembly of the paired cardiac crescents at the myocardial plate
b. Coalescence of the cardiac crescents to form the primitive heart tube, establishment of the definitive heart
c. Cardiac looping, assurance of proper alignment of the future cardiac chambers
d. Septation and heart chamber formation
e. Development of the cardiac conduction system and coronary vasculature

The development of each component occurs at specified time intervals under the orchestration of a cascade of genes and gene products resulting in a series of complex processes coordinating cell migration and extracellular matrix formation (Gittenberger-de Groot *et al.,* 2005). Therefore, CHD is generally the result of an alteration in the development of the embryonic structure, or a failure of the structure to develop beyond an early embryonic or foetal stage. Further structural and functional developments are generally influenced by the anatomical defect. Even though descriptions of abnormal heart development in foetuses and babies have remained unclear, considerable advances in the knowledge about CHD aetiology have been made during the last decade (Sayasathid *et al.,* 2015; Bax *et al.,* 2010).

Some cardiac malformations may be associated with the consequences of exposure to environmental toxins or diets, or may be directly inherited through vertical gene transfer, thus a genetic disorder (Lander, 2011). Alternatively, it is also possible that random errors in cell migration leading to improper cardiac development can result in CHD. Together, these findings emphasize the complex and multifactorial causes of CHD and warrants the need for future research (Sayasathid *et al.,* 2015).

## 2.3 Classification of congenital heart disease

Congenital heart defects may be classified as acyanotic or cyanotic depending on whether the patients clinical picture exhibit signs of cyanosis. Acyanotic lesions can be further divided into left-to-right shunts and obstructive lesions and by definition, cyanotic lesions present as right-to-left shunts (Rao, 2015; Thiene and Frescura, 2010).

### 2.3.1 Acyanotic heart defects

#### 2.3.1.1 Obstructive lesions

A significant narrowing of a blood vessel or a valve result in increased pressure proximal to the obstruction in comparison to the pressure distal to the obstructed vessel or valve. However, this pressure gradient is necessary to maintain flow across the stenotic area. The clinical presentation of the patient will be determined by the degree of hypertrophy of the cardiac chamber proximal to the obstruction and flow disturbances across the area of obstruction and their effects (Rao, 2015; Thiene and Frescura, 2010).

#### 2.3.1.2 Left-to-right shunts

A defect in the partition between the left and right heart structures result in oxygenated blood being shunted from left-to-right because of normally lower pressure and/or resistance in the right heart than the left heart. The physical findings are either a sign of flow across the defects or due to effects of excessive flow across the cardiac chambers (volume overload) and valves. The clinical presentation and symptoms of the patients are determined by the magnitude of the shunt (Rao, 2015; Thiene and Frescura, 2010).

### 2.3.2 Cyanotic heart defects

#### 2.3.2.1 Right-to-left shunts

Cyanotic heart defects can be described as systemic venous blood that bypasses the pulmonary circulation and gets shunted across into the left side of the heart resulting in systemic arterial desaturation. Cyanotic CHD does not include pulmonary venous desaturation secondary to congestive heart failure and cyanosis due to intrapulmonary right-to-left shunting. Obstruction to pulmonary blood flow, parallel rather than in-series circulation, and complete admixture of pulmonary and systemic venous returns are the causes of right-to-left shunts and cyanosis (Rao, 2015; Thiene and Frescura, 2010).

## 2.4 Treatment procedures for congenital heart disease

Many children living with a congenital heart defect do not need treatment, but some do (National Heart, Lung, and Blood Institute, 2015). The treatment options available to treat CHD includes catheter procedures or open-heart surgery. In some cases, catheter and surgical procedures are combined to repair complex heart defects (National Heart, Lung, and Blood Institute, 2015; Gaca *et al.,* 2008).

The type and severity of the child's defect will determine the choice of treatment (Gaca *et al.,* 2008). Other factors influencing the choice of treatment include age, size and the general health of the child (National Heart, Lung, and Blood Institute, 2015; Gaca *et al.,* 2008). Some children with complex CHD may need numerous catheter or surgical procedures over a period of time (years) (National Heart, Lung, and Blood Institute, 2015).

### 2.4.1 Catheter procedures

Catheter procedures put less stress on patients than open-heart surgery (Fuchs *et al.,* 2015). It only involves a needle puncture to the skin and the catheter is inserted either

into a vein or an artery. There is no need to surgically open the chest of the patient or to operate directly on the heart. This results in a faster and easier recovery period for the patient (Fuchs *et al.,* 2015; National Heart, Lung, and Blood Institute, 2015). Catheter procedures have become the preferred method to repair many simple heart defects, such as atrial septal defects (ASD) and pulmonary valve stenosis (Fuchs *et al.,* 2015; National Heart, Lung, and Blood Institute, 2015). However, unfortunately not all lesions can be repaired via catheter procedures and warrants open-heart surgery.

### 2.4.2 Open-heart surgery

The surgical treatment used for CHD in paediatric patients are referred to as open-heart surgery using CPB (Jaggers and Ungerleider, 2006). The first corrective surgery with CPB for intra-cardiac malformations was performed in 1950 at the Mayo Clinic, University of Minnesota, United States (US) (Lillehei *et al.,* 1956).

The surgeon makes an incision through the breastbone (sternum) while the child is under general anaesthesia. The surgeon then places cannulas in the heart to connect the patient to the heart-lung machine. The physiologic effects of open-heart surgery with CPB on neonates, infants and paediatric patients are significantly different than the effects on adults (Rao, 2015; Gaca *et al.,* 2008; Jaggers and Ungerleider, 2006). During open-heart surgery, the paediatric patients are exposed to biological extremes not seen in adults, including haemodilution, deep hypothermia, low perfusion pressures, wide variation in pump flow rates and different blood pH management techniques (Jaggers and Ungerleider, 2006). All these factors contribute to the possibility of these children developing complications not only intraoperative but also postoperative.

For this study emphasis will be placed on open-heart surgery as treatment modality for the repair of CHD in infants.

## 2.5 Cardiopulmonary bypass (CPB) and associated complications

CPB refers to the heart and lungs being bypassed, during open-heart surgery. Blood is diverted to and through a heart-lung machine as it returns to the heart; the heart-lung machine oxygenates the blood before returning it to the patient's arterial circulation. The oxygenation is achieved through membrane oxygenation which acts like the lungs (Machin and Allsager, 2006). The heart-lung machine does the work of the heart (by pumping the blood), and the lungs (supplying oxygen and removing carbon dioxide from the red blood cells) (Sandham, 2014; Machin and Allsager, 2006).

CPB remains a non-physiological procedure despite significant improvements; the effects of altered perfusion, hypothermia, embolization, haemodilution, acid-base management, and the systemic inflammatory response have been challenging, particularly in neonates and infants. The smaller circulatory volume, increased capillary membrane permeability, and the immaturity of most organ systems in neonates and infants are primarily related to these challenges (Jones and Elliot, 2006; Jonas *et al.,* 2003).

The correction of congenital cardiac defects in paediatric patients with the use of CPB has a profound physiologic effect on most organ systems of the body (Giacomuzzi *et al.,* 2008). These physiological effects include, alterations in the normal concentrations of formed blood elements, plasma proteins and activation of the humoral cascade systems; alterations in the normal concentration of fluid and electrolyte balances; effects on the central nervous system (CNS); alterations to the renal system; effects on the splanchnic, visceral and hepatic systems; effects on the pulmonary system; inflammatory and immunological responses; endocrine, metabolic, and stress responses; and, probably most importantly, the myocardium in the form of myocardial ischemia (Hessel *et al.,* 2013). Paediatric cardiac procedures with CPB often require extremely low temperatures and perfusion flow rates, and therefore, haemodilution.

Surgical techniques are constantly being refined to limit the time spent on CPB or in deep hypothermic circulatory arrest (DHCA) (Onuzo, 2006). Therefore, although CPB is still

an essential assisting method for open-heart surgery it remains one of the most important factors linked to postoperative mortality and morbidity in open-heart surgery (Wang *et al.,* 2011). Some of the most important complications encountered during open-heart surgery is summarized below.

### 2.5.1 Myocardial damage

Advances in paediatric cardiac surgery were accompanied by improvements in CPB technology leading to significant improvements in surgical outcomes (Vakamudi *et al.,* 2012; Bronicki and Chang, 2011; Hasegawa *et al.,* 2005). However, perioperative myocardial damage remains the most common cause of morbidity and mortality after successful surgical correction. A study conducted by Hasegawa *et al.* (2005) reported that the younger the patient, the more susceptible the myocardium is to injury caused by ischemia during definitive repair of CHD. Consequently, perioperative care for paediatric patients with CHD need to take into consideration the dependence of the myocardial damage on age and ischemic time (Vakamudi *et al.,* 2012; Hasegawa *et al.,* 2005).

Myocardial cell damage in infants exposed to open-heart surgery can directly be associated with varying combinations of histo-chemical, microscopic, and gross myocardial necrosis in up to 90% of patients who do not survive the perioperative period (Daniels, 2008). The observed modifications within the myocardium can potentially be attributed to the heart anomaly itself, preoperative hemodynamic instability and its treatment, cardiopulmonary bypass, myocardial protection strategies, surgical techniques, and postoperative medical care (Daniels, 2008).

In addition, patients with CHD are at increased risk of developing myocardial ischemia or premature coronary artery disease (CAD). The increased risk is a result of:

- Congenital coronary artery abnormalities
- Previous cardiac surgery
- Myocardial ischemia which is not directly related to coronary artery anomalies but presenting after an arterial switch operation for transposition of the great

arteries (TGA) and in patients with a congenital corrected transposition of the great arteries (ccTGA) (Daniels, 2008)

It is generally accepted that the immature heart has a greater tendency to tolerate ischemia than the mature heart, most of this is based on laboratory data acquired from normal hearts (Jaggers and Ungerleider, 2006). With pre-existing conditions such as hypertrophy, cyanosis, or acidosis, it is unclear what the ischemic tolerance is. In neonates and infants who require surgical correction of heart defects. Many of these pre-existing conditions may be present and may compromise myocardial protection (Jaggers and Ungerleider, 2006).

During CPB the hypoxic conditions and the ischemic effects can affect cardiomyocytes by inducing rapid or gradual injury to the membrane systems (Asano *et al.,* 2003).

The reperfusion of the myocardium also has negative consequences during circulatory interruption (Buckberg and Allen, 1995; Follette *et al.,* 1981). Interrupted coronary circulation is required in nearly all cardiac surgeries and the potential for reperfusion damage is considerable. The initial damage caused by a reperfusion injury may contribute to impaired cardiac performance that develops immediately after surgery possibly leading to myocardial fibrosis (Castañeda *et al.,* 1994; Kirklin and Barratt-Boyes, 1993). Therefore, myocardial protection during surgically induced myocardial ischemia is important. Hypothermic cardioplegia is the method of choice for myocardial protection (Mayer, 1998). Incomplete myocardial protection during surgically induced myocardial ischemia has a prominent effect on postoperative surgical outcomes, including low cardiac output, requirements for increased inotropic support, and elevated atrial filling pressures (Mayer, 1998).

During CPB the surgeon cross-clamp the aorta to allow for intervention on the aortic root, the aortic valve, and the left ventricular outflow tract (LVOT). Myocardial perfusion is retrograde during CPB; therefore, during the aortic cross clamping the heart is stopped and is not perfused (Hirleman and Larson, 2008; Jaggers and Ungerleider, 2006; Mayer, 1998). Long aortic cross-clamp times therefore are, thus a likely cause of ischemic injury to the heart.

### 2.5.2 Haemodilution

Haemodilution during CPB was introduced in the 1950s to decrease the use of homologous blood (Neptune *et al.,* 1960) and has been thought to improve microcirculatory flow (Cooper and Slogoff, 1993). However, haemodilution may also reduce perfusion pressure, which increases the risk of an adverse neurological outcome after CPB (Murphy *et al.,* 2009; Jonas *et al.,* 2003; Gold *et al.,* 1995). Additionally, haemodilution increases cerebral blood flow (Murphy *et al.,* 2009; Jonas *et al.,* 2003; Sungurtekin *et al.,* 1999) and in doing so might increase the microembolic load to the brain (Newburger and Bellinger, 2006; Nollert and Reichart, 2001). Lastly, haemodilution reduces the oxygen carrying capacity of blood; in combination with the leftward shift of oxyhaemoglobin dissociation induced by hypothermia. This condition might be aggravated using an alkaline pH strategy.

Experience with cardiovascular surgery in adults refusing blood transfusions suggests that very low haematocrit levels can be tolerated (Murphy *et al.,* 2009; Cooper, 1990). The optimal haematocrit level for cerebral protection during hypothermic CPB has not been defined. Published expert opinions (Murphy *et al.,* 2009; Hammon *et al.,* 2001) proposed that haematocrit levels of greater than 15% to 20% are safe during CPB in adults.

Several studies have found that the severity of haemodilution during CPB correlates strongly with increased perioperative morbidity and/or mortality (Murphy *et al.,* 2009; Habib *et al.,* 2005; Karkouti *et al.,* 2005; Habib *et al.,* 2003; Jonas *et al.,* 2003; Fang *et al.,* 1997). Habib *et al.* (2005) found that haematocrit levels lower than 22 is associated with an increased risk for cardiac and renal complications, sepsis, prolonged ventilation, and longer ICU stays.

### 2.5.3 Systemic Inflammatory Response Syndrome (SIRS)

SIRS is common after cardiac surgery for CHD (Brix-Christensen, 2001). SIRS is characterized by the release of proinflammatory cytokines, but the mechanisms initiating

this cascade remain ill defined (Stocker *et al*., 2004). The systemic inflammatory response is mainly triggered by the generation of shear forces from roller pumps driving blood through the bypass circuit, hypothermia as blood is expelled through the extracorporeal circuit, surgical trauma, ischemia and contact activation of plasma protein systems as circulating blood is exposed to artificial surfaces in the bypass circuit (Larmann and Theilmeier, 2004).

CPB also initiates profound physiological alterations which include:

- Blood is in direct contact with large artificial surfaces
- Pulsatile flow is converted to laminar flow
- Exposure of the heart to global ischemia with cardioplegic protection
- The body temperature is lowered by several degrees (Larmann and Theilmeier, 2004)

These alterations activate the inflammatory response by activating the endothelium, platelets, complement system, leukocytes and the coagulation cascade. Surgical trauma itself also contributes to the inflammatory response present after surgery (Larmann and Theilmeier, 2004).

### 2.5.4 Electrolyte imbalances

Electrolytes such as potassium, magnesium, calcium and phosphate play important roles in cellular metabolism and energy transformation and contribute in the regulation of cellular membrane potentials, especially those of muscle and nerve cells (Polderman and Girbes, 2004). Depletion of these electrolytes can induce a wide range of clinical disorders, including neuromuscular dysfunction and severe arrhythmias. The risk for these disorders increases significantly when more than one electrolyte is deficient and increases still further in the presence of ischaemic heart disease (Ducceschi *et al*., 2000).

Electrolyte disturbances during cardiac surgery are common. Polderman *et al*. (2004) measured the levels of sodium, potassium, calcium, magnesium, and phosphate in 500

consecutive patients undergoing cardiac surgery with CPB. Despite receiving a cardioplegic solution containing potassium and magnesium as well as supplemental intravenous potassium and magnesium as required intraoperatively, all electrolyte levels decreased significantly when compared with 250 patients admitted to the ICU after other major surgical procedures. Eighty-eight percent of the cardiac patients met the criteria for clinical deficiency in one or more electrolytes as compared with 20% of control subjects. The study authors speculated that the mechanism for electrolyte loss was likely a combination of increased urinary excretion and an intracellular shift. However, it should be noted that all cardiac patients received low-dose dopamine, which may have enhanced any urinary electrolyte loss.

Intraoperative disturbances in sodium have been shown to be a predictor of postoperative delirium (Fitzsimons and Agnihotri, 2007). Potassium management is important not only for weaning from CPB, but also to reduce the incidence of postoperative dysrhythmias (Young, 2012). Mild intraoperative hypocalcaemia is common and are usually the cause of haemodilution, binding to citrate in transfused blood, binding to albumin, and because of hypomagnesemia (Young, 2012). Hypomagnesemia can contribute to several adverse hemodynamic consequences which include cardiac arrhythmias, hypertension, and coronary vasoconstriction (Kimura *et al*., 1989).

### 2.5.5 Lactate production leading to hyperlactatemia

According to literature several intraoperative parameters can influence a patients' peri- or postoperative outcome e.g. age, oxygen supply and demand, mean arterial blood pressure, bypass flow rates, type of flow (pulsatile versus non-pulsatile), haematocrit (Hct), haemodilution, systemic oxygen delivery, $Na^+$, $K^+$, lactate, temperature, acid-base management, myocardial protection, CPB time, aortic cross-clamp time, genetic factors, neurodegenerative disorders, and comorbidities such as systemic hypertension, chronic kidney disease, and diabetes mellitus (Murphy *et al.,* 2009; Lelis and Auler Junior, 2004). Hyperlactatemia during cardiac surgery is a common complication encountered during cardiac surgery and warrants therapeutic intervention (Oguz *et al.,* 2014).

For this study emphasis will be placed on increased intraoperative lactate levels as a predictor of postoperative complications and outcomes in CHD children receiving CPB.

Elevated blood lactate levels are not clearly and universally defined but most studies use cut-offs between 2.0-2.5mmol/L (Kruse *et al.,* 2011), whereas "high" lactate has been defined as a lactate level of >4mmol/L in several studies (Callaway *et al.,* 2009; Howell *et al.,* 2007; Shapiro *et al.,* 2005). Additionally, the "normal value" may vary depending on the analyses used. The terms lactic acid and lactate are often used interchangeably but lactate (the constituent measured in blood) is strictly a weak base whereas lactic acid is the corresponding acid. "Lactic acidosis" is often used clinically to describe elevated lactate but should be reserved for cases where there is a corresponding acidosis (pH<7.35) (Luft *et al.,* 1983).

#### 2.5.5.1 History of lactate production

Berzelius first described lactate in 1807 when he discovered it in its modified form in meat juices (Siegel *et al.,* 1996). Lactic acidosis in the setting of severe illness dates back in history to the 1800s when Johann Joseph Scherer first measured lactic acid levels in post-mortem blood from two females dying of puerperal fever. In 1858, Folwarczny described elevated lactate levels in living patients with leukaemia (Kompanje *et al.,* 2007) followed by Salomon in 1878, who observed increased lactate levels in patients with pneumonia, solid tumours, chronic obstructive pulmonary disease, and congestive heart failure (Kompanje *et al.,* 2007). Several years later, Fletcher described how skeletal muscles produces lactic acid under anaerobic conditions, noting that when oxygen was readily available, it "either restrains by some guidance of chemical event the yield of acid in the muscle, or can remove it after its production" (Fletcher, 1907).

Lactate has been used as a marker of tissue malperfusion and cellular hypoxia, and hyperlactatemia has been associated with postoperative complications and mortality. In clinical practice, lactate levels are often used as a surrogate for illness severity and to gauge response to therapeutic interventions (Andersen *et al.,* 2013; Koliski *et al.,* 2005).

Particularly, high blood lactate concentrations have been associated with increased morbidity and mortality in paediatric patients after cardiac operations (Siegel *et al.,* 1996).

Blood lactate concentrations are more easily obtained and measured than other monitoring variables. Blood lactate levels used as a clinical prognostic tool was first suggested in 1964 by Broder and Weil when they observed that a lactate excess of >4mmol/L was associated with poor outcomes in patients with undifferentiated shock (Broder and Weil, 1964). The use of blood lactate concentrations as a clinical endpoint has been studied in surgical, septic, trauma, and critical ill patients (Andersen *et al.,* 2013; Koliski *et al.,* 2005).

### 2.5.5.2 Physiology and pathophysiology of lactate production

Lactate is a glycolytic product that is either used within the cells or transported through the plural interstitial and vasculature to nearby and anatomically distributed cells for utilization. As such, lactate is a quantitatively important oxidizable substrate and gluconeogenetic precursor, and a means by which metabolism in different tissues are coordinated (Brooks, 2002; Stacpoole *et al.,* 1994). Furthermore, lactate measurements in the critically ill can provide information on illness severity and prognosis. High blood lactate levels are usually, but not always, the result of anaerobic metabolism, particularly when it's associated with metabolic acidosis (Handy, 2006).

The metabolism of pyruvic acid results in the production of lactic acid, a reaction that is catalysed by lactate dehydrogenase and one that involves the conversion of NADH into $NAD^+$ (reduced and oxidized nicotine adenine dinucleotide, respectively) (Phypers, 2006; Philp *et al.,* 2005). Under anaerobic conditions, lactate is a product of glycolysis and feeds into the Cori cycle as a substrate for gluconeogenesis (Figure 2.1) (Philp *et al.,* 2005; Bellomo, 2002). The pyruvate is converted by lactate dehydrogenase (LDH) to lactic acid. In aerobic conditions, the pyruvate is converted to acetyl coenzyme A (CoA) to enter the Kreb's cycle, largely bypassing the production of lactate. Lactic acid dissociates almost completely to lactate and H+b in aqueous solutions (Phypers, 2006). Once believed that the lack of oxygen in contracting skeletal muscles are the consequence of lactate

production, it is now known that lactate is also formed and utilized continuously under aerobic conditions (Brooks, 2002).

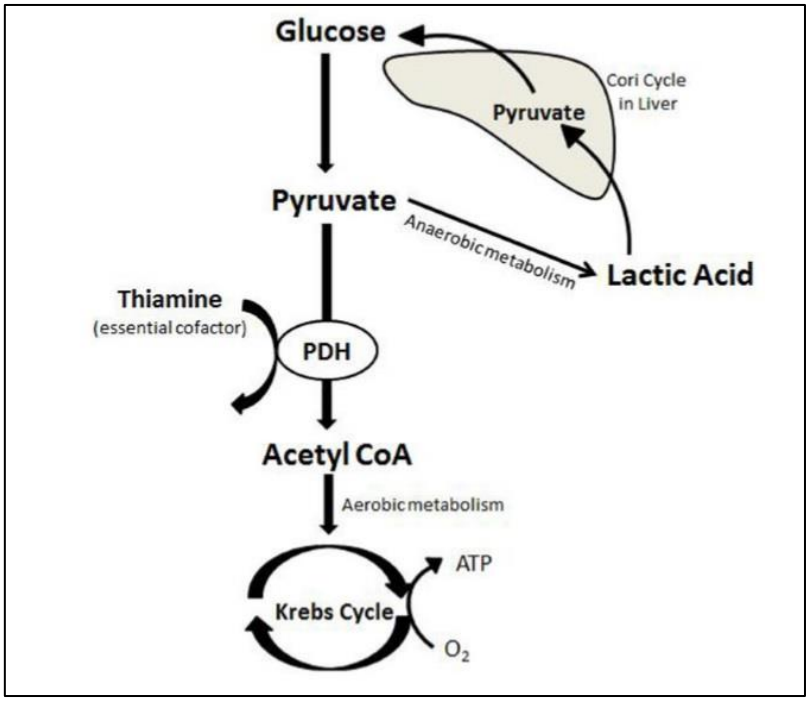



**Figure 2.1 Aerobic and anaerobic metabolism** (adapted from Andersen *et al.,* 2013)

Normal basal lactate production is 0.8mmol/kg/hour (1300mmol/day) and normal plasma lactate concentration is 0.3-1.3mmol/L (3-12mg/dL) (Levy, 2006; Phypers, 2006). Normal subjects produce lactic acid between 15-20mmol/kg/day, most of which is generated in skeletal muscle, skin, intestine, brain, and red blood cells, either from glucose via the glycolytic pathway or from the deamination of alanine (Levy, 2006; Huckabee, 1961). During intense exertion or severe illness its concentration can rise to over 20mmol/L (180 mg/dL) (Mizock and Falk, 1992).

Lactate production occurs in many other tissues during severe illness, for example during acute lung injury (De Backer *et al.,* 1997). The splanchnic organs, such as the intestines and liver, are another potential source of lactate production and can be predominantly vulnerable to inconsistent vasoconstriction in low perfusion states. Whether this mechanism contributes to elevated gut lactate in sepsis remains controversial (De Backer *et al.,* 2001). During phagocytosis, leukocytes can also produce large amounts of lactate (Borregaard and Herlin, 1982).

In nature, lactate has two chemical isomers L-lactate and D-lactate. L-lactate is because of anaerobic glycolysis in humans and has been used as a marker of tissue malperfusion and cellular hypoxia. L-lactate can only be produced or consumed from pyruvate via the enzyme LDH in the cytosol, by means of a process of fermentation during normal metabolism and exercise (Mizock, 1989). The concentration does not increase until the rate of lactate production exceeds the rate of lactate removal, a process which is governed by numerous factors (Andersen *et al.,* 2013). D-lactate, is produced from large amounts of unabsorbed carbohydrates by bacteria in the human colon. In the setting of varying degrees of intestinal flora and a high carbohydrate load (such as in short bowel syndrome) there will be an excess production of D-lactate, which can cross into the bloodstream and potentially cause neurological symptoms (Petersen, 2005). The D isomer is mostly exogenous from Ringer's lactate solution infusion, and its non-iatrogenic presence in humans is uncommon. Its clearance is much slower than L-lactate, with the clearance mainly dependent on liver function (Uribarri *et al.,* 1998).

Tissue sources of lactate production include perivenous hepatocytes, skeletal myocytes, erythrocytes and skin with the highest production found in skeletal muscles (Van Hall, 2010; Consoli *et al.,* 1990). The liver is the major organ of lactate utilization, followed by the kidneys (Levraut *et al.,* 1998; Consoli *et al.,* 1990; Mizock, 1989; Connor *et al.,* 1982; Huckabee, 1961). About 70% of lactate is removed by the liver and less than 5% of lactate is renally excreted. In the liver, lactate uptake involves both a monocarboxylate transporter and the less efficient process of diffusion, while renal fraction may increase and become more clinically significant during hyperlactatemia (Phypers, 2006; Levraut *et al.,* 1998).

The pathophysiology in various disease conditions resulting in elevated lactate levels is likely multifactorial, disease-specific, and patient-specific. In general, elevated lactate can be caused by increased production, decreased clearance, or a combination of both. Elevated lactate's aetiology is perhaps best studied in shock states (Donnino *et al.,* 2010; Jones and Puskarich, 2009; Trzeciak *et al.,* 2007; James *et al.,* 1999; Gore *et al.,* 1996; Rady, 1992). Contributing factors appear to include: mitochondrial dysfunction (including potential lack of key enzymatic co-factors), the presence of a hypermetabolic state, and hypoperfusion due to macro- and/or microcirculatory dysfunction, among others

(Donnino *et al.,* 2010; Jones and Puskarich, 2009; Trzeciak *et al.,* 2007; James *et al.,* 1999; Gore *et al.,* 1996; Rady, 1992). Liver dysfunction may contribute to both decreased clearance and increased production, which becomes even more important in states of hypoperfusion.

### 2.5.5.3 Hyperlactatemia

A plasma lactate level exceeding 4mmol/L is defined as hyperlactatemia, and results during conditions where production exceeds utilization. Hyperlactatemia can be associated with normal blood pH, acidosis, and alkalosis, and can also be found in conditions of normoxia, hypoxia and anoxia (Handy, 2006).

Hyperlactatemia's pathological causes were historically divided between those with evidence of one or another of the well-known causes of hypoxia; and those with no detectable disturbance in oxygen transport in the usual sense (Huckabee, 1961). According to the Cohen-Woods classification hyperlactatemia may occur (primary/Type B) due to an underlying disease process (B1), medication (B2), or an inborn error of metabolism (B3), or with (secondary/Type A) decreased tissue perfusion or tissue oxygenation (Mizock, 1989), although, many critically ill patients can have hyperlactatemia because of both these mechanisms (Phypers, 2006).

**a.) Primary (Type B) hyperlactatemia**

Hyperlactatemia not associated with poor tissue perfusion is clinically more prevalent (i.e., alkalosis or increased metabolic activity). Often during critical illness, patients have continued elevations in lactate production without ongoing evidence of cellular ischemia or hypoxia. In such cases, a decrease in pH can be compensated for by body-buffering mechanisms (Smith *et al.,* 2001).

Primary hyperlactatemia is caused by increased lactate production which is stimulated irrespective of tissue hypoxia, as a response to inflammatory mediators or through other mechanisms (Chiolero *et al.,* 2000). The causes of primary hyperlactatemia are divided, into Type B1 (related to underlying diseases), Type B2 (related to the effect of drugs and

toxins), and Type B3 (associated with inborn errors of metabolism) (Mizock, 1989; Woods and Cohen, 1976) (Table 2.1).

**Table 2.1** **Causes of elevated primary hyperlactatemia** (adapted from Vernon and LeTourneau, 2010)

| Causes of Type B lactic acidosis | |
|---|---|
| **Type B1** | • Renal failure<br>• Hepatic failure<br>• Diabetes mellitus<br>• Malignancy<br>• Systemic inflammatory response syndrome<br>• Human immunodeficiency virus (HIV) |
| **Type B2** | • Acetaminophen<br>• Alcohols (ethanol, methanol, diethylene glycol, isopropanol, and propylene glycol)<br>• Antiretroviral nucleoside analogues (zidovudine, didanosine, and lamivudine)<br>• b-Adrenergic agonists (epinephrine, ritodrine, and terbutaline)<br>• Biguanides (phenformin and metformin)<br>• Cocaine, methamphetamine<br>• Cyanogenic compounds (cyanide, aliphatic nitrates, and nitroprusside)<br>• Diethyl ether<br>• Fluorouracil<br>• Halothane<br>• Iron<br>• Isoniazid<br>• Linezolid<br>• Nalidixic acid<br>• Niacin<br>• Propofol<br>• Salicylates<br>• Strychnine<br>• Sugars and sugar alcohols (fructose, sorbitol, and xylitol)<br>• Sulfasalazine<br>• Total parenteral nutrition<br>• Valproic acid<br>• Vitamin deficiencies (thiamine and biotin) |
| **Type B3** | • Glucose-6-phosphatase deficiency (von Gierke disease)<br>• Fructose-1,6-diphosphatase deficiency<br>• Pyruvate carboxylase deficiency<br>• PDH deficiency<br>• Methylmalonic aciduria<br>• Kearns-Sayre syndrome<br>• Pearson syndrome<br>• Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS)<br>• Myoclonic epilepsy with ragged red fibres (MERRF) |

**(HIV – human immunodeficiency virus, MELAS – mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes, MERRF – myoclonic epilepsy with ragged red fibres)**

### b.) Secondary (Type A) hyperlactatemia

Secondary hyperlactatemia is caused by tissue hypoperfusion, or when the body-buffering mechanisms are not able to compensate for the decreasing pH (Smith *et al.,* 2001; Chiolero *et al.,* 2000). This type of hyperlactatemia is the most common type of hyperlactatemia post cardiac surgery. Secondary hyperlactatemia is frequently caused by hypoperfusion and tissue hypoxia that are associated with significant cardiopulmonary compromise. Either systemic or regional hypoperfusion may result in hyperlactatemia (Mizock and Falk, 1992). The major causes for secondary hyperlactatemia are regional hypoperfusion (limb, mesenteric ischemia), shock (cardiogenic, haemorrhagic, hypovolemic, or septic), severe anaemia, severe respiratory acidosis (asthma) and severe hypoxemia (Juneja *et al.,* 2011; Mizock, 1989).

#### 2.5.5.3.1 Predictive factors for hyperlactatemia

Hyperlactatemia appears in association with peripheral circulatory failure (tachycardia, sweating, reduced arterial blood pressure and mental confusion), with low arterial blood $O_2$ saturation, and with acid-base disturbances (O'Connor and Fraser, 2010). Dangerous hypoperfusion and substantial hyperlactatemia can exist despite the lack of acidosis.

### a.) Operative factors contributing to hyperlactatemia

Lactic acidosis is often observed as being related to low output syndrome, hypoxemia and cardiac surgery with CPB, which usually show clinical evidence of poor tissue oxygen delivery. Despite evidence of good cardiac output, early postoperative hyperlactatemia is seen in some children after surgical repair of CHD. Severe hypovolemia or cardiac arrest triggers anaerobic metabolism and hyperlactatemia, all of which can be pre-, intra- or postoperatively due to the many cardiac or resuscitation problems found in paediatric CHD patients. Changes in lactate levels in post-cardiac surgery patients are not homogenous in nature, since early hyperlactatemia and late hyperlactatemia differ in both risk profile and physiological rationale (O'Connor and Fraser, 2010).

### i.) Preoperative factors contributing to hyperlactatemia

The electivity/urgency of surgery can influence postoperative lactate levels. According to Maillet *et al*. (2003) the more elective the surgery, the lower the postoperative blood lactate levels. Urgent or emergency surgery is usually performed on hemodynamically unstable patients, therefore, the preoperative lactate values might already be abnormal in these patients. According to Demers *et al*. (2000) pre-operative risk factors like arteriosclerosis, congestive heart failure, and left ventricular ejection fraction less than 30% was associated with increased lactate levels intra- and postoperative.

### ii.) Intra- and postoperative factors contributing to hyperlactatemia

Intraoperatively, CPB has been associated with increased risk of postoperative complications and outcomes in both adults and children (Molina-Hazan and Paret, 2014). CPB can initiate systemic inflammatory response syndrome (SIRS) that impairs multiple organ functions and result in hemodynamic instability and early morbidity in new-borns, more so than in infants and children (Roth *et al.,* 2006). In several previous reports, prolonged CPB and aortic cross-clamp times were cited as risk factors for major postoperative complications and increased mortality (Gessler *et al.,* 2009; Barach *et al.,* 2008; Joao and Faria, 2003). Roodpeyma *et al.* (2013) studied 143 patients that underwent CPB, the patients who died had significantly longer CPB and aortic cross-clamp times compared to the surviving patients.

Hyperlactatemia occurring early after CPB may be the result of intraoperative or early postoperative impaired lactate clearance, tissue oxygen debt, or both (Molina-Hazan and Paret, 2014). It may, however, follow CPB despite a normal perioperative course and well-maintained oxygen delivery. The length of CPB and, especially, the episode of hypotension at the start of the bypass period appear to be related to the development of lactic acidosis.

Non-pulsatile, hypothermic CPB itself can contribute to the impairment of peripheral perfusion thus altering the metabolic balance. It is linked to the collapse and slugging of capillary vessels influenced by the duration of CPB and lactate concentration fluctuations

(increase after the commencement of CPB, remaining elevated during CPB, decreasing after CPB, and increasing again after surgery) (Molina-Hazan and Paret, 2014).

Lactate levels of 4mmol/L or higher in patients who underwent congenital cardiac surgery tend to have a significantly longer CPB time, aortic cross-clamp time, and a decreased haemoglobin value (Demers *et al.,* 2000). The administration and frequent use of vasopressors intraoperatively is also associated with the occurrence of postoperative hyperlactatemia (Maillet *et al.,* 2003).

During cardiac surgery, the infusion of exogenous D-lactate Ringer's solution can also cause iatrogenic hyperlactatemia in infants with immature liver function (Zhou and Liu, 2011).

Metabolic disturbances, such as electrolytic composition and blood acid-base balance, hyperlactatemia and hyperglycaemia, are factors that frequently complicate the early postoperative period in patients after cardiac surgery under extracorporeal circulation. Mostly, Hyperlactatemia is seen post-cardiac surgery and a reduction in hepatic lactate clearance may contribute to the condition. Early postoperative measurable side effects, such as maximal anion gap, base deficit and bicarbonate levels, were significantly different between patients with postoperative hyperlactatemia and patients with low-normal lactatemia in the early postoperative period (i.e. less than 12 hours after admission to ICU) (Abrahams *et al.,* 2010; Chiolero *et al.,* 2000).

Inadequate tissue oxygen delivery because of impaired cardiac output after paediatric cardiac surgery is a common problem which can be expressed in the early stages by hyperlactatemia, and has been associated with significant morbidity and mortality (Chakravarti *et al.,* 2009). Clinical indicators used for diagnosing decreased cardiac output other than hyperlactatemia include; low peripheral temperature/core temperature gradient, high pulse and low blood pressure, long capillary refill time, decreased urine output and base deficit (Bohn, 2011). However, most of these indicators do not reflect cardiovascular performance very well (Tibby *et al.,* 1997).

Average renal and cerebral oxygen saturation ($rSO_2$) levels of less than 65% measured by near-infrared spectroscopy (NIRS) predict hyperlactatemia (>3mmol/L) in acyanotic children after congenital heart surgery (Chakravarti *et al.,* 2009). Chakravarti *et al*. (2009) reported that an averaged renal and cerebral $rSO_2$ was a good predictor of lactate status, with a value ≥65%, predicting a lactate level ≥3mmol/L, with a sensitivity of 95% and a specificity of 83% in the studied patients. Therefore, monitoring of $rSO_2$ could aid in the prompt identification of patients at risk of hyperlactatemia and low-cardiac output syndrome (Chakravarti *et al.,* 2009).

Patients with higher blood lactate levels during CPB were also more likely to have myocardial infarction and postoperative hemodynamic, pulmonary, neurologic, digestive, or renal complications (Demers *et al.,* 2000). Postoperative episodes of hyperglycaemia, hypotension, the use of norepinephrine, epinephrine and dobutamine were also more frequently seen in patients with hyperlactatemia following cardiac surgery compared to patients with non-elevated blood lactate levels (Maillet *et al.,* 2003).

## 2.6 Myocardial protection during cardiac surgery

The past century has witnessed the emergence and advancement of techniques to protect the heart and allow for the safe conduct of increasingly more complex cardiac surgeries. During the last couple of decades, advances in myocardial protection were closely linked to strategies designed to provide global organ protection, most notably of the kidneys and brain (Bigelow *et al.,* 1950). Myocardial protection is an essential component of cardiac surgery, with key principles being the reduction of metabolic activity by hypothermia and cessation of mechanical and electrical activity of the heart (Bove *et al.,* 1988; Grice *et al.,* 1987). These principles remain essential in cardiac surgery of the paediatric population.

The paediatric cardiac surgeon is confronted with hearts in varying stages of maturity. This is a significant variation since, as the myocardium matures, fundamental changes occur that directly influence the ability of the heart to withstand periods of ischemia and injury. The point at which the heart transitions to be more robust is most likely to occur during the earlier stages of life and potentially within the first 3 months of life; however,

the exact transition point is still debatable (Bove *et al.,* 1988; Grice *et al.,* 1987). In general, there is a belief that the normal neonatal myocardium is more resistant to ischemia and reperfusion injury than the mature adult myocardium (Bove *et al.,* 1988; Grice *et al.,* 1987). These differences must be considered when considering the best possible strategy for myocardial protection during neonatal and infant cardiac surgery.

### 2.6.1 Clinical mechanisms of myocardial protection

The most widely practiced methods to ensure myocardial protection during paediatric cardiac surgery include:

i) Hypothermia, to reduce metabolic activity during ischemia
ii) The administration of cardioplegia with potassium as the main ingredient to achieve electrical and contractile arrest (Mayer, 1998)

For neonatal and infant cardiac surgery, there is no clear consensus among surgeons regarding the optimal strategy for myocardial protection. However, most institutions incorporate both hypothermia and the administration of cardioplegia during their paediatric cardiac procedures (Mayer, 1998).

### 2.6.2 Methods providing myocardial protection during cardiac surgery

Hypothermia and cardioplegic arrest can be used to provide myocardial protection during cardiac surgery.

#### 2.6.2.1 Hypothermia

A significant amount of myocardial protection can be provided by hypothermia alone and may be the single most important factor contributing to myocardial protection during neonate and infant cardiac surgery (Doenst *et al.,* 2003; Bull *et al.,* 1984). When cooling the human body to 32 degrees Celsius (˚C) total body oxygen consumption is reduced by 45% (Bigelow *et al.,* 1950). At temperatures below 12˚C the oxygen consumption of the

heart is below 1% of what is considered normal and contractile function ceases (Niazi and Lewis, 1955). More profound selective myocardial hypothermia is also often used during the cross-clamping of the aorta to aid in the preservation of the ischemic myocardium (Niazi and Lewis, 1955).

Myocardial hypothermia can be achieved in two ways: by topical application of ice slush or cold pericardial lavage, or by coronary perfusion with a cold cardioplegic solution. The optimal temperature for myocardial protection is controversial; however, Swanson *et al.* (1980) have demonstrated superior protection at temperatures as low as 2-4˚C, if alkalosis is present. The heart is promptly arrested during cooling, and freezing temperatures are avoided (Swanson *et al.,* 1980).

#### 2.6.2.2 Cardioplegia

During cardiac surgery, cardioplegia provides an additional level of myocardial protection. Cardioplegia is essentially used to induce the cessation of all contractile and electrical activity of the heart. Because of the cessation, there is a significant reduction in energy consumption, even during normothermia (Buckberg, 1995). Almost all cardioplegic solutions exert their protective effects through the hyperpolarization or depolarization of the myocardial cell's membrane and the mechanical arrest of the heart. Hyperpolarizing cardioplegic solutions contain high levels of potassium, sodium, and magnesium, while depolarizing cardioplegic solutions contain low electrolyte levels (Martin and Benk, 2006).

The composition of a cardioplegic solution differs according to the mechanism involved during ischemic-reperfusion injury. The mechanisms include; elevated osmotic pressure to prevent oedema formation, addition of free radical scavengers, addition of buffering agents to reduce acidosis, and the supplementation with substrates to improve energy production during the process of rewarming and reperfusion (Allen *et al.,* 2001; Bilfinger *et al.,* 1992).

The focus has shifted to the development of cardioplegic solutions directed at prolonging the tolerance of the myocardium to ischemia by maintaining the heart in a state of

"reversible injury". Potassium depolarization arrest through hyperkalaemia has developed into the primary component of cardioplegic solutions (Conti *et al.,* 1978). Depolarization arrest significantly reduces the metabolic energy demands of myocytes. There are indications that normothermic arrest at 37˚C decreases the $O_2$ demands of the heart by 90% to 1ml $O_2$/100 gram (g)/minute (Buckberg *et al.,* 1977). Currently, hyperkalaemic cardioplegic solutions are the clinical standard and have an elevated potassium concentration ranging between 12 and 25mmol/L. In cardiac cells, the resting membrane potential is around -90mV, these hyperkalaemic solutions lead to membrane potential depolarization (-50mV). The sodium channels are also inactivated at this membrane potential and the heart is arrested in a flaccid diastolic state (Segurola and Kelly, 2004). However, at this membrane potential, other ionic mechanisms such as sodium-hydrogen exchange may cause a slow influx of sodium which could lead to calcium overload during reperfusion, which is toxic to the myocardium (Segurola and Kelly, 2004).

Even though depolarization arrest has become an essential component of cardioplegia, the features of hyperpolarization arrest warrant some consideration. Hyperpolarization arrest maintains the membrane of the myocardium near the resting membrane potential (Segurola and Kelly, 2004). There are certain energy dependent processes, such as the sarcolemma and sarcoplasmic reticular $Na^+$-$K^+$-ATPase and $Ca^{2+}$-ATPase pumps, which remains active during depolarization arrest (Cohen *et al.,* 1993).

Hyperpolarization causes complete arrest of the sinus node. A key property of hyperpolarization is its potassium agonistic property which offers a more complete and persistent arrest of the heart than depolarization. This property led to the use of hyperpolarizing agents for the induction of cardiac arrest with cardioplegia instead of depolarizing agents. A more balanced transmembrane gradient is offered by the hyperpolarized state, which maintains ionic balances during ischemia. Polarized arrest has been associated with improved recovery of myocardial function and reduced ionic imbalance (Segurola and Kelly, 2004).

A hyperpolarized state is possible with the use of several drugs like adenosine, sodium channel blockers (lidocaine, procaine, and tetrodotoxin), or potassium channel openers

(pinacidil and nicorandil). Reduction of myocardial arrest time and recovery after reperfusion is significantly better when using adenosine cardioplegic solutions alone or in combination with potassium (Segurola and Kelly, 2004).

For this study emphasis will be placed on St Thomas II cardioplegia and Bretschneider custodiol cardioplegia.

### i.) St Thomas II cardioplegia

The initial St Thomas' Hospital cardioplegic solution was first introduced into clinical practice at St Thomas' Hospital, in London, by Braimbridge in 1975 (Chamber and Hearse, 2001). This cardioplegic solution was later modified to become the St Thomas II cardioplegic solution (Chamber and Hearse, 2001), which was approved in the US by the Food and Drug Administration (FDA) and was produced commercially as Pegisol. Such was the success of this rationalized cardioplegic solution that, within a very short space of time, this cardioplegic solution had been accepted for use by most major cardiac centres, almost completely replacing the use of coronary perfusion and other procedures (Chamber and Hearse, 2001).

St Thomas II cardioplegia is an extracellular cardioplegic solution which contains high concentrations of sodium, magnesium and calcium (Geissler and Mehlhorn, 2004) (Table 2.2). The high calcium content in the solution is to avoid calcium inconsistency during the reperfusion phase and to maintain cell membrane integrity. The high magnesium content stabilizes the myocardial membrane by inhibiting a myosin phosphorylase which protects adenosine triphosphate (ATP) reserved for post ischemic activity. Sodium bicarbonate is added prior to use to buffer the St Thomas II solution; rendering the solution slightly alkaline thus helping to compensate for metabolic acidosis that accompany ischemia (Athanasuleas and Buckberg, 2009).

**Table 2.2 Ionic composition of St Thomas II cardioplegia** (adapted from Athanasuleas and Buckberg, 2009)

| Electrolyte | Volume |
|---|---|
| $Na^+$ (mmol/L) | 120 |
| $K^+$ (mmol/L) | 16 |
| $Mg^{2+}$ (mmol/L) | 16 |
| $Ca^{2+}$ (mmol/L) | 1.2 |
| $HCO^3$ (mmol/L) | 0 |
| $NaHCO^3$ (mmol/L) | 10 |
| pH | 7.8 |
| Haematocrit (%) | 0 |
| Osmolarity (mOsmol/kg $H_2O$) | 285-300 |

($Na^+$ – sodium ion, $K^+$ - potassium ion, $Mg^{2+}$ - magnesium ion, $Ca^{2+}$ - calcium ion, $HCO^{3-}$ - bicarbonate, $NaHCO_3$ – sodium bicarbonate, mmol/L – millimoles per litre, % - percentage, mOsmol/kg $H_2O$ – milliosmoles per kilogram of water)

## The metabolic effects associated with St Thomas II cardioplegia

St Thomas II cardioplegia is a depolarizing cardioplegia that utilizes extracellular hyperkalaemia to depolarize the membrane potential of the myocardial cell membranes, resulting in the depletion of the energy stores and calcium overload (Cohen *et al.,* 1993). Depolarization of the myocardial cell membranes is associated with an ongoing cellular metabolic process and derangements in transmembrane ionic gradients (Cohen *et al.,* 1993). It is also associated with the influx of sodium through the sodium "window current", influx of calcium through the calcium "window current", leakage of calcium from the sarcoplasmic reticulum, and exchange of intercellular sodium for calcium via the sodium-calcium exchange (Cohen and Lederer, 1988). All these factors contribute to myocardial calcium overload and are associated with myocardial injury during arrest.

When depolarization is dependent on potassium it results in elevated intracellular calcium by means of voltage-dependent calcium channels, with an increase in energy consumption (Sternbergh *et al.,* 1989).

### ii.) Bretschneider custodiol cardioplegia

Bretschneider custodiol cardioplegic solution was first introduced by Bretschneider in the 1970s (Schaper *et al.,* 1986). Custodiol cardioplegia is a solution based on the intracellular level of electrolytes hence its low sodium and calcium concentrations (Viana *et al.,* 2013) (Table 2.3). This type of cardioplegia is used for myocardial protection in complex cardiac surgery and for organ preservation during transplant surgery. The cardioplegia is administered as a single dose which is attractive for cardiac surgeons and it claims to offer myocardial protection for a period of up to three hours (Gebhard *et al.,* 1984; Bretschneider, 1980). The protection period enables complex cardiac surgical procedures to be performed without interruption. Custodiol cardioplegia prolongs ischemic tolerance of the heart and decreases the incidence of arrhythmia, inotropic support, and ICU length of stay because of less myocardial oedema formation and better left ventricular (LV) performance post CPB surgery (Lui *et al.,* 2008; Sauer *et al.,* 2003; Careaga *et al.,* 2001).

**Table 2.3** **Ionic composition of Bretschneider custodiol cardioplegia** (adapted from Viana *et al.,* 2013)

| Electrolyte | Volume |
|---|---|
| $Na^+$ (mmol/L) | 15 |
| $K^+$ (mmol/L) | 9 |
| $Mg^{2+}$ (mmol/L) | 4 |
| $Ca^{2+}$ (mmol/L) | 0.015 |
| Histidine (mmol/L) | 198 |
| Tryptophan (mmol/L) | 2 |
| Ketoglytarate (mmol/L) | 1 |
| Mannitol (mmol/L) | 3 |
| pH | 7.02-7.20 |

($Na^+$ – sodium ion, $K^+$ - potassium ion, $Mg^{2+}$ - magnesium ion, $Ca^{2+}$ - calcium ion, mmol/L – millimoles per litre)

### The metabolic effects associated with Bretschneider custodiol cardioplegia

Bretschneider custodiol cardioplegia is a hyperpolarizing cardioplegic solution based on the intracellular level of electrolytes (Viana *et al.,* 2013). The cardiac myocytes natural resting state is a hyperpolarized state (Cohen *et al.,* 1993). During hyperpolarization, few

channels or pumps are activated, and metabolic demand on the ventricular myocyte is minimal (Cohen *et al.,* 1993). The depletion of sodium in the extracellular space causes hyperpolarization of the myocyte plasma membrane, inducing cardiac arrest in diastole. This mechanism of action differs from that of conventional 'extracellular' cardioplegic solutions, which are high in potassium content and cause arrest by depolarizing the myocardial cell's membrane (Chamber, 2003).

The high histidine content of Bretschneider custodiol cardioplegia acts as a buffer for acidosis caused by the accumulation of anaerobic metabolites during extended ischemic periods. Tryptophan acts by stabilizing the cell membrane, and ketoglutarate acts by improving ATP production during reperfusion. Custodiol cardioplegia also contains mannitol which acts as a free-radical scavenger and decreases cellular oedema (Bretschneider, 1980). Kresh *et al.* (1987) noted that the histidine protein buffer might be superior to bicarbonate in stabilizing intracellular pH and facilitating recovery of post-ischemic mechanical and biochemical parameters.

Despite the widespread use of Bretschneider custodiol cardioplegia in Europe, there is limited data comparing the efficacy of custodiol cardioplegia to other crystalloid cardioplegias (Ji *et al., 2*012; Kim *et al.,* 2011). There is also a lack of data comparing Bretschneider custodiol with other solutions for heart preservation during transplantation (Ji *et al., 2*012; Kim *et al.,* 2011). The adequacy of myocardial protection offered by only a single dose of cardioplegia is a concern. Concerns have been raised about the hyponatremia that follows the rapid administration of the requisite high volume of this low sodium cardioplegic solution (Ji *et al., 2*012; Kim *et al.,* 2011). The adverse effects of severe hyponatremia can result in damage to the central nervous system and are associated with seizures (Arieff, 1986).

Bretschneider custodiol cardioplegic solution can be improved by the inclusion of additional substrates such as aspartate and glutamate. The use of amino acids through anaerobic pathways via the infusion of three amino acids (ornithine, aspartate, and glutamate) during ischemia augmented the recovery of contractile function in isolated rabbit hearts (Rau *et al.,* 1979).

## 2.7 Postoperative complications and outcomes after CPB surgery

### 2.7.1 Postoperative complications

Postoperative complications are defined as any deviation from the ideal postoperative course that may or may not be directly related to the disease for which the surgery was done or to the surgery itself (Dindo and Clavien, 2008). The postoperative complications and outcomes associated with cardiac surgery are depicted in table 2.4.

Morbidity refers to the diseased state of the patient and may potentially lead to mortality. Mortality is the fatal outcome of morbidity (Laffey *et al.,* 2002). In paediatric cardiac surgery, it has been shown that higher surgical volume is associated with improved survival rate, particularly for high risk surgery (Welke *et al.,* 2009). National benchmark data have revealed that overall mortality after congenital heart surgery is <4% at most institutions (Agarwal *et al*., 2014).

Prolonged aortic cross-clamp time is a significant risk factor predicting postoperative morbidity and mortality (Bezon *et al.,* 2006). Complex cardiac surgery requiring prolonged aortic cross-clamping is associated with high morbidity and mortality from direct damage to the myocardium (Rady *et al.,* 1998; Turner *et al.,* 1995). Prolonged aortic cross-clamping, CBP and DHCA times are associated with cardiac arrest in ICU (Suominen *et al.,* 2001). This is in line with findings of Rady *et al.* (1998) in which long aortic cross-clamp times (120min) and CPB times (140min) were predictors of postoperative mortality in elderly patients. Even in children, prolonged aortic cross-clamp and CPB times have been independent predictors of major adverse events during the postoperative phase (Duke *et al.,* 1997).

The extent of the inflammatory response to CPB has been associated with preoperative conditions such as heart failure and shock (Mou *et al.,* 2002); intraoperative factors such as the duration of CPB and cardioplegic arrest (Kirklin *et al.,* 1983) and genetic differences (Gaudino *et al.,* 2003; van Deventer, 2000). Several studies have found a relationship

between the inflammatory response to CPB and the development of multi-organ dysfunction and postoperative morbidity (Seghaye *et al.,* 1993; Kirklin *et al.,* 1983). The combination of prolonged CPB time and cardiac disease were found to be associated with prolonged intubation and mechanical ventilation (Nyawawa *et al.,* 2009).

**Table 2.4 STS congenital database: postoperative complications** (adapted from Society of Thoracic Surgeons Database, 2011)

| **Postoperative complications** | |
|---|---|
| **Cardiovascular** | Cardiac Arrest<br>Mechanical circulatory support<br>Arrhythmia<br>Heart block<br>Low cardiac output<br>Acidosis<br>Pericardial effusion requiring drainage<br>Pulmonary Hypertension |
| **Pulmonary** | Pneumothorax<br>Pleural effusion requiring drainage<br>Pneumonia<br>Chylothorax<br>Tracheostomy<br>Phrenic or recurrent laryngeal nerve injury<br>Respiratory insufficiency requiring mechanical ventilation >7 days postoperatively or reintubation |
| **Neurologic** | Transient or permanent neurologic deficit<br>New onset seizures |
| **Infectious** | Wound/Sternal dehiscence or infection<br>SIRS<br>Mediastinitis<br>Endocarditis |
| **Renal** | Acute renal failure |
| **Surgical** | Sternum left open<br>Bleeding requiring reoperation |
| **Gastrointestinal** | Gastrointestinal haemorrhage<br>Acalculous cholecystitis<br>Acute pancreatitis<br>Liver failure<br>Mesenteric ischemia |
| **Mortality** | 30-day mortality |

**(SIRS – systemic inflammatory response syndrome).**

The presence of pulmonary hypertension and poor myocardial protection during CPB has been associated with low cardiac output states, hence a delay in achieving good hemodynamic states postoperatively. The presence of a low pH at the end of CPB might be a predictor of poor myocardial protection during CPB. Long lasting surgery might be the

cause of postoperative wound infection. Similarly, prolonged duration of aortic cross-clamp has been associated with high morbidity and mortality rates and prolonged mechanical ventilation and ICU stay (Szekely *et al.,* 2006; Davis *et al.,* 2004).

An elevated lactate level >2mmol/L has been associated with an increased risk for morbidity and mortality following paediatric cardiac surgery (Kanazawa *et al.,* 2015; Basaran *et al.,* 2006; Charpie *et al.,* 2000; Cheifetz *et al.,* 1997; Duke *et al.,* 1997) contradicted by Perfecto *et al*. (2012) and Shime *et al*. (2001) stating that elevated intraoperative lactate levels is associated with increased morbidity and mortality. Elevated blood lactate levels were associated with postoperative complications in hemodynamically stable surgical patients and a higher mortality rate, and failure of serum lactate levels to reach normal values within a specific time during critical illness could be even more closely related to survival than the initial level (Meregalli *et al.,* 2004). During and post-CPB hyperlactatemia has been linked to increased morbidity and mortality in children undergoing surgical repair of complex CHD (Cheung *et al.,* 2005; Munoz *et al.,* 2000). Several factors contribute to lactic acidosis because of the hypo circulatory state during cardiopulmonary resuscitation and the global ischemia occurring during circulatory arrest. Oxygen deficiency leads to anaerobic metabolism and therefore to overproduction of lactate. At the same time, liver function may be impaired due to the profound ischemic state, leading to reduced lactate clearance.

In a prospective study Basaran *et al.* (2006) included 60 infants undergoing surgery for CHD and showed that mortality was higher in the group with a mean lactate of greater than 4.8mmol/L in the early postoperative period. Blood lactate levels have been shown to be even superior to mixed venous blood saturation in predicting outcome (Duke *et al.,* 1997). The time it takes for serum lactate levels to reach normal values postoperatively is also a useful predictor of mortality in children undergoing repair or palliation of CHD under CPB, while initial and peak lactate levels have a poor positive predictive value for mortality (Kalyanaraman *et al.,* 2008).

### 2.7.2 Postoperative outcomes

The parameters regarded as postoperative outcomes in this study included inotropic support, time of ventilation and ICU stay.

#### 2.7.2.1 Inotropic support

Inadequate pharmacological treatment (inotropes and vasopressors) for low cardiac output and reduced oxygen delivery may contribute to multiple organ failure which is one of the main causes of prolonged hospital stay and postoperative morbidity and mortality (Duranteau *et al.,* 1999).

Myocardial inotropy refers to the intrinsic ability of the myocardial cells to contract vigorously. Therefore, a positive inotropic agent causes an increase in the force of myocardial contraction, contributing to the improvement of left ventricular pump function, thus improving perfusion to vital organs including the central nervous system, kidney and heart (Choudhury and Saxena, 2003).

During paediatric cardiac surgery, maintenance of adequate oxygen balance is one of the primary objectives. Cardiac output (CO) is a major contributor of oxygen delivery so maintenance of CO is very important. Therefore, inotropes and vasodilators are used to improve cardiac performance after cardiac surgery.

Large multinational randomized controlled trials are still needed to assess the optimal use of inotropes and vasopressors. However, some recommendations can be made (Lahtinen *et al.,* 2011; Mebazaa *et al.,* 2010; Mebazaa *et al.,* 2004; Duranteau *et al.,* 1999):

a. All catecholamine's have positive inotropic and chronotropic effects. There is evidence that the myocardial oxygen balance is better preserved using dobutamine when compared to the other commonly used drugs. Dobutamine increases heart rate and stroke volume. Combinations of dobutamine-norepinephrine are frequently used if blood pressure is low.

b. In the case of low blood pressure due to vasoplegia norepinephrine should be used to maintain an adequate perfusion pressure and the preload should be regularly assessed to avoid hypovolemia caused by vasopressors.
c. Compared to dobutamine, phosphodiesterase III inhibitors are potent vasodilators and cause less tachyarrhythmia. Phosphodiesterase III inhibitors have a more favourable effect on the myocardial oxygen balance compared to the catecholamine's.

Recently a calcium sensitizer, levosimendan, has been successfully introduced for the treatment of low cardiac output in the perioperative period (Joshi *et al.,* 2016).

Tabib *et al*. (2016) reported that delayed sternal closure, sepsis, re-intubation, vasoactive inotropic score (VIS) and numbers of inotropes used would be independent predictors for mechanical ventilation more than 72 hours.

#### 2.7.2.2 Ventilation management

Pulmonary complications are frequently seen postoperatively even in patients with healthy lungs. These complications include; diminished functional residual capacity (FRC) following muscle relaxants and general anaesthesia, reductions in vital capacity (VC) following median sternotomy and intrathoracic manipulation, increased intravascular lung water, atelectasis, and increased capillary leakage and extravascular lung water due to the inflammatory response to CPB and surgery (Apostolakis *et al.,* 2010; Kilpatrick and Singer, 2010). Excessive fluid loading and multiple blood product transfusions may further compromise lung function. Acute arterial hypoxemia due to ventilation-perfusion mismatch and shunting is a result of acute FRC reduction. In the early postoperative phase, the primary goals are the restoration of FRC and maintenance of adequate gas exchange in the face of rising oxygen consumption ($VO_2$) and the rate of carbon dioxide elimination ($VCO_2$), which can be achieved by a lung-protective ventilation strategy with adequate levels of Positive End-Expiratory Pressure (PEEP) (Apostolakis *et al.,* 2010).

There is still an ongoing debate regarding optimal extubation time and window of opportunity (Higgins, 1995). Several studies showed good results on outcome, after extubation in the operating room, which makes it feasible (Djaiani *et al.,* 2001; Lee and Jacobsohn, 2000). However, about 4hours after CPB the nadir of ventricular function occurs. Also, the first few hours after cardiac surgery are characterized by periods of hemodynamic instability, increased mediastinal blood loss, temperature dysregulation, and other homeostatic disturbances (Van Mastrigt *et al.,* 2006). The deterioration of patients can occur rapidly in this early postoperative phase and it is believed that the instabilities can be best anticipated and treated in an ICU setting in ventilated and sedated patients. Therefore, the window of opportunity for extubation is between 2 and 6hours postoperatively (Van Mastrigt *et al.,* 2006).

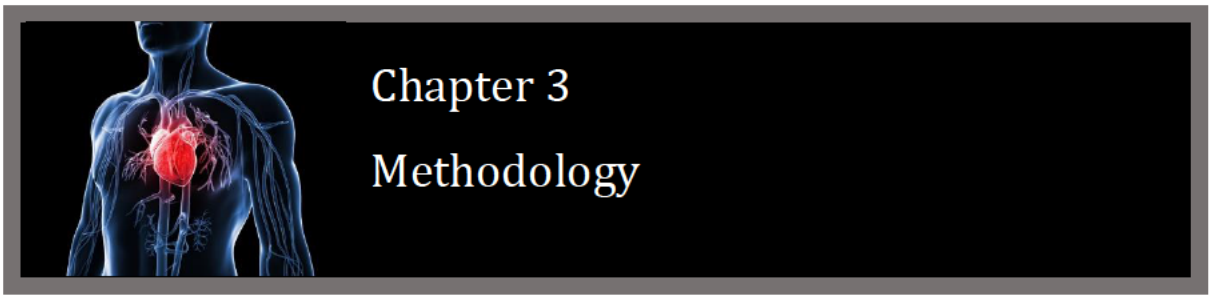
#### 2.7.2.3 ICU stay

Recent improvements in facilities in paediatric ICU's have increased the survival rates among children suffering from CHDs, including those suffering from the more complex conditions (Joao and Faria, 2003). The patient's course after successful heart surgery depends on diverse factors such as the severity of CHD, condition of the patient before surgery, patient's age, events in the operating room, and the quality of postoperative care (Bernstein, 2007). In a retrospective study done by Burstein *et al.* (2011) which included 20 922 patients, they found that the median length of ICU stay for paediatric cardiac patients were 6 days. Paediatrics who undergo an uncomplicated cardiac surgery, with good intraoperative care should need little postoperative management for a smooth recovery (Backer *et al.,* 2003).

Medical care of cardiac surgical patients in the perioperative setting has for several decades consisted of high-dose opioid stress-free anaesthesia and prolonged mechanical ventilation in the ICU. The concepts of fast-track cardiac anaesthesia, early extubation and short-stay intensive care have in recent years become the backbone of modern perioperative care (Myles and McIlroy, 2005; Hawkes *et al.,* 2003).

Crucial "pre-considered" steps in the development of fast-track cardiac surgery include alterations in anaesthetic protocol using short-acting sedative hypnotics and analgesics,

less invasive surgical and perfusion techniques, preservation of normothermia, fluid restriction, haemostasis management, and the reduction of the inflammatory response (Paone *et al.,* 1998).



# Chapter 3
# Methodology

## 3.1 Introduction

The objectives of this study were to determine whether a peak intra-operative lactate value ≥4mmol/L is associated with increased postoperative complications (STS database) and outcomes (length of inotropic support, ventilation time, time spend in ICU). As a sub-objective an evaluation was done to determine whether the use of St Thomas hospital II cardioplegia or Bretschneider custodiol cardioplegia is associated with increase postoperative complications (STS database) and outcomes (length of inotropic support, ventilation time, time spend in ICU).

## 3.2 Study location

The study was performed in the Department of Paediatric Cardiology and Cardiothoracic Surgery (CTS) at Red Cross War Memorial Children's Hospital located in Cape Town, South Africa.

## 3.3 Study population

A research population is also known as a well-defined collection of individuals known to have similar characteristics. All the individuals within a certain population usually have a common, binding characteristic or trait. Therefore, data files of 96 paediatric patients (aged 0-12 years) that presented with a confirmed diagnosis of CHD and received corrective congenital surgery via cardiopulmonary bypass from 2012 to 2014 were evaluated.

### 3.3.1 Study cohorts

**Objective 1&2:** The 96 patients were divided into two cohorts. Group 1 consisted of patients with all peak intraoperative blood lactate values less than 4mmol/L and group 2, patients with at least one peak intra-operative blood lactate value equal or higher than 4mmol/L.

**Sub-objective:** The 96 patients were divided according to the cardioplegic solution received during corrective cardiac surgery. Group 1 consisted of patients that received St Thomas II cardioplegic solution and group 2, patients that received Bretschneider custodiol cardioplegic solution.

### 3.3.2 In- and exclusion criteria

To address the objectives and sub-objective of the study, the selection criteria for the patients were based on two main variables namely they must present with a confirmed congenital heart defect and the need to undergo corrective congenital cardiac surgery. The specific requirements for the inclusion and exclusion of patients in this study are outlined in the inclusion and exclusion criteria below.

#### 3.3.2.1 Inclusion criteria

Participants were included in the study if they met the following criteria:

i. Paediatric patients aged 0-12 years
ii. Patients diagnosed with CHD
iii. Patients that received CPB, hypothermia (≤32°C) during surgery, with the use of either St Thomas II or Bretschneider custodiol cardioplegia solution
iv. Aortic cross-clamp time >90 minutes
v. A baseline preoperative lactate value of <2mmol/L
vi. Complete patient (data) files

#### 3.3.2.2 Exclusion criteria

The following participants were excluded from the study:

i. Patients older than 12 years of age
ii. Patients not presenting with CHD
iii. Patients that received off-pump cardiac surgery with hypothermia (≥32°C), patients that did not receive St Thomas II or Bretschneider custodiol cardioplegic solution
iv. Aortic cross-clamp time <90 minutes
v. A baseline preoperative lactate value of >2mmol/L
vi. Incomplete patient (data) files

## 3.4 Study design

The study was a retrospective analytical cohort including paediatric patients presenting with congenital heart defects who underwent CPB surgery between 2012 and 2014.

## 3.5 Conceptual framework for data collection

The data was collected according to the conceptual framework summarized in Figure 3.1 and Figure 3.2.

### 3.5.1 Objective 1 and 2 – Lactate <4mmol/L versus ≥4mmol/L

Group 1 consisted of patients with peak intraoperative blood lactate values less than 4mmol/L and group 2, patients with peak intraoperative lactate values equal or higher than 4mmol/L. Prior to CPB surgery (hypothermia ≤32˚C) the patient's demographic data (age, gender, weight, height, body surface area (BSA), and ethnicity) clinical data (type of CHD lesion) and preoperative metabolic data (lactate and Hct) were recorded. During CPB, arterial blood gas (ABG) analysis was done after the initiation of bypass and

every 15 minutes thereafter, until the termination of CPB. From the ABG's the peak intraoperative lactate and Hct were recorded. Oesophageal temperature was also recorded. Additionally, the type of cardioplegia used (St Thomas II or Bretschneider custodiol), aortic cross-clamp time and total bypass time were recorded.

Postoperatively, the patients' lactate and Hct values were recorded upon admission to ICU and 24h, 48h, and 72h thereafter.

The STS database was used to document the postoperative complications (cardiac arrest, arrhythmia, heart block, low cardiac output, acidosis, pericardial effusion requiring drainage, pulmonary hypertension, pneumothorax, pleural effusion requiring drainage, pneumonia, chylothorax, tracheostomy, phrenic or recurrent laryngeal nerve injury, respiratory insufficiency requiring mechanical ventilation >7 days postoperatively or reintubation, transient or permanent neurologic deficit, new onset seizures, wound/sternal dehiscence, infection/SIRS, endocarditis, acute renal failure, sternum left open, bleeding requiring reoperation). The postoperative outcomes recorded for both groups included; the time of inotropic support, time spent on a ventilator, ICU stay and mortality (Figure 3.1).

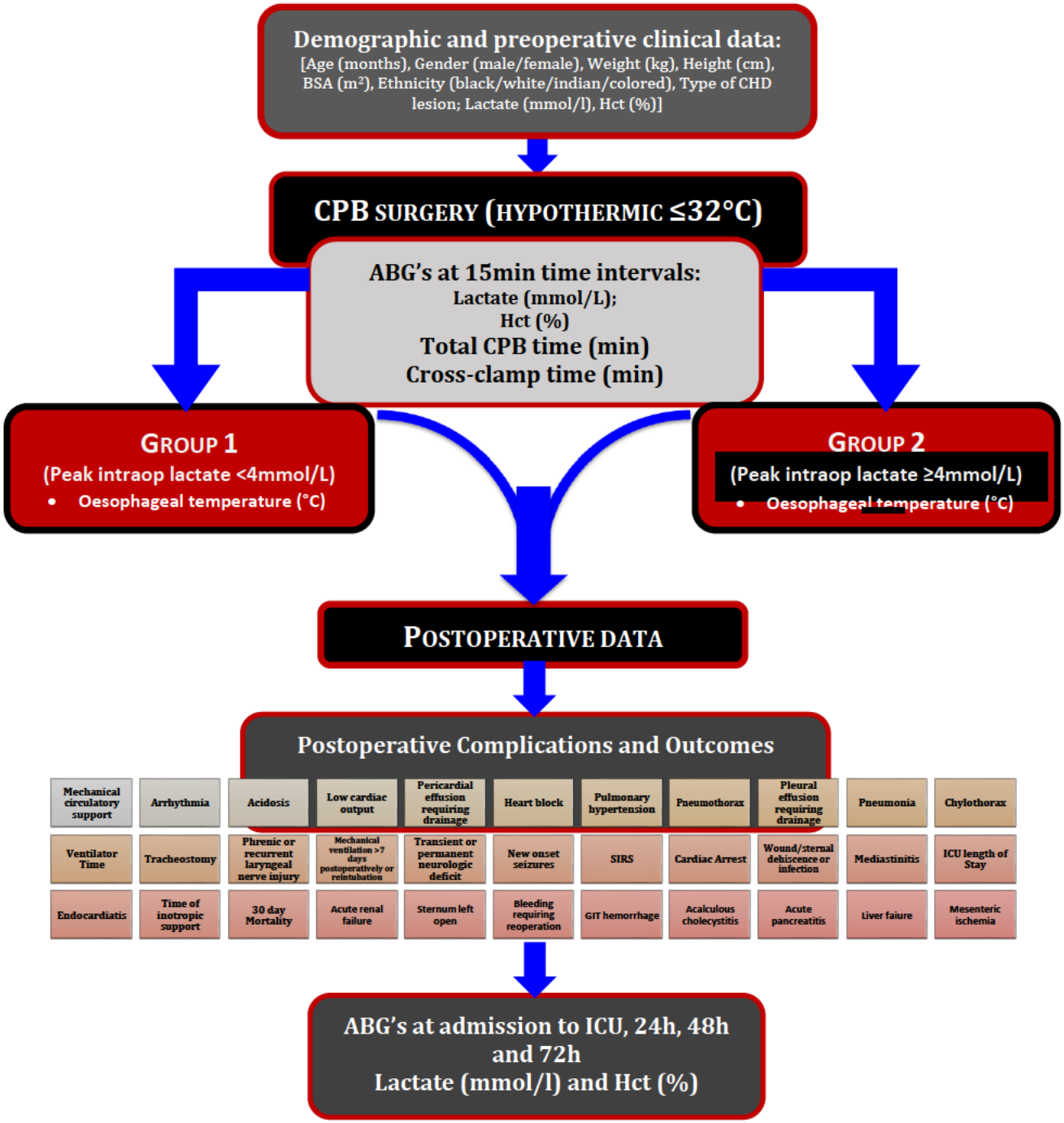



**Figure 3.1** **Conceptual framework for data collection – Lactate <4mmol/L versus ≥4mmol/L**

(BSA – body surface area; CHD – congenital heart disease, Hct – haematocrit; ICU – intensive care unit; ABG – arterial blood gas, SIRS – systemic inflammatory response syndrome, Intraop – intraoperative, mmol/L – millimoles per litre, % - percentage)

### 3.5.2 Sub-objective – St Thomas II versus Bretschneider custodiol cardioplegia

CPS 1 consisted of patients that received St Thomas II cardioplegia solution, and CPS 2, patients that received Bretschneider custodiol cardioplegia solution. Prior to CPB surgery (hypothermia ≤32˚C) the patient's demographic data (age, gender, weight, height, body surface area (BSA), and ethnicity) clinical data (type of CHD lesion) and preoperative metabolic data (lactate, Hct, $K^+$ and $Na^+$) were recorded. During CPB ABG analysis was done after the initiation of bypass and every 15 minutes thereafter, until the termination of CPB. From the ABG's the peak intraoperative lactate, Hct, $K^+$ and $Na^+$ were recorded. Additionally, the aortic cross-clamp time, total bypass time and oesophageal temperature (°C) were recorded.

Postoperatively, the patient's lactate, Hct, $K^+$ and $Na^+$ were recorded upon admission to ICU and 24h, 48h, and 72h thereafter.

The STS database was used to document the postoperative complications (cardiac arrest, arrhythmia, heart block, low cardiac output, acidosis, pericardial effusion requiring drainage, pulmonary hypertension, pneumothorax, pleural effusion requiring drainage, pneumonia, chylothorax, tracheostomy, phrenic or recurrent laryngeal nerve injury, respiratory insufficiency requiring mechanical ventilation >7 days postoperatively or reintubation, transient or permanent neurologic deficit, new onset seizures, wound/sternal dehiscence, infection/SIRS, endocarditis, acute renal failure, sternum left open, bleeding requiring reoperation,). In addition to the postoperative complications, postoperative outcomes were recoded; the time of inotropic support, time spent on a ventilator, ICU stay and mortality.

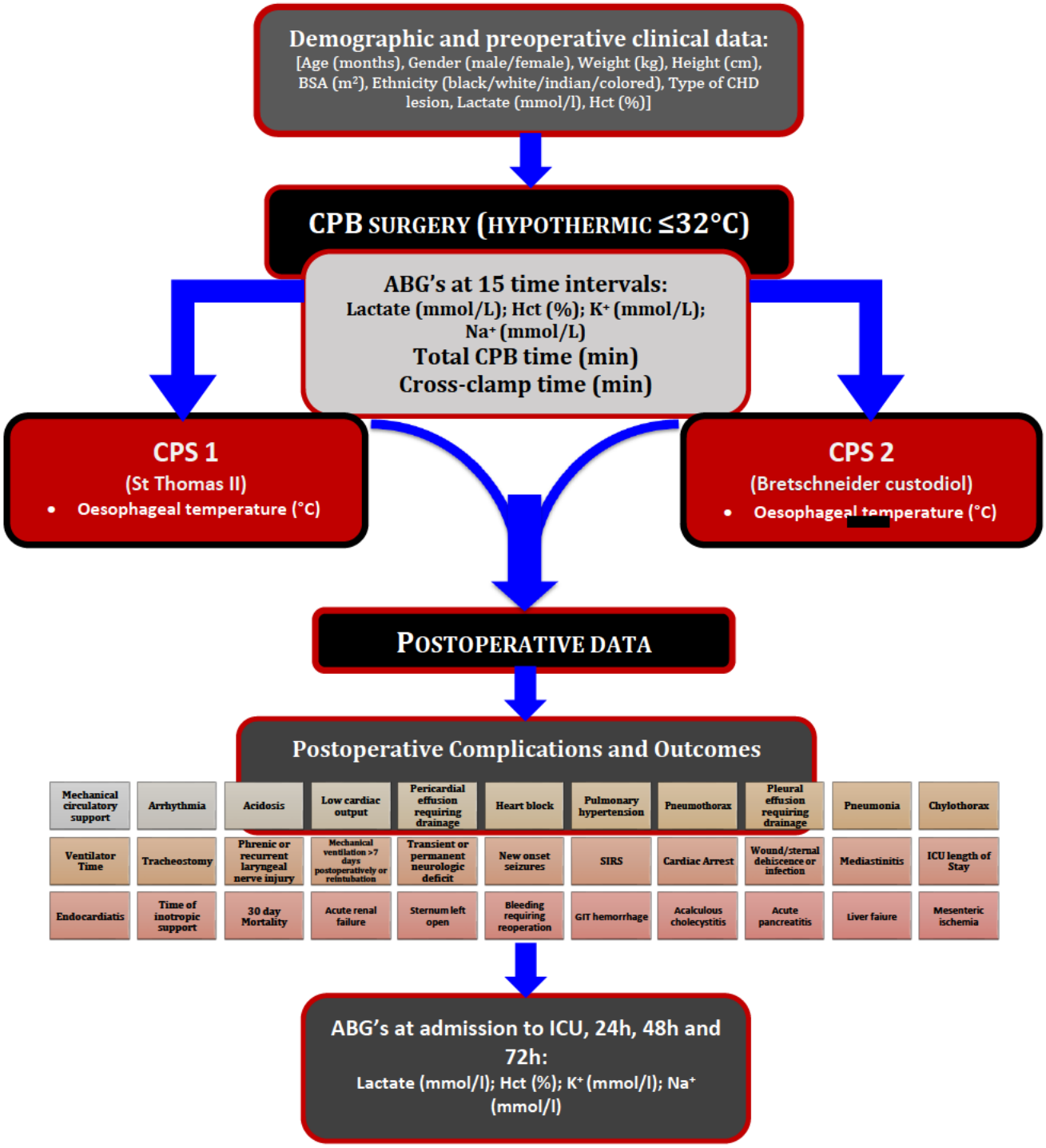



**Figure 3.2** **Conceptual framework for data collection – St Thomas II versus Bretschneider custodiol cardioplegia** (BSA – body surface area; CHD – congenital heart disease, Hct – haematocrit; $Na^+$ – sodium; $K^+$ – potassium; ICU – intensive care unit; ABG – arterial blood gas, SIRS – systemic inflammatory response syndrome, Intraop – intraoperative, mmol/L – millimoles per litre, % - percentage)

## 3.6 Special investigations

Demographic, clinical, intraoperative and postoperative data were recorded for each patient that met the inclusion criteria of the study. All the data were sourced from the patients' medical files.

### 3.6.1 Preoperative data

The following demographic and clinical data were recorded for each participant prior to surgery:

- Age (months/years)
- Gender (male/female)
- Ethnicity (black/white/indian/coloured)
- Weight (kg)
- Height (cm)
- BSA ($m^2$)
- Type of CHD lesion

### 3.6.2 Intraoperative data

#### 3.6.2.1 Metabolic data

In theatre but prior to surgery, one millilitre of whole blood was drawn in a pre-heparinized syringe for ABG analysis. The blood was drawn from an indwelling radial artery catheter after induction of anaesthesia (preoperative baseline values).

During CPB, blood was drawn from the sample port of the oxygenator after the initiation of bypass and every 15 minutes thereafter until termination of CPB. The following metabolic data were recorded from the ABG analysis:

- Lactate (mmol/L)

- Hct (%)
- K+ (mmol/L)
- Na+ (mmol/L)

Table 3.1 presents the references ranges (normal and abnormal) for the metabolic parameters analysed.

**Table 3.1 Normal and abnormal reference ranges for recorded metabolic data** (adapted from Fauci *et al.*, 2008)

| Arterial blood gas (ABG) Variable (Unit) | Normal reference range | For this study, abnormal values were defined as: |
|---|---|---|
| **Hct (%)** | New-borns: 55% - 68%<br>One week of age: 47% - 65%<br>One month of age: 37% - 49%<br>Three months of age: 30% - 36%<br>One year of age: 29% - 41%<br>Ten years of age: 36% - 40% | <24% |
| **$Na^+$ (mmol/L)** | 135-145mmol/L | <130mmol/L |
| **$K^+$ (mmol/L)** | 3.5-5.0mmol/L | >6mmol/L |
| **Lactate (mmol/L)** | <2mmol/L | >4mmol/L |

**(Hct – haematocrit; $Na^+$ – sodium; $K^+$ – potassium; ABG – arterial blood gas, mmol/L – millimoles per litre, % - percentage, < - less than, > - greater than)**

### 3.6.2.2 Perfusion and cardioplegia

Intraoperative perfusion data were recorded from the perfusion chart. The data included the aortic cross-clamp time (minutes), total CPB time (minutes) and the type of cardioplegic solution used.

The following two cardioplegic solutions were used during surgery, depending on surgeon's preference:

**i.) St Thomas II cardioplegia solution**

- 1000ml St Thomas II cardioplegia solution (Ref: SXA3024, Adcock Ingram Critical Care (PTY) Ltd, Johannesburg, RSA).
- 10ml 8.5% Sodium Bicarbonate (Intramed Sodium Bicarbonate Injection 8.5% (50ml) m/v, Ref: FSS850050, Fresenius Kabi for Bodene (PTY) Ltd trading as Intramed, Port Elisabeth, RSA).

**ii.) Bretschneider custodiol cardioplegia solution**

- 1000ml Bretschneider custodiol cardioplegia solution (Ref: Custodiol®, Dr. F. Köhler Chemie, Alsbach, Germany).

### 3.6.2.3 Cardiopulmonary bypass (CPB) surgery

All the patients included in this study underwent CPB surgery and had an aortic cross-clamp time exceeding 90 minutes. Table 3.2 is a summary of the surgical procedure.

**Table 3.2 Summarized surgical procedure for paediatric patients undergoing corrective cardiac surgery**

| Surgical Procedure | |
|---|---|
| **Pre-surgery** | • Soma sensors for In-Vivo Optical Spectroscopy (INVOS).<br>• Electrocardiogram (ECG) lead placement.<br>• Peripheral lines insertion.<br>• Arterial line insertion.<br>• Anaesthesia.<br>• Central venous line insertion. |
| **Surgery** | • Median sternotomy.<br>• Full systemic heparinization. Dosage 4mg/kg Heparin Sodium (Fresenius Kabi for Bodene (PTY) Ltd trading as Intramed, Port Elizabeth, RSA).<br>• Activated clotting time (ACT) 5 mins post-heparinization.<br>• Arterial cannulation (ascending aorta).<br>• Venous cannulation (superior and inferior vena cava).<br>• Commencement of CPB.<br>• Systemic hypothermia (≤32°C).<br>• Antegrade cardioplegia cannulation (Aortic root, proximal to aortic cannula).<br>• Aorta cross-clamped (between aortic cannula and antegrade cardioplegia cannula.<br>• Cold (±4°C) crystalloid cardioplegia infusion (repeated every 20 to 90 minutes).<br>• Topical ice slush applied on heart.<br>• Cardiac lesion repair.<br>• Patient rewarming.<br>• Aortic root de-air (left ventricle vent cannula).<br>• Aortic cross-clamp removed.<br>• Weaned from CPB at normothermia.<br>• Inotropic support commenced.<br>• Protamine for the reversal of heparinization. Dosage ¾ of heparin dose, 3mg/kg Protamine Sulphate (Pharmaceuticals LTD, Wrexham).<br>• Chest drains inserted (mediastinal and pericardial).<br>• Sternum closed.<br>• Skin closure. |

**(INVOS – in-vivo optical spectroscopy, ECG – electrocardiogram, ACT – activated clotting time, CPB – cardiopulmonary bypass, mg – milligram, kg – kilogram, PTY – proprietary, LTD – limited, °C – degrees Celsius, RSA – Republic of South Africa).**

## 3.6.3 Postoperative data

### 3.6.3.1 Metabolic data

Postoperative blood samples were drawn for ABG analysis from a radial arterial line. ABG samples were drawn at specified time intervals: upon admission to ICU and at 24hr, 48hr, and 72hr during the postoperative period in ICU. The same metabolic data was recorded from the ABG as mentioned intraoperatively.

#### 3.6.3.2 Postoperative clinical outcomes and complications

The clinical outcomes and complications recorded for each patient were based on the STS database as outlined (Society of Thoracic Surgeons, 2011) in Figure 3.1.

## 3.7 Statistical analysis

The statistical analyses were performed by a qualified biostatistician. Data were captured electronically by the researcher using Microsoft Excel. Statistical analyses were done with **R** software [**R** version 3.2.2 (2015-08-14), Copyright © 2015. The **R** Foundation for Statistical Computing, International Standard Book Number (ISBN) 3-900051-07-0, Platform: x86_64-pc-mingw32/x64 (64-bit)]. **R** is an open source programming language and software environment for statistical computing and graphics, t-tests and the calculation of confidence intervals were done with XLSTAT (XLSTAT Version 2016.03.30846). Data and results generated with **R** and XLSTAT and, where possible, validated with Microsoft ® Excel ® 2013 (Microsoft Corporation, Redmond, US).

Normally distributed continuous data was expressed as means and standard deviations, not-normally distributed data as medians and percentiles, and categorical data as frequencies and percentages. Data was compared using Student's t-test for normally distributed continuous variables, the Mann-Whitney test for continuous data that was not normally distributed and the $\chi^2$ or Fisher's exact $\chi^2$ test for categorical variables.

## 3.8 Ethical aspects and good clinical practice

### 3.8.1 Ethical clearance

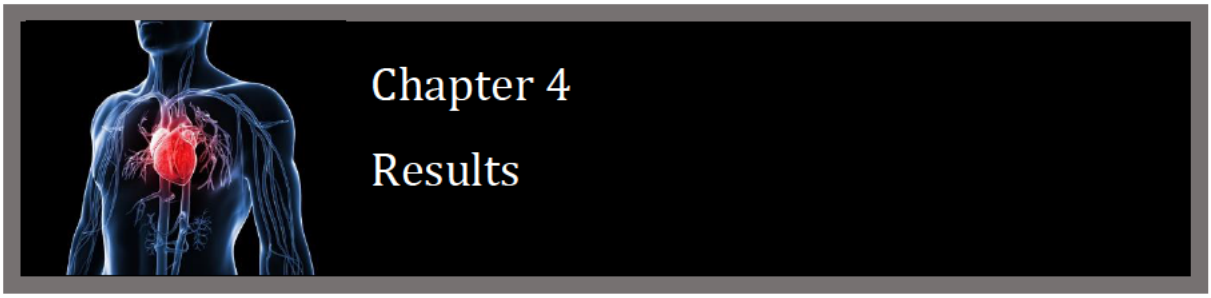
The study only commenced after ethical approval was granted by the Ethics committee of the University of the Free State (ECUFS NR 241/2015) (Appendix A).

### 3.8.2 Good clinical practice (GCP) / quality assurance

All clinical work conducted during this research project was subjected to the good clinical practice guidelines. The Declaration of Helsinki's basic principle number 3, states that research should be conducted only by scientifically qualified people and under the supervision of adequately qualified personnel involved (South African Good Clinical Practice guidelines, 2006; World Medical Association Declaration of Helsinki, 2013). Fundamentally GCP requires oversight of the local ethics committee, verification of the investigator's qualifications, a study protocol, informed consent and essential documentation needed to undertake the study, monitoring, submission of reports and maintenance of records. The application of GCP guidelines in this research study provides public assurance that the rights, safety and well-being of the participants are protected and that the research data are credible.

### 3.8.3 Confidentiality

Personal details of patients participating in this study were kept confidential, as far as possible. At no time during the research were the identity of patients revealed to persons not part of the research team. During the study, patients were identified by their hospital number (e.g. RXH 123 456 789), thus preventing the disclosure of the patient's personal details and ensuring patient confidentiality at all times.




## 4.1 Introduction

This chapter presents the results of the preoperative, intraoperative and postoperative variables recorded for ninety-six (n=96) patients that received corrective congenital heart surgery.

The demographic, anthropometric, clinical and postoperative complications and outcomes were compared between the lactate and cardioplegia groups. The results were analysed using the following statistical analysis methods; descriptive analysis, frequency tables, student's t-test, non-parametric Mann-Whitney test also known as the Wilcoxon rank-sum test, and the $Chi^2$ / Fisher exact test.

## 4.2 Peak intraoperative lactate <4mmol/L (group 1) versus peak intraoperative lactate ≥4mmol/L (group 2)

Ninety-six patients were divided into two cohorts. Group 1 (n=52; 54%) consisted of patients with all peak intraoperative blood lactate values less than 4mmol/L and group 2 (n=44; 46%), patients with at least one peak intraoperative lactate value equal or higher than 4mmol/L.

The demographic, anthropometric, clinical and postoperative complications and outcomes were compared between group 1 (peak intraoperative lactate <4mmol/L) and group 2 (peak intraoperative lactate value ≥4mmol/L). Results are presented in the form of figures and tables.

### 4.2.1 Demographic and anthropometric data

The demographic and anthropometric data were recorded preoperatively, and the summary statistics are depicted in Table 4.1. The summary statistics were calculated for the entire patient population (n=96) and per lactate group. The patients in group 1 were older and weigh more (median age 14.5 months; median weight 7.9kg) versus the patients with a peak intraoperative lactate value ≥4mmol/L (group 2) (median age 2.4 months; median weight 3.8kg).

**Table 4.1 Demographic and anthropometric data for all patients and individual lactate groups**

| Patient groups | Parameter / variable | Mean | SD | Median | Min | Max |
|---|---|---|---|---|---|---|
| **All patients (n=96)** | Age (months) | 32.928 | 44.236 | 12.000 | 0.097 | 181.000 |
| | Weight (kg) | 9.875 | 8.491 | 7.070 | 2.180 | 41.000 |
| | Height (cm) | 76.922 | 29.215 | 68.00 | 42.000 | 154.000 |
| | BSA ($m^2$) | 0.468 | 0.355 | 0.370 | 0.170 | 2.670 |
| **Group 1 (n=52)** | Age (months) | 29.377 | 33.562 | 14.500 | 1.000 | 157.000 |
| | Weight (kg) | 9.319 | 6.327 | 7.900 | 2.400 | 33.900 |
| | Height (cm) | 77.327 | 24.002 | 72.000 | 44.000 | 154.000 |
| | BSA ($m^2$) | 0.482 | 0.375 | 0.390 | 0.180 | 2.670 |
| **Group 2 (n=44)** | Age (months) | 37.125 | 54.349 | 2.400 | 0.097 | 181.000 |
| | Weight (kg) | 10.532 | 10.536 | 3.800 | 2.180 | 41.000 |
| | Height (cm) | 76.443 | 34.669 | 58.000 | 42.000 | 148.000 |
| | BSA ($m^2$) | 0.453 | 0.332 | 0.245 | 0.170 | 1.290 |

**(kg – kilograms; cm – centimetres; $m^2$ – meter square; BSA – body surface area; n – number of patients, SD – standard deviation, Min – minimum, Max - maximum).**

The gender and ethnicity are summarized in the frequency table below (Table 4.2). In both group 1 and group 2 most patients were female (52% vs 55%), coloured (52% vs 55%) patients (Figure 4.1 and 4.2).

**Table 4.2 Gender and ethnicity of all patients and individual lactate groups**

| Variable | Detail | All patients (n=96) | Group 1 (n=52) | Group 2 (n=44) |
|---|---|---|---|---|
| Gender | Male | 45 (47%) | 25 (48%) | 20 (45%) |
| | Female | 51 (53%) | 27 (52%) | 24 (55%) |
| Ethnicity | White | 5 (5%) | 2 (4%) | 3 (7%) |
| | Coloured | 51 (53%) | 27 (52%) | 24 (55%) |
| | Black | 37 (39%) | 21 (40%) | 16 (36%) |
| | Asian | 3 (3%) | 2 (4%) | 1 (2%) |

(n – number of patients, % - percentage)

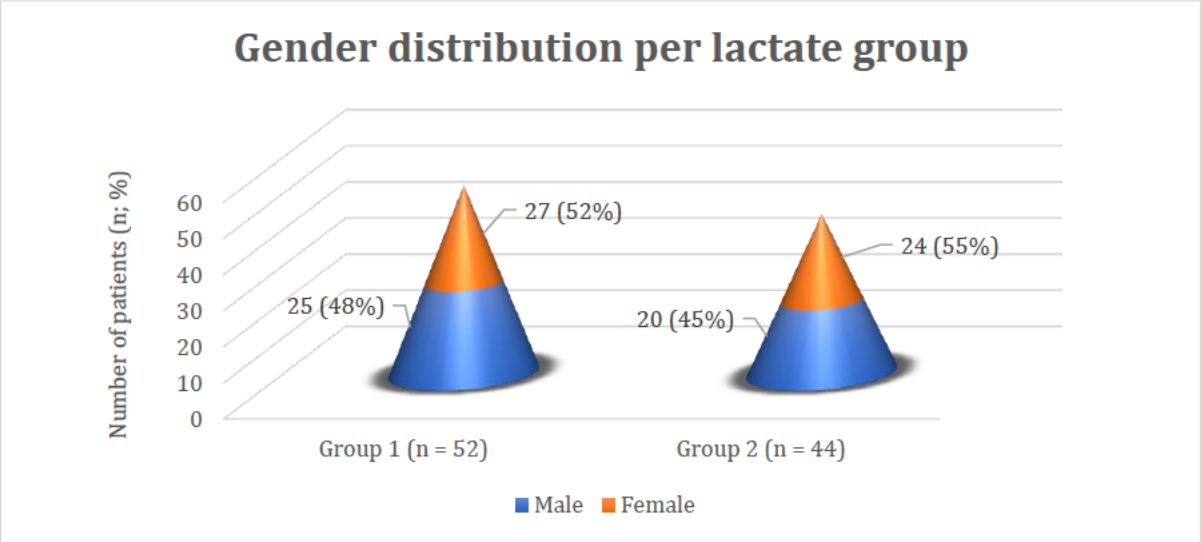



**Figure 4.1 Gender distribution per lactate group** (n – number of patients, % - percentage)

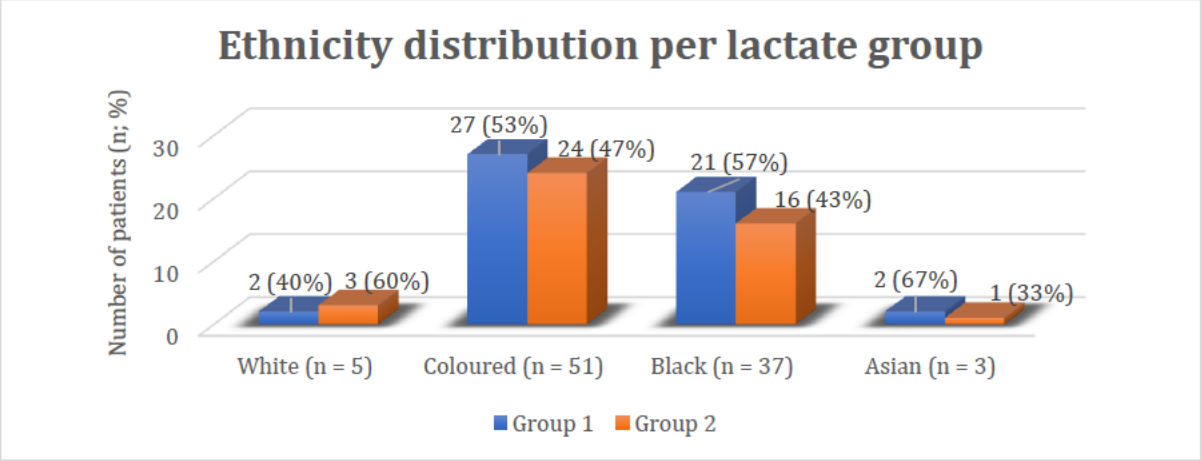



**Figure 4.2 Ethnicity distribution per lactate group** (n – number of patients, % - percentage)

#### 4.2.1.1 Demographic and anthropometric data: comparison between group 1 and 2

The two groups were comparable with regards to the demographic variables; weight, height and BSA, as well as for gender and ethnicity. All p-values were much higher than the 0.05 significant limit (Table 4.3), except for age (p = 0.0438).

**Table 4.3 Demographic and anthropometric data: comparison between group 1 and 2**

| Variable | Category | Group 1 (n=52) | Group 2 (n=44) | p-value | Method of comparison |
|---|---|---|---|---|---|
| **Age (months)** | | 29.377 | 37.125 | 0.0438* | Mann- Whiney U |
| **Weight (kg)** | | 9.317 | 10.532 | 0.1623 | Mann- Whiney U |
| **Height (cm)** | | 77.327 | 76.443 | 0.1701 | Mann- Whiney U |
| **BSA ($m^2$)** | | 0.482 | 0.453 | 0.1063 | Mann- Whiney U |
| **Gender** | Male | 25 | 20 | 0.9591 | $Chi^2$ |
| | Female | 27 | 24 | | |
| **Ethnicity** | White | 2 | 3 | 0.8924 | Fisher's Exact test |
| | Coloured | 27 | 24 | | |
| | Black | 21 | 16 | | |
| | Asian | 2 | 1 | | |

(* statistical significance; kg – kilograms; cm – centimetres; $m^2$ – meter square; n – number of patients)

### 4.2.2 Type of cardiac lesion

The type of cardiac lesions recorded for group 1 and group 2 are illustrated in Figure 4.3. In group 1 most patients presented with transposition of the great arteries (n=15; 34%) and in group 2 the most prevalent cardiac lesion was an AVSD (n=10; 19%).

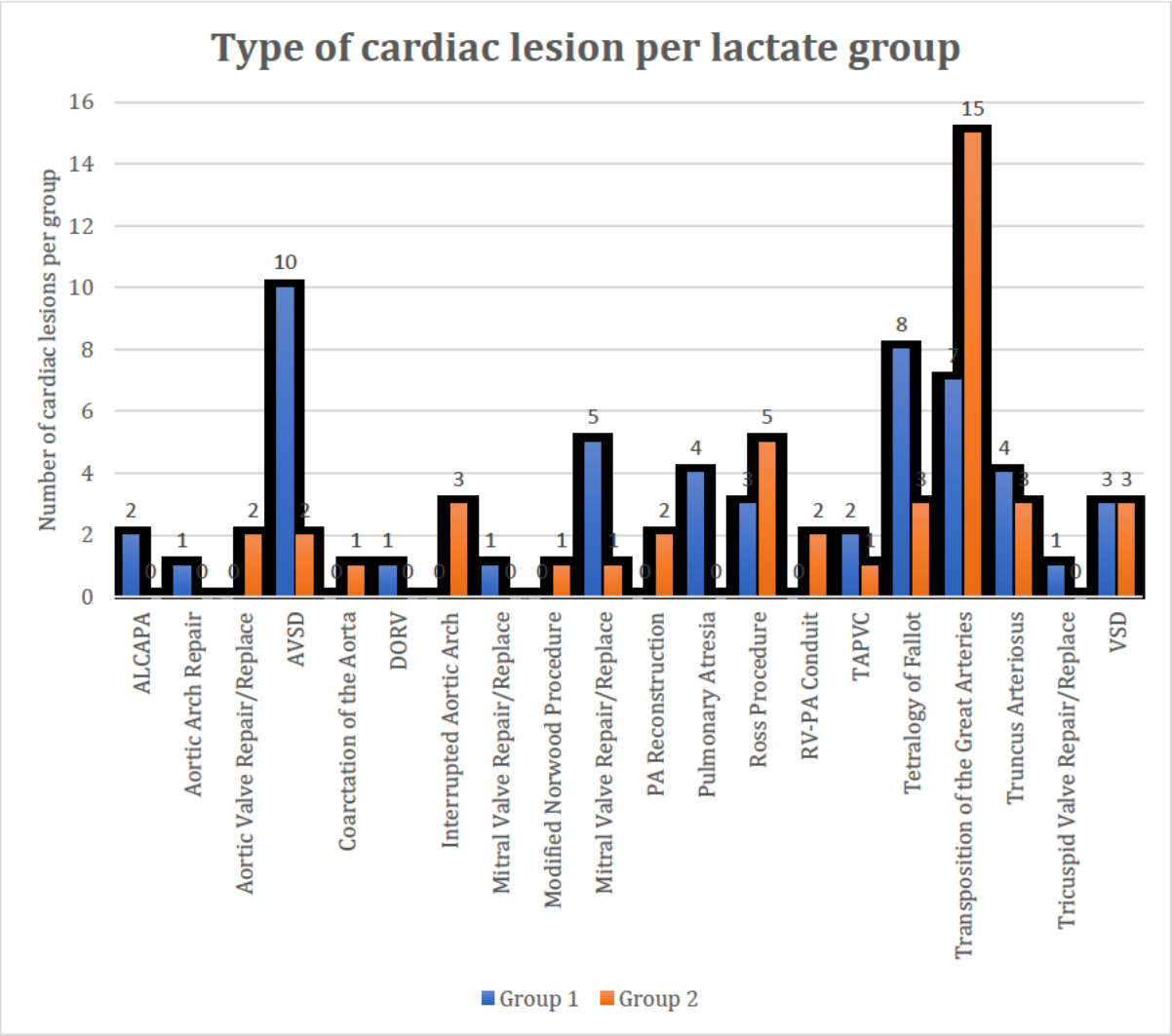



**Figure 4.3** **Type of cardiac lesion per lactate group** (ALCAPA – Anomalous left coronary artery from the pulmonary artery, AVSD – Atrioventricular septal defect, DORV – Double outlet right ventricle, PA – Pulmonary artery, RV – Right ventricle, TAPVC – Total anomalous pulmonary venous connection, VSD – Ventricular septal defect)

### 4.2.3 Metabolic data

Lactate (mmol/L) haematocrit (%), sodium (mmol/L) and potassium (mmol/L) were recorded preoperatively, intraoperatively and postoperatively at specific time points. Only lactate and haematocrit values were analysed per lactate group because $Na^+$ and $K^+$ values are influenced by the type of cardioplegic solution used during bypass. These two parameters were analysed when the patients were divided based on the type of cardioplegic solution used during CPB.

### 4.2.3.1 Lactate (mmol/L)

The lactate values intraoperatively per time point included a preoperative CPB value (Pre-CPB) and an intraoperative CPB peak lactate value (Intra-CPB-High) (Table 4.4). Postoperatively lactate values were recorded upon admission to ICU (Post-CPB-ICU) and then after 24h (Post-CPB-24h), 48h (Post-CPB-48h) and 72h (Post-CPB-72h) (Table 4.4). The data were analysed descriptively, and the values are listed in Table 4.4.

**Table 4.4 Lactate values (mmol/L) over time per lactate group**

| Time Point | Group 1 (n=52) | | | | | | Group 2 (n=44) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Median | Min | Max | n | Mean | SD | Median | Min | Max | n |
| **Pre-CPB** | 1.230 | 0.437 | 1.100 | 0.500 | 2.000 | 52 | 1.070 | 0.368 | 1.000 | 0.300 | 2.000 | 44 |
| **Intra-CPB-High** | 2.400 | 0.745 | 2.350 | 1.200 | 3.900 | 52 | 5.100 | 2.378 | 4.600 | 1.400 | 11.300 | 44 |
| **Post-CPB-ICU** | 2.190 | 0.837 | 1.900 | 0.900 | 3.900 | 49 | 4.030 | 1.945 | 4.000 | 1.100 | 7.900 | 42 |
| **Post-CPB-24h** | 1.580 | 0.584 | 1.600 | 0.600 | 3.500 | 49 | 2.850 | 2.022 | 2.300 | 0.800 | 9.800 | 42 |
| **Post-CPB-48h** | 1.180 | 0.497 | 1.000 | 0.600 | 2.600 | 46 | 1.790 | 1.568 | 1.300 | 0.600 | 8.200 | 41 |
| **Post-CPB-72h** | 1.240 | 0.603 | 1.100 | 0.600 | 3.200 | 41 | 1.300 | 1.264 | 1.050 | 0.000 | 6.300 | 44 |

**(SD – standard deviation, Min – minimum, Max – maximum, n – number of patients, Pre-CPB – preoperative cardiopulmonary bypass, Intra-CPB – intraoperative cardiopulmonary bypass, Post-CPB – postoperative cardiopulmonary bypass, h - hour)**

Because group 1 and 2 were created based on high and low lactate values it is no surprise that statistical significance is present intraoperatively between group 1 and 2 ($p<0.0001$). Postoperatively, the lactate values in group 1 was significantly lower compared to those in group 2, explaining the statistical significance between the 2 groups (Table 4.5). However, at 48h post-CPB both groups had normal mean lactate values of <2mmol/L (group 1 = mean 1.180mmol/L; group 2 = mean 1.785mmol/L).

**Table 4.5 Mean lactate values (mmol/L) over time: comparison between lactate group 1 and 2**

| Time point | Group 1 (n=52) | Group 2 (n=44) | p-value |
|---|---|---|---|
| **Pre-CPB** | 1.225 | 1.066 | 0.0558 |
| **Intra-CPB-High** | 2.402 | 5.098 | <0.0001* |
| **Post-CPB-ICU** | 2.186 | 4.031 | <0.0001* |
| **Post-CPB-24h** | 1.582 | 2.848 | 0.0003* |
| **Post-CPB-48h** | 1.180 | 1.785 | 0.0221* |
| **Post-CPB-72h** | 1.225 | 1.634 | 0.0753 |

(* statistical significance, n – number of patients, Pre-CPB – preoperative cardiopulmonary bypass, Intra-CPB – intraoperative cardiopulmonary bypass, Post-CPB – postoperative cardiopulmonary bypass, h – hour)

The graphical presentation of these values is available as Figure 4.4.

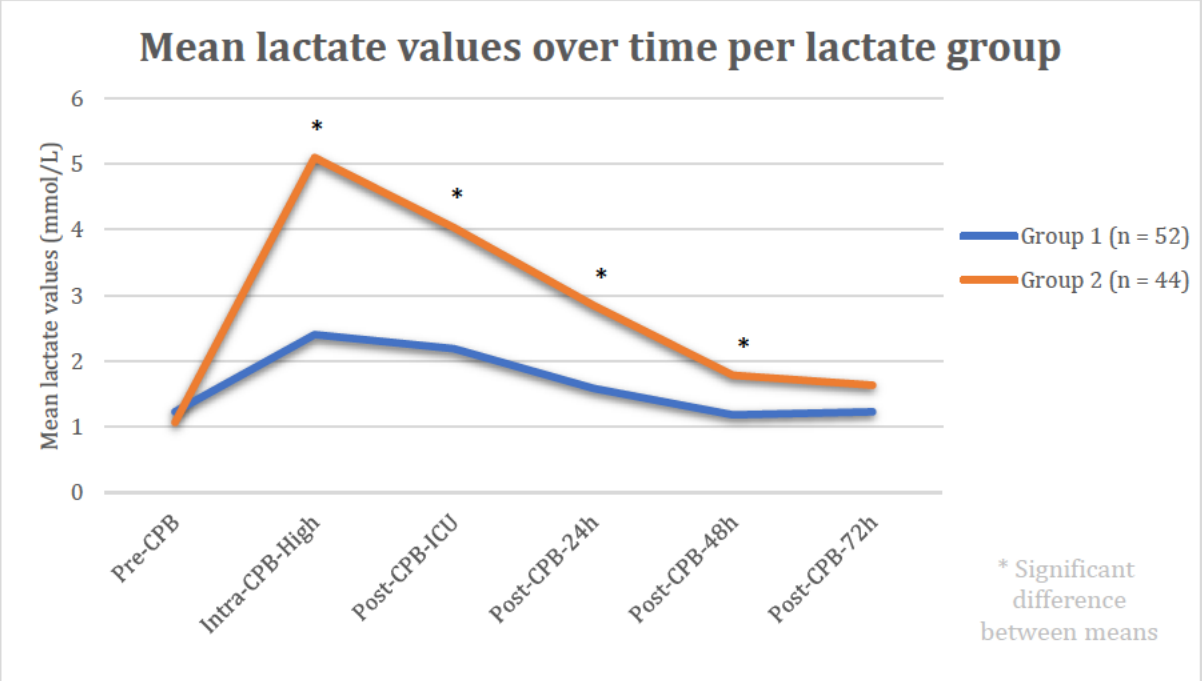



**Figure 4.4 Graphical presentation of mean lactate values over time per lactate group** (n – number of patients, Pre-CPB – preoperative cardiopulmonary bypass, Intra-CPB – intraoperative cardiopulmonary bypass, Post-CPB – postoperative cardiopulmonary bypass, h – hour)

### 4.2.3.2 Haematocrit (%)

The haematocrit values for each time point (Pre-CPB, Intra-CPB-low, Post-CPB-ICU, Post-CPB-24h, Post-CPB-48h, Post-CPB-72h) were analysed descriptively and the values are listed in Table 4.6. Note that intraoperatively the lowest haematocrit value (Intra-CPB-low) in each group were recorded. In both groups, the highest mean haematocrit values

were recorded upon admission to ICU post-CPB surgery (group 1, 40.57% versus group 2, 42.55%) (Table 4.6).

**Table 4.6 Haematocrit values (%) over time per lactate group**

| Time Point | Group 1 (n=52) | | | | | | Group 2 (n=44) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Median | Min | Max | n | Mean | SD | Median | Min | Max | N |
| Pre-CPB | 39.04 | 9.728 | 36.00 | 21.00 | 65.00 | 52 | 38.80 | 10.866 | 35.00 | 24.00 | 65.00 | 44 |
| Intra-CPB-Low | 27.71 | 4.317 | 27.00 | 19.00 | 44.00 | 52 | 26.64 | 4.895 | 26.00 | 16.00 | 40.00 | 44 |
| Post-CPB-ICU | 40.57 | 7.340 | 40.00 | 29.00 | 63.00 | 49 | 42.55 | 6.432 | 41.50 | 32.00 | 62.00 | 42 |
| Post-CPB-24h | 38.24 | 7.061 | 38.00 | 27.00 | 60.00 | 49 | 39.52 | 6.078 | 40.00 | 24.00 | 52.00 | 42 |
| Post-CPB-48h | 35.35 | 5.083 | 33.50 | 26.00 | 46.00 | 46 | 37.44 | 5.496 | 37.00 | 26.00 | 50.00 | 41 |
| Post-CPB-72h | 34.60 | 4.278 | 34.00 | 27.00 | 45.00 | 40 | 36.2 | 5.930 | 35.00 | 25.00 | 50.00 | 35 |

(SD – standard deviation, Min – minimum, Max – maximum, CPB – cardiopulmonary bypass, ICU – intensive care unit, n=number of patients, Pre-CPB – preoperative cardiopulmonary bypass, Intra-CPB – intraoperative cardiopulmonary bypass, Post-CPB – postoperative cardiopulmonary bypass, h - hour)

The haematocrit values for the two groups presented with no statistical significant differences ($p>0.05$) at the recorded time points (Table 4.7) utilising the Student's t-test. The graphical presentation of these values is available as Figure 4.5 and according to the line graphs all the Hct values at all the recorded time-points are very similar between the 2 groups.

**Table 4.7 Mean haematocrit values (%) over time: comparison between lactate group 1 and 2**

| Time point | Group 1 (n=52) | Group 2 (n=44) | p-value |
|---|---|---|---|
| Pre-CPB | 39.038 | 38.795 | 0.9091 |
| Intra-CPB-Low | 27.711 | 26.636 | 0.2610 |
| Post-CPB-ICU | 40.571 | 42.548 | 0.1745 |
| Post-CPB-24h | 38.245 | 39.524 | 0.3556 |
| Post-CPB-48h | 35.348 | 37.439 | 0.0701 |
| Post-CPB-72h | 34.600 | 36.200 | 0.1907 |

(CPB – cardiopulmonary bypass, ICU – intensive care unit, n – number of patients, Pre-CPB – preoperative cardiopulmonary bypass, Intra-CPB – intraoperative cardiopulmonary bypass, Post-CPB – postoperative cardiopulmonary bypass, h - hour)

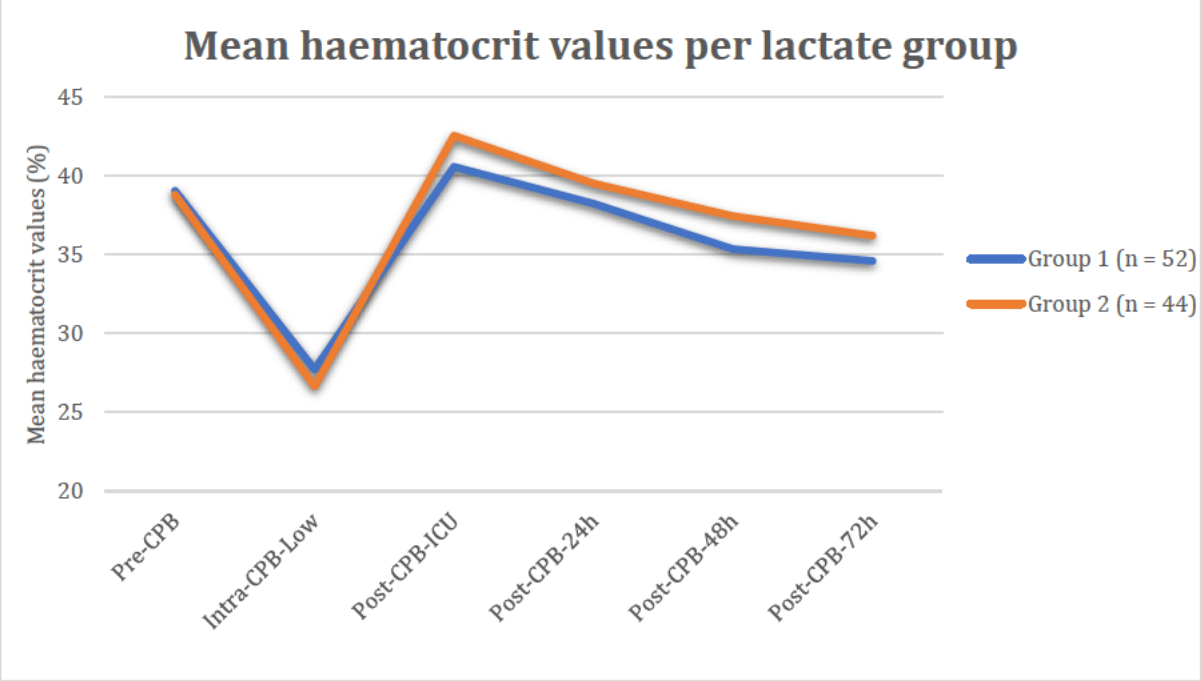



**Figure 4.5** **Graphical presentation of mean haematocrit values over time per lactate group** (n – number of patients, Pre-CPB – preoperative cardiopulmonary bypass, Intra-CPB – intraoperative cardiopulmonary bypass, Post-CPB – postoperative cardiopulmonary bypass, h – hour)

### 4.2.4 Aortic cross-clamp time (min), CPB time (min) and oesophageal temperature (°C)

The aortic cross-clamp time, total CPB time, and oesophageal temperature were recorded intraoperatively and the descriptive statistics per group is summarized in Table 4.8. The mean aortic cross-clamp time and total bypass time were much longer in group 2 (144.5min; 221.4min) compared to group 1 (125.3min; 178.1min). The mean oesophageal temperature was much higher in group 1 (28°C) compared to group 2 (26°C) (Table 4.8).

**Table 4.8 Intraoperative aortic cross-clamp time (min), CPB time (min) and oesophageal temperature (°C) per lactate group**

| Time Point | Group 1 (n=52) | | | | | | Group 2 (n=44) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Median | Min | Max | n | Mean | SD | Median | Min | Max | N |
| Aortic cross-clamp time (min) | 125.30 | 32.230 | 115.00 | 78.00 | 212.00 | 52 | 144.50 | 39.880 | 130.50 | 99.00 | 261.00 | 44 |
| Total CPB time (min) | 178.10 | 53.720 | 163.00 | 102.00 | 342.00 | 52 | 221.40 | 66.640 | 217.00 | 119.00 | 418.00 | 44 |
| Oesophageal temperature (°C) | 27.95 | 3.7190 | 28.15 | 19.70 | 32.00 | 52 | 25.51 | 4.523 | 25.00 | 18.80 | 32.00 | 44 |

(SD – standard deviation, Min – minimum, Max – maximum, min – minutes, n – number of patients, Pre-CPB – preoperative cardiopulmonary bypass, Intra-CPB – intraoperative cardiopulmonary bypass, Post-CPB – postoperative cardiopulmonary bypass, h – hour)

The mean values were compared between the 2 groups (Student's t-test) and the p-values are listed in Table 4.9. All three recorded variables presented with statistical significance between the two (2) groups, with the most significant being the total time spent on CPB (p=0.0007) (Table 4.9).

**Table 4.9 Mean intraoperative aortic cross-clamp time (min), CPB time (min) and oesophageal temperature (°C): comparison between group 1 and 2**

| Variable | Group 1 (n=52) | Group 2 (n=44) | p-value |
|---|---|---|---|
| Aortic cross-clamp time (min) | 125.3 ± 32.2 | 144.5 ± 39.9 | 0.0106* |
| Total CPB time (min) | 178.1 ± 53.7 | 221.4 ± 66.6 | 0.0007* |
| Oesophageal temperature (°C) | 28.0 ± 3.7 | 25.5 ± 4.5 | 0.0045* |

(* - Statistical significance) (min – minutes, °C – degrees Celsius, n – number of patients, Pre-CPB – preoperative cardiopulmonary bypass, Intra-CPB – intraoperative cardiopulmonary bypass, Post-CPB – postoperative cardiopulmonary bypass, h – hour)

### 4.2.5 Postoperative complications and clinical outcomes

#### 4.2.5.1 Postoperative complications

The postoperative complications per lactate group are depicted in Table 4.10 and is expressed as percentages. Wound/Sternal dehiscence (p=0.0208) and sternum left open (p=0.0157) were the only two postoperative complications that presented with statistical

differences (Table 4.10). The percentages of the postoperative complications per lactate group are presented graphically in Figure 4.6. The postoperative complications that occurred 0% in both group 1 and 2 were excluded from Table 4.10 and Figure 4.6.

**Table 4.10 Postoperative complications per lactate group**

| Variable | Group 1 (n=52) n/% | Group 2 (n=44) n/% | p-value | Method of Comparison |
|---|---|---|---|---|
| Cardiac arrest | 6/52 (11.5%) | 5/44 (11.4%) | >0.9999 | Fisher's Exact test |
| Arrhythmia | 8/52 (15.4%) | 9/44 (20.5%) | 0.7039 | Chi² test |
| Heart block | 7/52 (13.5%) | 8/44 (18.2%) | 0.7244 | Chi² test |
| Low cardiac output | 2/52 (3.8%) | 4/44 (9.1%) | 0.4080 | Fisher's Exact test |
| Acidosis | 15/52 (28.8%) | 15/44 (34.1%) | 0.7403 | Chi² test |
| Pericardial effusion requiring drainage | 2/52 (3.8%) | 3/44 (6.8%) | 0.6580 | Fisher's Exact test |
| Pulmonary hypertension | 3/52 (5.8%) | 0/44 (0%) | 0.2474 | Fisher's Exact test |
| Pneumothorax | 7/52 (13.5%) | 5/44 (11.4%) | >0.9999 | Fisher's Exact test |
| Pleural effusion requiring drainage | 8/52 (15.4%) | 9/44 (20.5%) | 0.7039 | Chi² test |
| Pneumonia | 9/52 (17.3%) | 6/44 (13.6%) | 0.8325 | Chi² test |
| Chylothorax | 1/52 (1.9%) | 2/44 (4.5%) | 0.5917 | Fisher's Exact test |
| Tracheostomy | 1/52 (1.9%) | 0/44 (0.0%) | >0.9999 | Fisher's Exact test |
| Phrenic or recurrent laryngeal nerve injury | 2/52 (3.8%) | 2/44 (4.5%) | >0.9999 | Fisher's Exact test |
| Respiratory insufficiency requiring mechanical ventilation >7 days postoperatively or reintubation | 10/52 (19.2%) | 12/44 (27.3%) | 0.4899 | Chi² test |
| Transient or permanent neurologic deficit | 1/52 (1.9%) | 0/44 (0%) | >0.9999 | Fisher's Exact test |
| New onset seizures | 1/52 (1.9%) | 3/44 (6.8%) | 0.3297 | Fisher's Exact test |
| Wound/sternal dehiscence | 2/52 (3.8%) | 9/44 (20.5%) | 0.0208* | Fisher's Exact test |
| Infection/SIRS | 24/52 (46.2%) | 28/44 (63.6%) | 0.1317 | Chi² test |
| Endocarditis | 1/52 (1.9%) | 2/44 (4.5%) | 0.5917 | Fisher's Exact test |
| Acute renal failure | 12/52 (23.1%) | 10/44 (22.7%) | >0.9999 | Chi² test |
| Sternum left open | 6/52 (11.5%) | 15/44 (34.1%) | 0.0157* | Chi² test |
| Bleeding requiring reoperation | 1/52 (1.9%) | 3/44 (6.8%) | 0.3297 | Fisher's Exact test |

(* - Statistical significance, SIRS – systemic inflammatory response syndrome, n – number of patients, Pre-CPB – preoperative cardiopulmonary bypass, Intra-CPB – intraoperative cardiopulmonary bypass, Post-CPB – postoperative cardiopulmonary bypass, h – hour)

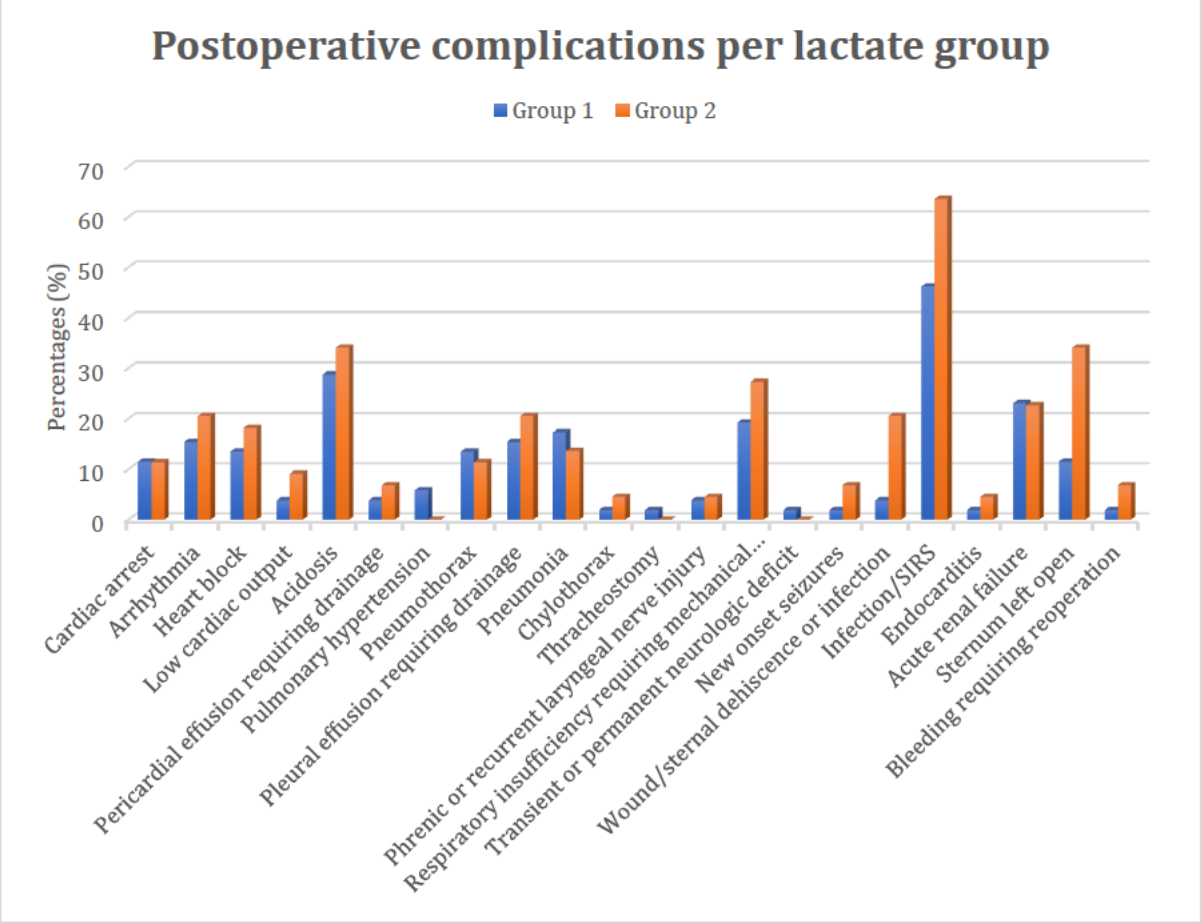



**Figure 4.6** **Postoperative complications as percentages per lactate group** (SIRS – systemic inflammatory response syndrome)

### 4.2.5.2 Postoperative clinical outcomes

The descriptive statistics of the postoperative clinical outcomes which included inotropic support time (hr), intubation time (hr) and ICU stay (days) per lactate group are summarized in Table 4.11. The patients in group 2 received inotropic support for longer (mean 137.40 hr), were intubated longer (mean 95.20 hr) and stayed longer in ICU (mean 8.96 days) compared to group 1 (Table 4.11).

**Table 4.11 Postoperative clinical outcomes per lactate group**

| Variable | Group 1 (n=52) | | | | | | Group 2 (n=44) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Median | Min | Max | n | Mean | SD | Median | Min | Max | n |
| Inotropic support time (hr) | 106.70 | 92.70 | 76.50 | 1.00 | 908.00 | 46 | 137.40 | 150.20 | 94.00 | 0.00 | 28.001 | 43 |
| Intubation time (hr) | 70.30 | 74.30 | 45.00 | 0.00 | 384.00 | 46 | 95.20 | 91.4 | 69.00 | 2.00 | 316.00 | 43 |
| ICU stay (days) | 6.80 | 6.00 | 5.00 | 1.00 | 41.00 | 47 | 8.96 | 8.00 | 6.00 | 1.00 | 27.00 | 43 |

(SD – standard deviation, Min – minimum, Max – maximum, ICU – intensive care unit, hr – hour, n – number of patients)

The mean postoperative clinical outcome values were compared between the two lactate groups and the p-values calculated (Student's t-test). No statistical significant differences were calculated for any of the postoperative outcome variables between the two groups ($p>0.05$) (Table 4.12).

**Table 4.12 Postoperative clinical outcomes: comparison between group 1 and 2**

| Variables | Group 1 (n=52) (mean ±SD) | Group 2 (n=44) (mean ±SD) | p-value |
|---|---|---|---|
| Inotropic Support Time (hr) | 106.7 ±92.7 | 137.4 ±150.2 | 0.2434 |
| Intubation Time (hr) | 70.3 ±74.3 | 95.2 ±91.4 | 0.1604 |
| ICU stay (days) | 6.8 ±6.0 | 8.96 ±8.0 | 0.1646 |

(SD – standard deviation, hr – hours, ICU – intensive care unit, n – number of patients).

The mortality rate for both lactate groups are presented in Table 4.13. There is no statistical difference between the two lactate groups with regard to mortality ($p=0.6805$) (Table 4.13).

**Table 4.13 Mortality rate per lactate group**

| | Group 1 (n=52) | Group 2 (n=44) | p-value |
|---|---|---|---|
| **No mortality** | 45 (86%) | 36 (82%) | 0.6805 |
| **Mortality <30 days** | 4 (8%) | 5 (11%) | |
| **Mortality >30 days** | 2 (4%) | 3 (7%) | |
| **Unknown** | 1 (2%) | 0 (0%) | |

(n – number of patients)

### 4.2.6 Cardioplegic solutions

In group 1 most patients received St Thomas II cardioplegic solution (75%) and in group 2 the majority of patients received Bretschneider custodiol cardioplegic solution (55%). The comparison between the two groups are statistically significant (p=0.0036) (Table 4.14).

**Table 4.14 Cardioplegic solutions per lactate group**

| Cardioplegic solution | Group 1 (n=52) | Group 2 (n=44) | p-value |
|---|---|---|---|
| **St Thomas II cardioplegic solution** | 39 (75%) | 20 (45%) | 0.0036* |
| **Bretschneider custodiol cardioplegic solution** | 13 (25%) | 24 (55%) | |

(* - Statistical significance, n – number of patients)

## 4.3 St Thomas II versus Bretschneider custodiol cardioplegic solution

Ninety-six (n=96) CHD patients were divided according to the cardioplegic solution used during CPB surgery. These two groups are presented as cardioplegic solution one (CPS 1) which is patients that received St Thomas II cardioplegia [n=59 (61%)] and cardioplegic solution two (CPS 2) which is patients that received Bretschneider custodiol cardioplegia [n=37 (39%)] during CPB surgery.

The demographic, anthropometric, clinical and postoperative complications and outcomes were compared between CPS 1 and CPS 2. Results are presented as tables and figures.

### 4.3.1 Demographic and anthropometric data

The demographic and anthropometric data were recorded preoperatively, and the summary statistics are depicted in Table 4.15. The summary statistics were calculated per cardioplegia solution group. The patients that received St Thomas II solution (CPS 1; 61%) were older and weigh more (median age 19.00 months; median weight 8.3kg) compared to the patients that received Bretschneider custodiol solution (CPS 2; 39%) (median age 8.35 months; median weight 6.24kg) (Table 4.15).

**Table 4.15 Demographic and anthropometric data per cardioplegia group**

| Patient group | Parameter or variable | Mean | SD | Median | Min | Max |
|---|---|---|---|---|---|---|
| CPS 1 (n=59) | Age (months) | 40.96 | 44.726 | 19.00 | 0.3 | 157.0 |
| | Weight (kg) | 11.52 | 8.682 | 8.30 | 2.4 | 41.0 |
| | Height (cm) | 83.79 | 28.653 | 76.00 | 42.0 | 154.0 |
| | BSA (m2) | 0.54 | 0.392 | 0.43 | 0.2 | 2.7 |
| CPS 2 (n=37) | Age (months) | 20.12 | 40.820 | 8.35 | 0.1 | 181.0 |
| | Weight (kg) | 7.25 | 7.567 | 6.24 | 2.2 | 35.0 |
| | Height (cm) | 65.97 | 27.003 | 50.00 | 42.0 | 144.0 |
| | BSA (m2) | 0.35 | 0.251 | 0.34 | 0.2 | 1.2 |

(kg – kilograms, cm – centimetres, $m^2$ – meter square, BSA – body surface area, n – number of patients, CPS – cardioplegic solution, Min – minimum, Max – maximum, SD – standard deviation)

The gender and ethnicity per cardioplegic group are summarized in the frequency table below (Table 4.16). In both CPS 1 and CPS 2 the majority of patients were female (54% vs. 51%), coloured (51% vs. 57%) patients (Figure 4.7 and 4.8).

**Table 4.16 Gender and ethnicity per cardioplegic group**

| Variable | Detail | CPS 1 (n=59) | CPS 2 (n=37) |
|---|---|---|---|
| Gender | Male | 27 (46%) | 18 (49%) |
| | Female | 32 (54%) | 19 (51%) |
| Ethnicity | White | 3 (5%) | 2 (5%) |
| | Coloured | 30 (51%) | 21 (57%) |
| | Black | 24 (41%) | 13 (35%) |
| | Asian | 2 (3%) | 1 (3%) |

(n – number of patients, % - percentage)

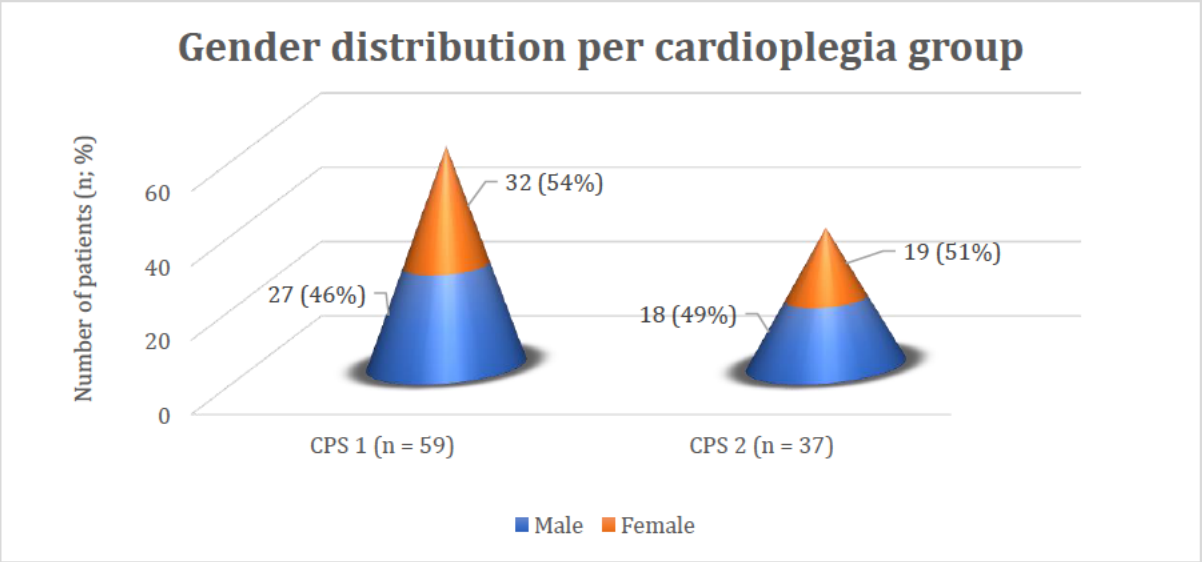



**Figure 4.7 Gender distribution per cardioplegia group** (n = number of patients, % - percentage)

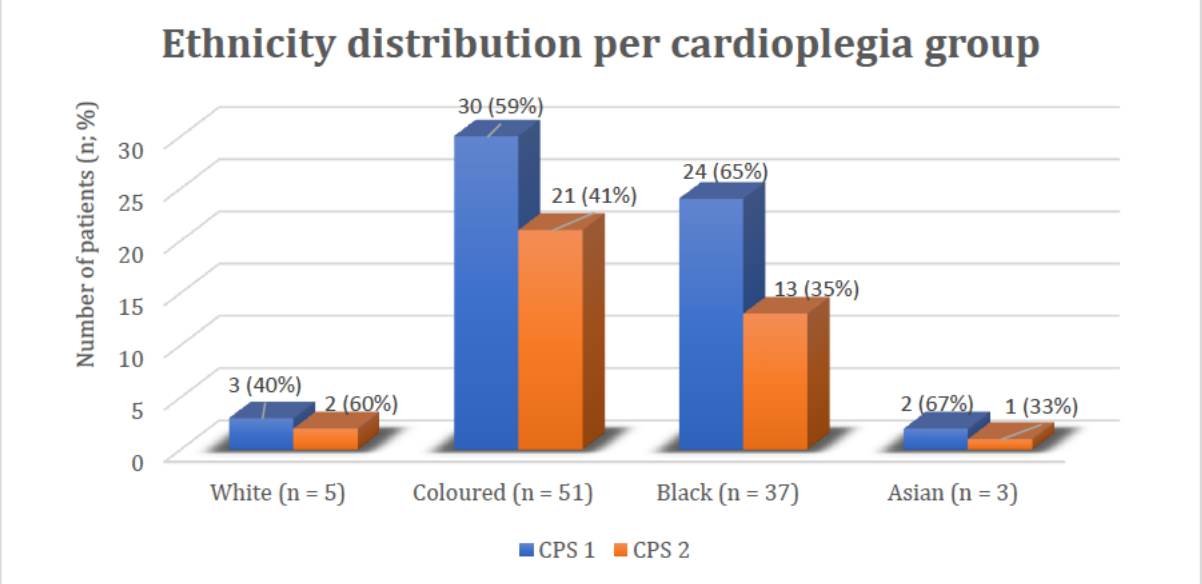



**Figure 4.8 Ethnicity distribution per cardioplegia group** (n = number of patients, % - percentage)

#### 4.3.1.1 Demographic and anthropometric data: comparison between CPS 1 and 2

The two cardioplegia groups were comparable regarding gender and ethnicity because the p-values were higher than the 0.05 significant limit (Table 4.17). However, for age, weight, height, and BSA the two (2) cardioplegia groups were statistically significant different with p-values significantly lower than the 0.05 limit (Table 4.17).

**Table 4.17 Demographic and anthropometric data: comparison between CPS 1 and 2**

| Variable | Category | CPS 1 (n=59) | CPS 2 (n=37) | p-value | Method of comparison |
|---|---|---|---|---|---|
| **Age (months)** | - | 40.96 | 20.12 | <0.0001* | Mann-Whiney U |
| **Weight (kg)** | - | 11.52 | 7.25 | 0.0004* | Mann-Whiney U |
| **Height (cm)** | - | 83.79 | 65.97 | 0.0003* | Mann-Whiney U |
| **BSA ($m^2$)** | - | 0.54 | 0.35 | 0.0002* | Mann-Whiney U |
| **Gender** | Male | 27 | 18 | 0.8354 | $Chi^2$ |
| | Female | 32 | 19 | | |
| **Ethnicity** | White | 3 | 2 | 0.9465 | Fisher's Exact test |
| | Coloured | 30 | 21 | | |
| | Black | 24 | 12 | | |
| | Asian | 2 | 1 | | |

(* statistical significance, kg – kilograms, cm – centimetres, $m^2$ – meter square, n – number of patients).

### 4.3.2 Type of cardiac lesion

Figure 4.9 illustrates the type of cardiac lesions recorded for CPS 1 and CPS 2. In CPS 1 most patients presented with AVSD (n=12; 20%) and Tetralogy of Fallot (n=11; 19%), and in CPS 2 the most prevalent cardiac lesion was transposition of the great arteries (n=20; 54%).

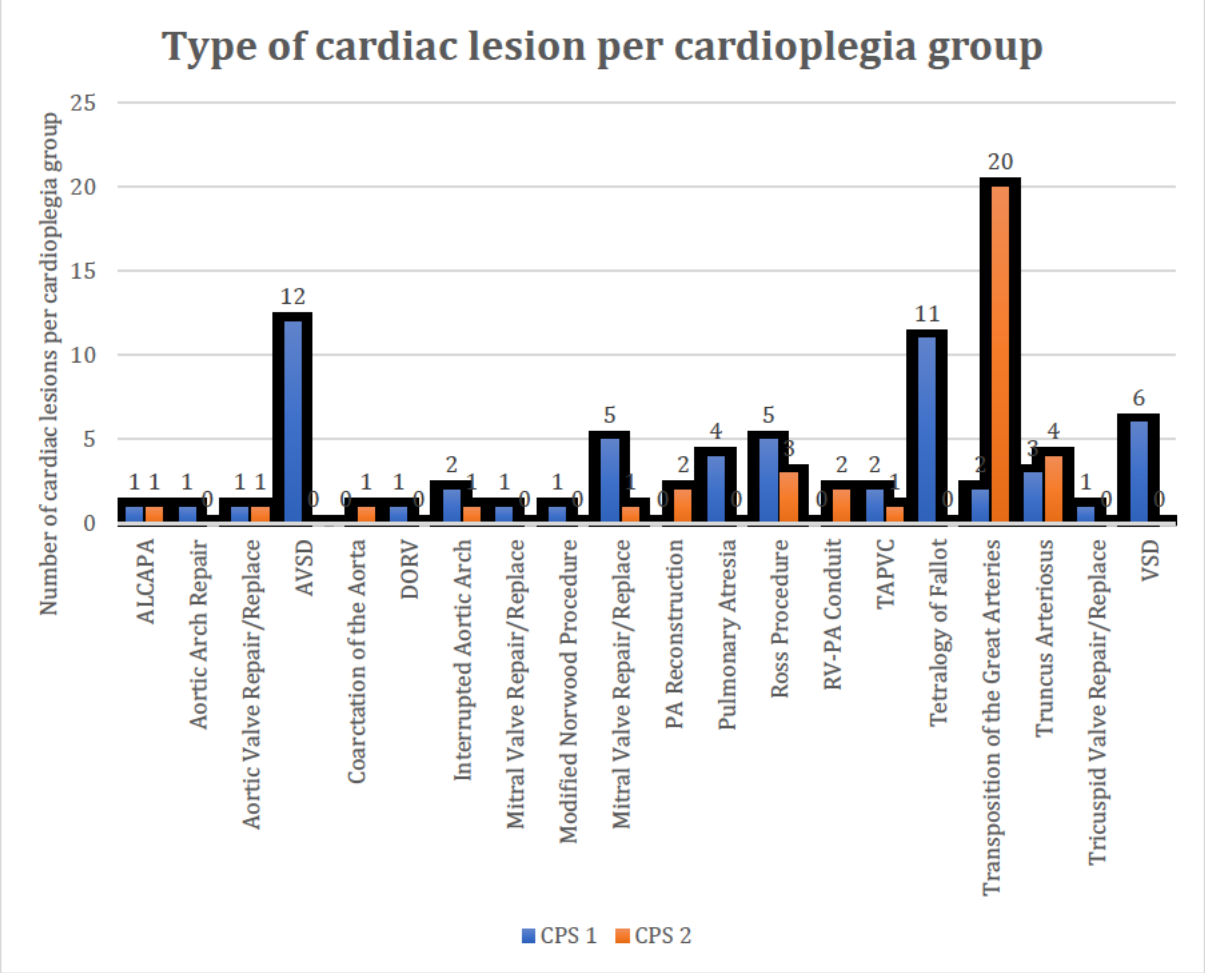



**Figure 4.9** **Type of cardiac lesion per cardioplegia group** (ALCAPA – Anomalous left coronary artery from the pulmonary artery, AVSD – Atrioventricular septal defect, DORV – Double outlet right ventricle, PA – Pulmonary artery, RV – Right ventricle, TAPVC – Total anomalous pulmonary venous connection, VSD – Ventricular septal defect, CPS 1 – cardioplegic solution group 1, CPS 2 – cardioplegic solution group 2)

### 4.3.3 Metabolic data

Serum lactate (mmol/L) haematocrit (%), sodium (mmol/L) and potassium (mmol/L) were recorded preoperatively, intraoperatively and postoperatively at specific time points for both CPS groups.

#### 4.3.3.1 Lactate (mmol/L)

The lactate values were recorded intraoperatively per time point. The preoperative CPB value (Pre-CPB) was recorded as the baseline value and intraoperatively, the peak lactate

value (Intra-CPB-High) was recorded for each patient during CPB surgery (Table 4.18). Postoperatively, lactate values were recorded upon admission to ICU (Post-CPB-ICU) and then after 24hr (Post-CPB-24h), 48hr (Post-CPB-48h) and 72hr (Post-CPB-72h). The baseline (Pre-CPB) lactate values of both cardioplegic groups were below <2mmol/L. Intraoperatively, CPS 2 had the highest mean lactate value (4.21mmol/L) compared to CPS 1 (3.28mmol/L). Postoperatively both CPS groups lactate values returned to normal within 48hr (1.37mmol/L; 1.61mmol/L), respectively (Table 4.18).

**Table 4.18 Mean lactate values (mmol/L) over time per cardioplegia group**

| Time Point | CPS 1 (n=59) | | | | | | CPS 2 (n=37) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Median | Min | Max | n | Mean | SD | Median | Min | Max | N |
| **Pre-CPB** | 1.21 | 0.427 | 1.10 | 0.30 | 2.00 | 59 | 1.06 | 0.376 | 1.00 | 0.50 | 2.00 | 37 |
| **Intra-CPB-High** | 3.28 | 2.269 | 2.50 | 1.20 | 11.30 | 59 | 4.21 | 1.876 | 4.30 | 1.50 | 11.10 | 37 |
| **Post-CPB-ICU** | 2.80 | 1.575 | 2.20 | 0.90 | 7.40 | 55 | 3.40 | 1.881 | 2.85 | 1.10 | 7.90 | 36 |
| **Post-CPB-24h** | 1.96 | 1.399 | 1.60 | 0.70 | 9.00 | 55 | 2.48 | 1.762 | 1.85 | 0.60 | 9.80 | 36 |
| **Post-CPB-48h** | 1.37 | 1.044 | 1.10 | 0.60 | 6.60 | 52 | 1.61 | 1.335 | 1.30 | 0.60 | 8.20 | 35 |
| **Post-CPB-72h** | 1.12 | 1.045 | 0.90 | 0.00 | 6.30 | 51 | 1.50 | 0.884 | 1.20 | 0.70 | 4.20 | 34 |

**(SD – standard deviation; Min – minimum; Max – maximum, CPB – cardiopulmonary bypass, ICU – intensive care unit, n – number of patients).**

The mean peak intraoperative lactate values (Intra-CPB-High) was higher in patients receiving Bretschneider custodiol cardioplegia (CPS 2; 4.21mmol/L) than patients receiving St Thomas II cardioplegic solution (CPS 1; 3.28mmol/L) showing a statistical significance between CPS 1 and CPS 2 (p=0.0332) (Table 4.19). The graphical presentation of these values is available in Figure 4.10.

**Table 4.19 Mean lactate values (mmol/L) over time: comparison between CPS 1 and CPS 2**

| Time point | CPS 1 (n=59) | CPS 2 (n=37) | p-value |
|---|---|---|---|
| **Pre-CPB** | 1.21 | 1.06 | 0.0733 |
| **Intra-CPB-High** | 3.28 | 4.21 | 0.0332* |
| **Post-CPB-ICU** | 2.80 | 3.40 | 0.1152 |
| **Post-CPB-24h** | 1.96 | 2.48 | 0.1374 |
| **Post-CPB-48h** | 1.37 | 1.61 | 0.3755 |
| **Post-CPB-72h** | 1.12 | 1.50 | 0.0787 |

**(* statistical significance, CPB – cardiopulmonary bypass, ICU – intensive care unit, n – number of patients, h – hour)**

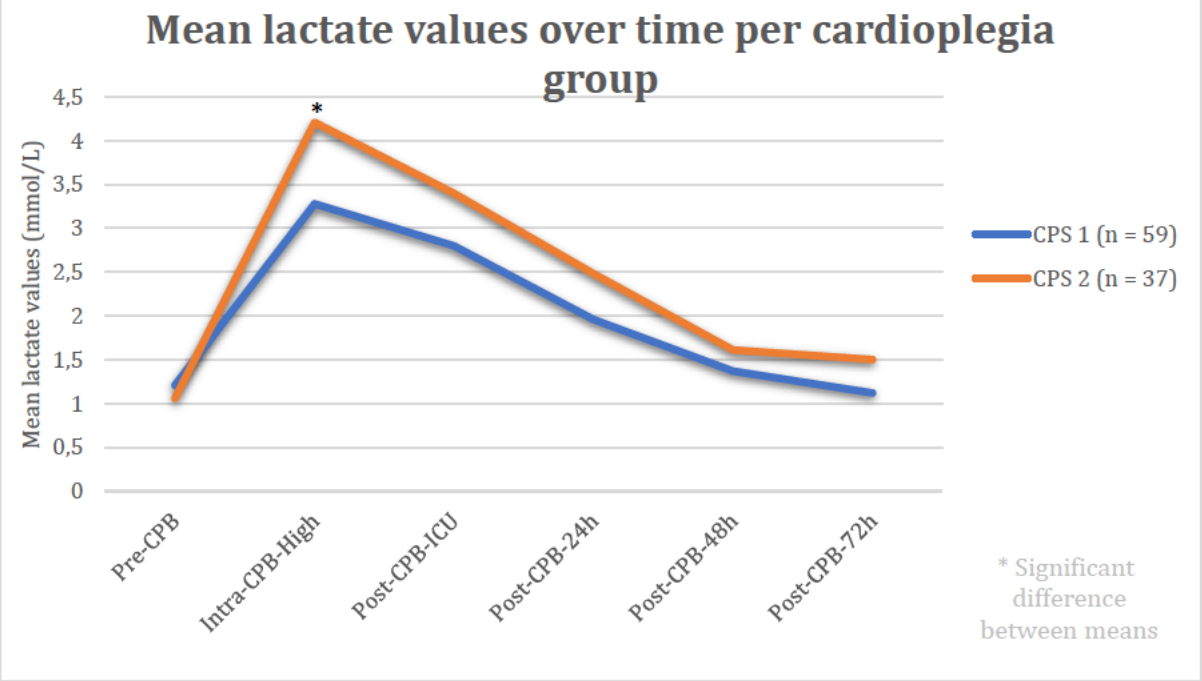



**Figure 4.10** **Graphical presentation of mean lactate values over time per cardioplegia group** (n – number of patients, Pre-CPB – preoperative cardiopulmonary bypass, Intra-CPB – intraoperative cardiopulmonary bypass, Post-CPB – postoperative cardiopulmonary bypass, h – hour)

### 4.3.3.2 Haematocrit (%)

The haematocrit values recorded for each time point includes; Pre-CPB, Intra-CPB-low, Post-CPB-ICU, Post-CPB-24h, Post-CPB-48h, Post-CPB-72h. Note that intraoperatively the lowest haematocrit value in each group were recorded (Table 4.20). In both groups, the highest mean haematocrit values were recorded upon admission to ICU post CPB surgery (CPS 1, 40.47%; CPS 2, 43.03%).

**Table 4.20 Haematocrit values (%) over time per cardioplegia group**

| Time Point | CPS 1 (n = 59) | | | | | | CPS 2 (n =37) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Median | Min | Max | n | Mean | SD | Median | Min | Max | N |
| Pre-CPB | 37.97 | 8.566 | 36.00 | 24.00 | 65.00 | 59 | 40.46 | 12.368 | 35.00 | 21.00 | 6.500 | 37 |
| Intra-CPB-Low | 26.76 | 4.049 | 26.00 | 19.00 | 40.00 | 59 | 27.95 | 5.338 | 28.00 | 20.00 | 44.00 | 37 |
| Post-CPB-ICU | 40.47 | 6.785 | 39.00 | 30.00 | 63.00 | 55 | 43.03 | 7.057 | 42.00 | 29.00 | 6.003 | 36 |
| Post-CPB-24h | 38.18 | 6.380 | 39.00 | 28.00 | 60.00 | 55 | 39.83 | 6.943 | 41.00 | 24.00 | 56.00 | 36 |
| Post-CPB-48h | 35.67 | 4.914 | 35.00 | 26.00 | 46.00 | 52 | 37.31 | 5.885 | 36.00 | 28.00 | 50.00 | 35 |
| Post-CPB-72h | 34.95 | 4.236 | 34.00 | 27.00 | 45.00 | 41 | 35.82 | 6.093 | 35.00 | 25.00 | 50.00 | 34 |

(SD – standard deviation; Min – minimum; Max – maximum, CPB – cardiopulmonary bypass, ICU – intensive care unit, n – number of patients)

The haematocrit data were analysed descriptively, and the mean values are listed in Table 4.21 and the graphical presentation as Figure 4.11. The two groups presented with no statistical differences ($p>0.05$) at the recorded time points. The line graphs are very similar for both CPS 1 and CPS 2 with CPS 1 presenting with slightly lower haematocrit values at all the recorded time points.

**Table 4.21 Mean haematocrit values (%) over time: comparison between CPS 1 and CPS 2**

| Time point | CPS 1 (n=59) | CPS 2 (n=37) | p-value |
|---|---|---|---|
| Pre-CPB | 37.97 | 40.46 | 0.2868 |
| Intra-CPB-Low | 26.76 | 27.95 | 0.2522 |
| Post-CPB-ICU | 40.47 | 43.03 | 0.0906 |
| Post-CPB-24h | 38.18 | 39.83 | 0.2559 |
| Post-CPB-48h | 35.67 | 37.31 | 0.1782 |
| Post-CPB-72h | 34.95 | 35.82 | 0.4835 |

(CPB – cardiopulmonary bypass, ICU – intensive care unit, n – number of patients)

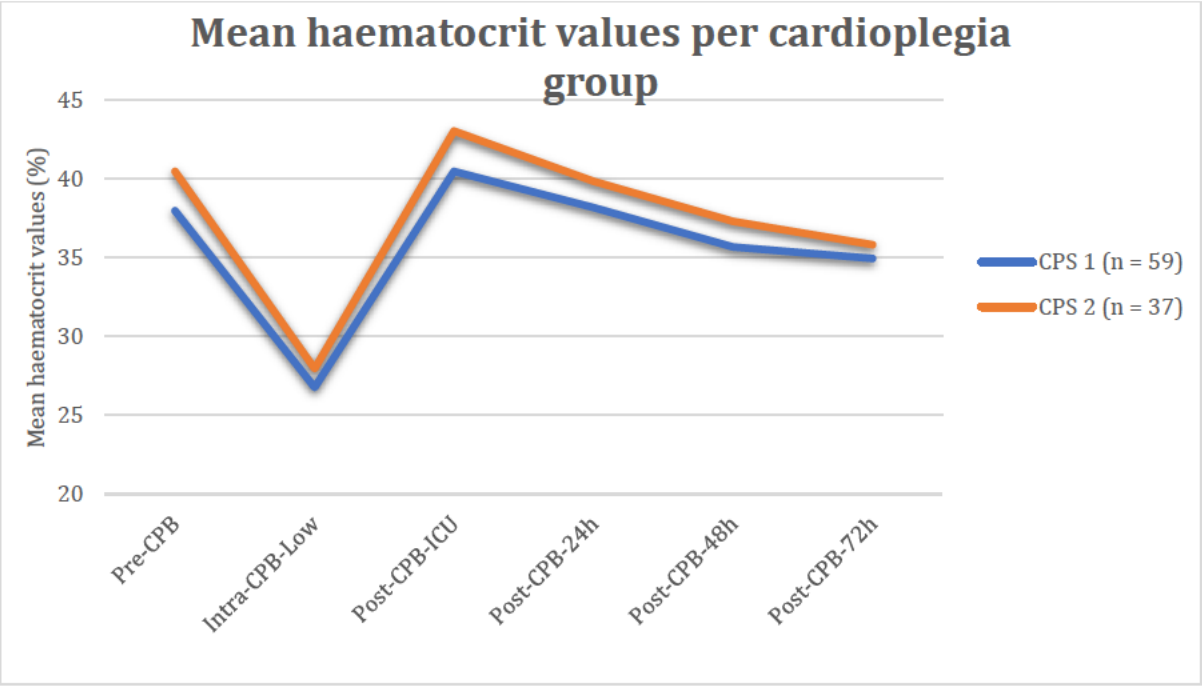



**Figure 4.11** **Graphical presentation of mean haematocrit values over time per cardioplegia group** (n – number of patients, Pre-CPB – preoperative cardiopulmonary bypass, Intra-CPB – intraoperative cardiopulmonary bypass, Post-CPB – postoperative cardiopulmonary bypass, h – hour)

### 4.3.3.3 Sodium (mmol/L)

The sodium values were recorded at specific time points (Pre-CPB, Intra-CPB-low, Post-CPB-ICU, Post-CPB-24h, Post-CPB-48h, Post-CPB-72h). Note that intraoperatively the lowest sodium value in each group were recorded. The highest mean sodium values were recorded upon admission to ICU for CPS 1 (139.58mmol/L) and Post-CPB-24h (139.33mmol/L) for CPS 2 (Table 4.22).

**Table 4.22 Sodium values (mmol/L) over time per cardioplegia group**

| Time Point | CPS 1 (n=59) | | | | | | CPS 2 (n=37) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Median | Min | Max | n | Mean | SD | Median | Min | Max | N |
| Pre-CPB | 134.06 | 2.942 | 134.00 | 127.00 | 141.00 | 54 | 135.03 | 3.571 | 135.00 | 126.00 | 142.00 | 37 |
| Intra-CPB-Low | 133.63 | 2.405 | 134.00 | 126.00 | 140.00 | 54 | 126.89 | 6.989 | 129.00 | 108.00 | 137.00 | 36 |
| Post-CPB-ICU | 139.58 | 3.599 | 139.00 | 131.00 | 148.00 | 55 | 137.41 | 4.106 | 136.00 | 129.00 | 148.00 | 37 |
| Post-CPB-24h | 139.39 | 3.563 | 140.00 | 132.00 | 146.00 | 54 | 139.33 | 4.395 | 139.00 | 130.00 | 147.00 | 36 |
| Post-CPB-48h | 137.25 | 4.137 | 138.00 | 128.00 | 146.00 | 53 | 138.86 | 3.720 | 138.00 | 131.00 | 147.00 | 36 |
| Post-CPB-72h | 133.62 | 20.249 | 136.00 | 129.00 | 145.00 | 47 | 137.69 | 3.694 | 137.50 | 131.00 | 146.00 | 36 |

(SD – standard deviation; Min – minimum; Max – maximum, CPB – cardiopulmonary bypass, ICU – intensive care unit, n – number of patients)

The two groups presented with statistical differences ($p<0.05$) at the recorded time points, Intra-CPB-low ($p<0.0001$) and Post-CPB-ICU ($p=0.018$). The graphical presentation of these values is available as Figure 4.12.

**Table 4.23 Mean sodium values (mmol/L) over time: comparison between CPS 1 and CPS 2**

| Time point | CPS 1 (n=59) | CPS 2 (n=37) | p-value |
|---|---|---|---|
| Pre-CPB | 134.06 | 135.03 | 0.1761 |
| Intra-CPB-Low | 133.63 | 126.89 | <0.0001* |
| Post-CPB-ICU | 139.58 | 137.41 | 0.0108* |
| Post-CPB-24h | 139.39 | 139.33 | 0.9498 |
| Post-CPB-48h | 137.25 | 138.86 | 0.0582 |
| Post-CPB-72h | 133.62 | 137.69 | 0.1826 |

(* statistical significance, CPB – cardiopulmonary bypass, ICU – intensive care unit, n – number of patients)

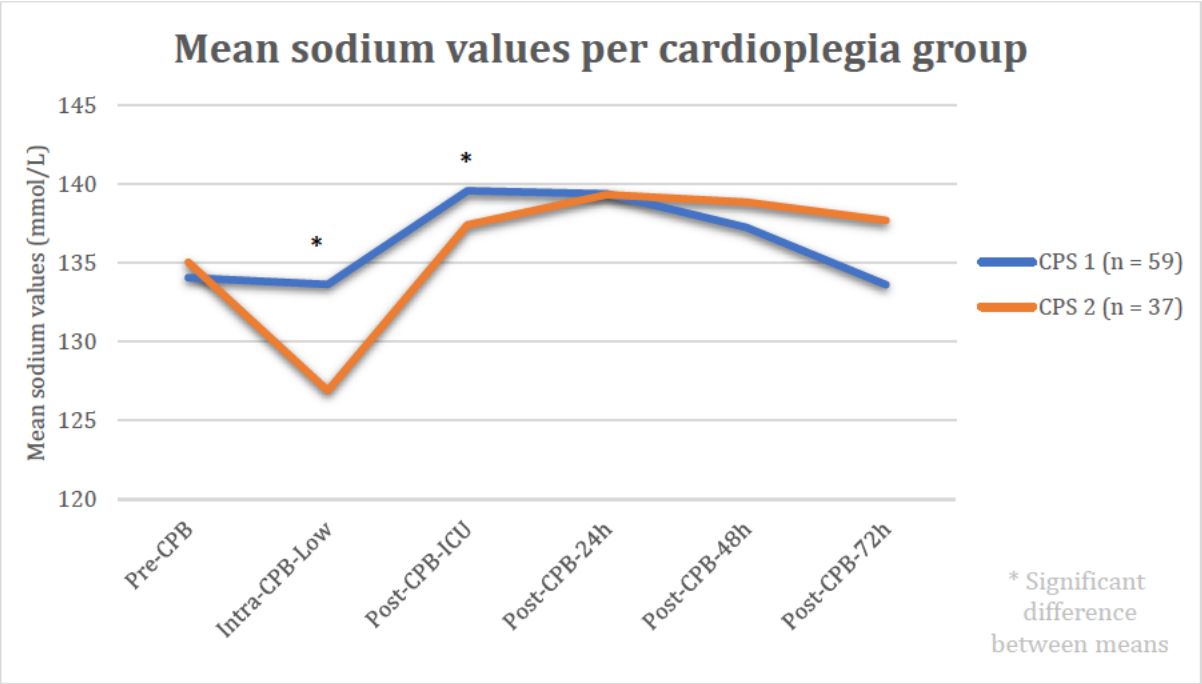



**Figure 4.12** **Graphical presentation of mean sodium values over time per cardioplegia group** (n – number of patients, Pre-CPB – preoperative cardiopulmonary bypass, Intra-CPB – intraoperative cardiopulmonary bypass, Post-CPB – postoperative cardiopulmonary bypass, h – hour)

### 4.3.3.4 Potassium (mmol/L)

The descriptive statistics of the potassium values recorded for each time point (Pre-CPB, Intra-CPB-high, Post-CPB-ICU, Post-CPB-24h, Post-CPB-48h, Post-CPB-72h) is presented in Table 4.24. Intraoperatively the highest potassium value in each CPS group was recorded. The highest mean sodium value was recorded intraoperatively during CPB for both CPS 1 (5.11mmol/L) and CPS 2 (5.04mmol/L) (Table 4.24).

**Table 4.24 Potassium values (mmol/L) over time per cardioplegia group.**

| Time Point | CPS 1 (n=59) | | | | | | CPS 2 (n=37) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Median | Min | Max | n | Mean | SD | Median | Min | Max | N |
| Pre-CPB | 4.04 | 0.462 | 4.00 | 2.90 | 5.10 | 59 | 4.02 | 0.639 | 4.00 | 2.70 | 5.70 | 37 |
| Intra-CPB-High | 5.11 | 0.790 | 5.00 | 3.70 | 8.60 | 59 | 5.04 | 0.778 | 5.00 | 3.30 | 6.60 | 37 |
| Post-CPB-ICU | 4.67 | 0.911 | 4.40 | 2.80 | 7.30 | 55 | 4.50 | 0.651 | 4.55 | 3.00 | 5.90 | 36 |
| Post-CPB-24h | 4.80 | 0.616 | 4.70 | 3.60 | 6.60 | 44 | 4.35 | 0.646 | 4.20 | 3.30 | 5.90 | 36 |
| Post-CPB-48h | 4.30 | 0.632 | 4.20 | 3.20 | 6.00 | 53 | 4.20 | 0.751 | 4.20 | 3.00 | 6.80 | 35 |
| Post-CPB-72h | 3.95 | 0.803 | 4.10 | 0.00 | 5.60 | 47 | 4.28 | 0.698 | 4.20 | 3.10 | 5.60 | 35 |

(SD – standard deviation; Min – minimum; Max – maximum, CPB – cardiopulmonary bypass, ICU – intensive care unit, n – number of patients)

The two groups presented with statistical significant differences ($p<0.05$) at the recorded time points, Post-CPB-24h ($p=0.0005$) and Post-CPB-72h (0.0492) (Table 4.25). The graphical presentation of these values is available as Figure 4.13.

**Table 4.25 Mean potassium values (mmol/L) over time: comparison between CPS 1 and CPS 2**

| Time point | CPS 1 (n = 59) | CPS 2 (n = 37) | p-value |
|---|---|---|---|
| Pre-CPB | 4.04 | 4.02 | 0.9151 |
| Intra-CPB-Low | 5.11 | 5.04 | 0.6575 |
| Post-CPB-ICU | 4.67 | 4.50 | 0.2842 |
| Post-CPB-24h | 4.80 | 4.35 | 0.0005* |
| Post-CPB-48h | 4.30 | 4.20 | 0.5030 |
| Post-CPB-72h | 3.95 | 4.28 | 0.0492* |

(* statistical significance, CPB – cardiopulmonary bypass, ICU – intensive care unit, n – number of patients)

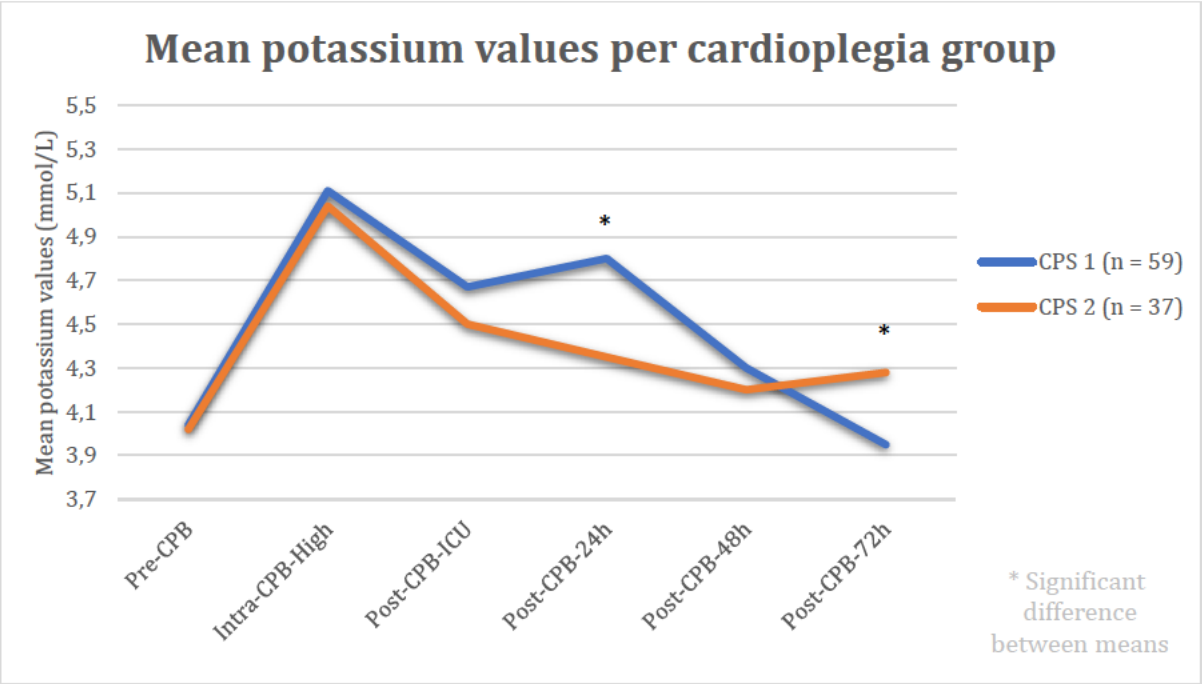



**Figure 4.13** **Graphical presentation of mean potassium values over time per cardioplegia group**

**(n – number of patients, Pre-CPB – preoperative cardiopulmonary bypass, Intra-CPB – intraoperative cardiopulmonary bypass, Post-CPB – postoperative cardiopulmonary bypass, h – hour)**

### 4.3.4 Aortic cross-clamp time (min), CPB time (min) and oesophageal temperature (°C)

The aortic cross-clamp time, total CPB time and oesophageal temperature were recorded intraoperatively during CPB, and the descriptive statistics per group is summarized in Table 4.26. The mean aortic cross-clamp time were longer and mean total CPB time were considerably longer in CPS 2 (140.86min; 215.38min) compared to CPS 1 (129.90min; 186.95min). The mean oesophageal temperature was much higher in CPS 1 (27.44°C) compared to CPS 2 (25.87°C) (Table 4.26).

**Table 4.26 Intraoperative aortic cross-clamp time (min), CPB time (min) and oesophageal temperature (°C) per cardioplegia group**

| Variable | CPS 1 (n=59) | | | | | | CPS 2 (n=37) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Median | Min | Max | n | Mean | SD | Median | Min | Max | N |
| Aortic cross-clamp time (min) | 129.90 | 36.680 | 118.00 | 78.00 | 261.00 | 59 | 140.86 | 37.036 | 130.00 | 99.00 | 238.00 | 37 |
| Total CPB time (min) | 186.95 | 62.137 | 167.00 | 102.00 | 418.00 | 59 | 215.38 | 62.471 | 201.00 | 119.00 | 359.00 | 37 |
| Oesophageal temperature (°C) | 27.44 | 4.202 | 28.00 | 18.80 | 32.00 | 59 | 25.87 | 4.243 | 25.10 | 19.50 | 32.00 | 37 |

(SD – standard deviation; Min – minimum; Max – maximum, min – minute, n – number of patients)

The mean values were compared between the CPS groups and the p-values are listed in Table 4.27. Only one recorded variable, the total time spent on CPB (Table 4.27) was statistically significant (p=0.0328).

**Table 4.27 Mean intraoperative aortic cross-clamp time (min), CPB time (min) and oesophageal temperature (°C) comparison between CPS 1 and CPS 2**

| Variable | CPS 1 (n=59) (mean ± SD) | CPS 2 (n=37) (mean ± SD) | p-value |
|---|---|---|---|
| Aortic cross-clamp time (min) | 129.90 ±36.68 | 140.86 ±37.04 | 0.1605 |
| Total CPB time (min) | 186.95 ±62.14 | 215.38 ±62.47 | 0.0328* |
| Oesophageal temperature (°C) | 27.44 ±4.20 | 25.87 ±4.24 | 0.0814 |

(* statistical significance, SD – standard deviation, min – minute, n – number of patients)

## 4.3.5 Postoperative complications and clinical outcomes

### 4.3.5.1 Postoperative complications

Table 4.28 reflects the postoperative complications recorded per CPS group. The percentages are presented graphically in Figure 4.14. Phrenic or recurrent laryngeal nerve injury (p=0.0199) and new onset seizures (p=0.0199) were the only two postoperative complications that differ statistically between CPS 1 and CPS 2 (Table

4.28). The postoperative complications that occurred 0% in both CPS 1 and CPS 2 were excluded from Table 4.28 and Figure 4.14.

**Table 4.28 Postoperative complications per cardioplegia group**

| Clinical outcome | CPS 1 (n=59) | CPS 2 (n=37) | p-value | Method of Comparison |
|---|---|---|---|---|
| Cardiac arrest | 6/59 (10.2%) | 5/37 (13.5%) | 0.7445 | Fisher's Exact test |
| Arrhythmia | 10/59 (16.9%) | 7/37 (18.9%) | >0.9999 | Chi² test |
| Heart block | 9/59 (15.3%) | 6/37 (16.2%) | >0.9999 | Chi² test |
| Low cardiac output | 5/59 (8.5%) | 1/37 (2.7%) | 0.4006 | Fisher's Exact test |
| Acidosis | 20/59 (33.9%) | 10/37 (27%) | 0.6307 | Chi² test |
| Pericardial effusion requiring drainage | 3/59 (5.1%) | 2/37 (5.4%) | >0.9999 | Fisher's Exact test |
| Pulmonary hypertension | 3/59 (5.1%) | 0/37 (0%) | 0.2819 | Fisher's Exact test |
| Pneumothorax | 9/59 (15.3%) | 3/37 (8.1%) | 0.3598 | Fisher's Exact test |
| Pleural effusion requiring drainage | 7/59 (11.9%) | 10/37 (27%) | 0.1054 | Chi² test |
| Pneumonia | 7/59 (11.9%) | 8/37 (21.6%) | 0.3209 | Chi² test |
| Chylothorax | 1/59 (1.7%) | 2/37 (5.4%) | 0.5569 | Fisher's Exact test |
| Tracheostomy | 1/59 (1.7%) | 0/37 (0%) | >0.9999 | Fisher's Exact test |
| Phrenic or recurrent laryngeal nerve injury | 0/59 (0%) | 4/37 (10.8%) | 0.0199* | Fisher's Exact test |
| Respiratory insufficiency requiring mechanical ventilation >7 days postoperatively or reintubation | 10/59 (16.9%) | 12/37 (32.4%) | 0.1318 | Chi² test |
| Transient or permanent neurologic deficit | 1/59 (1.7%) | 0/37 (0%) | >0.9999 | Fisher's Exact test |
| New onset seizures | 0/59 (0%) | 4/37 (10.8%) | 0.0199* | Fisher's Exact test |
| Wound/sternal dehiscence | 4/59 (6.8%) | 7/37 (18.9%) | 0.0996 | Fisher's Exact test |
| Infection/SIRS | 27/59 (45.8%) | 25/37 (67.6%) | 0.0606 | Chi² test |
| Endocarditis | 1/59 (1.7%) | 2/37 (5.4%) | 0.5569 | Fisher's Exact test |
| Acute renal failure | 10/59 (16.9%) | 12/37 (32.4%) | 0.1318 | Chi² test |
| Sternum left open | 10/59 (16.9%) | 11/37 (29.7%) | 0.2222 | Chi² test |
| Bleeding requiring reoperation | 3/59 (5.1%) | 1/37 (2.7%) | >0.9999 | Fisher's Exact test |

(* - statistical significance, SIRS – systemic inflammatory response syndrome, n – number of patients)

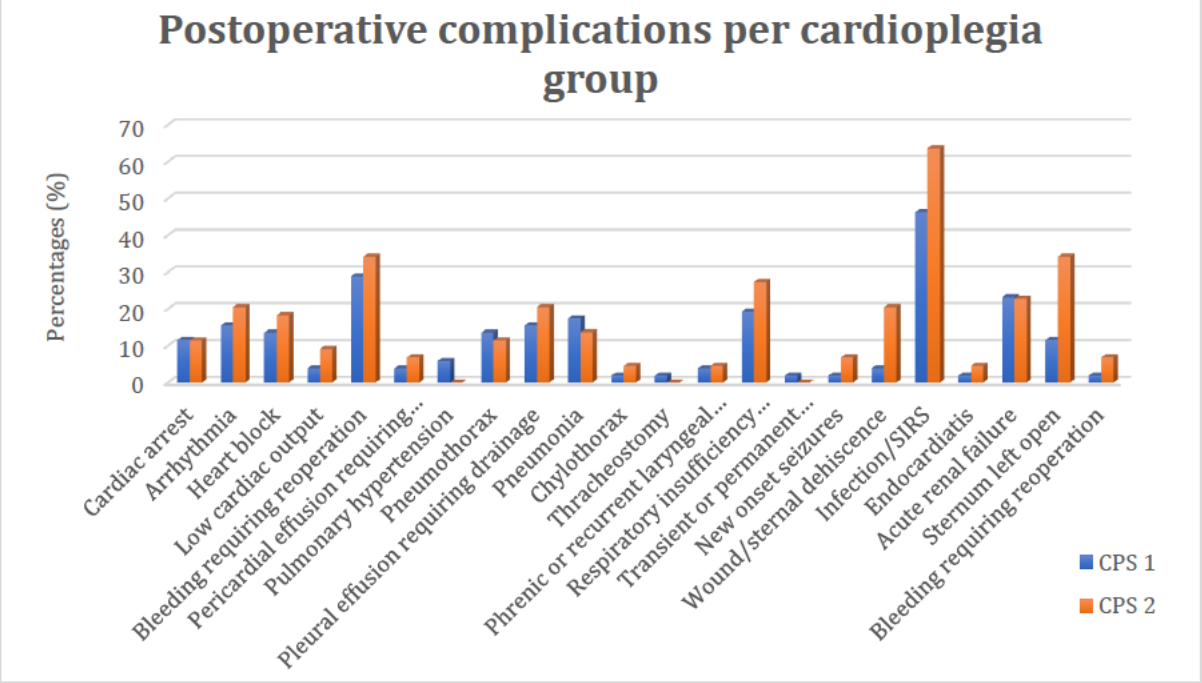



**Figure 4.14** **Postoperative complications as percentages per cardioplegia group** (SIRS – systemic inflammatory response syndrome)

### 4.3.5.2 Postoperative clinical outcomes

The patients in CPS 1 received inotropic support for longer (mean 124.2hr), and patients in CPS 2 were intubated longer (mean 91.8hr) and stayed longer in ICU (mean 8.3 days) compared to CPS 1 group (Table 4.29).

**Table 4.29 Postoperative clinical outcomes per cardioplegia group**

| Variable | CPS 1 (n=59) | | | | | | CPS 2 (n=37) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Median | Min | Max | n | Mean | SD | Median | Min | Max | N |
| Inotropic support time (hr) | 124.20 | 143.91 | 84.50 | 0.00 | 908.00 | 54 | 116.60 | 84.51 | 85.00 | 19.00 | 281.00 | 35 |
| Intubation time (hr) | 75.70 | 80.54 | 46.50 | 0.00 | 384.00 | 54 | 91.80 | 87.59 | 64.00 | 2.00 | 316.00 | 35 |
| ICU stay (days) | 7.40 | 7.72 | 5.00 | 1.00 | 41.00 | 55 | 8.30 | 5.82 | 7.00 | 2.00 | 27.00 | 35 |

(ICU – intensive care unit; hr – hour; CPS - cardioplegic solution group; SD – standard deviation; Min – minimum; Max – maximum, n – number of patients)

The mean postoperative clinical outcome values were compared between the cardioplegia groups and the p-values calculated (Student's t-test). No statistical

significant differences were calculated for any of the postoperative clinical outcome variables (p>0.05) (Table 4.30).

**Table 4.30 Postoperative clinical outcomes: comparison between CPS 1 and CPS 2**

| Variables | CPS 1 (n=52) (mean ± SD) | CPS 2 (n=44) (mean ± SD) | p-value |
|---|---|---|---|
| **Inotropic support time (hr)** | 124.2 ±143.91 | 116.6 ±84.51 | 0.7536 |
| **Intubation time (hr)** | 75.7 ±80.54 | 91.8 ±87.59 | 0.3845 |
| **ICU stay (days)** | 7.4 ±7.72 | 8.3 ±5.82 | 0.5417 |

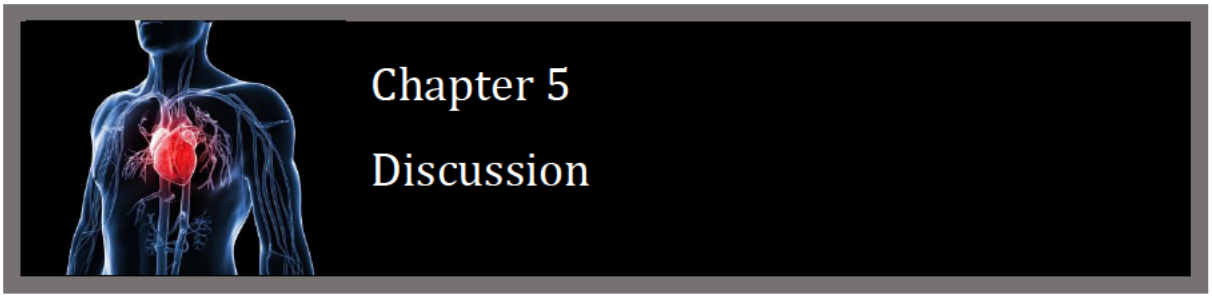
(ICU – intensive care unit; hr – hour; CPS - cardioplegic solution group; SD – standard deviation, n – number of patients)

The mortality data for CPS 1 and CPS 2 are reflected in Table 4.31. Again, no statistical significant difference with regard to mortality was recorded between the two CPS groups (p>0.9999) (Table 4.31).

**Table 4.31 Mortality rate per cardioplegia group**

| Variable | CPS 1 (n=59) (n; %) | CPS 2 (n=37) (n; %) | p-value |
|---|---|---|---|
| **No mortality** | 49 (83%) | 32 (87%) | > 0.9999 |
| **Mortality <30 days** | 6 (10%) | 3 (8%) | |
| **Mortality >30 days** | 3 (5%) | 2 (5%) | |
| **Unknown** | 1 (2%) | 0 (0%) | |

(n – number of patients, % - percentage)



# Chapter 5
# Discussion

## 5.1 Introduction

Predicting clinical outcome immediately after complex cardiac surgery remains a daunting task, as measurements of conventional hemodynamic parameters and risk scoring systems are still deemed inadequate for prognostic use (Bhukal *et al.*, 2012; Dupuis, 2008; Squara *et al.*, 1994; Balakrishnan *et al.*, 1992).

Several authors reported that increased serum lactate levels during and after paediatric cardiac surgery is associated with increased patient morbidity and mortality (Oguz *et al.*, 2014; Munoz *et al.*, 2002; Cheifetz *et al.*, 1997). Serum lactate levels may be used as a marker to establish adequate tissue perfusion because during CPB, tissue hypoperfusion with elevated serum lactate levels may occur despite normal blood gas concentrations, normal CPB flow rates and perceived acceptable hemodynamic parameters. Prolonged CPB and aortic cross-clamp time during the perioperative period are associated with increased serum lactate levels and lactate levels above 4mmol/L are directly associated with increased duration of mechanical ventilation and ICU stay (Shah *et al.*, 2015; Shinde *et al.*, 2005; Mizock and Falk, 2002; Demers *et al.*, 2000).

Despite the fact that elevated lactate levels have been associated with adverse outcomes in paediatric cardiac surgery (Mclean *et al.*, 2007), no specific peak lactate value has been identified as a constant indicator of adverse clinical outcomes. Limited literature of proposed peak lactate levels predicting adverse outcomes in the paediatric population is available. In adults, the predictive peak lactate values range from 3-5mmol/L (Yilmaz *et al.*, 2011; Toraman *et al.*, 2004). Demers *et al.* (2000) reported that a blood lactate level exceeding 4mmol/L or higher during CPB identifies with increased risk of postoperative morbidity and mortality. Based on this, a peak intraoperative lactate value exceeding

4mmol/L was chosen as the cut-off value to select a group of patients with predicted postoperative adverse clinical outcomes after undergoing CPB for the repair of congenital cardiac lesions.

This study aimed to answer the following questions:

- Is a peak intraoperative lactate value of 4mmol/L associated with a higher incidence of postoperative complications and clinical outcomes in CHD patients receiving CPB surgery?
- Can the use of cardioplegia (St Thomas II or Bretschneider custodiol) be associated with an increased incidence of postoperative complications and clinical outcomes in CHD patients receiving CPB surgery?

## 5.2 Peak intraoperative lactate <4mmol/L (group 1) versus peak intraoperative lactate ≥4mmol/L (group 2)

### 5.2.1 Preoperative demographics, anthropometrics and cardiac lesions

Ninety-six (96) paediatric cardiac patients that met the inclusion criteria were divided into two groups based on their peak intraoperative lactate values (group 1, n=52 and group 2, n=44). The patients in group 2 were much younger (median 2.4 months, range 0.097-181 months) compared to the patients in group 1 (median 14.5 months, range 1-157 months) at the time of cardiac surgery. A statistical significant difference was recorded for age (0.0438) between the two (2) groups, which is just below the 0.05 significant limit.

The two groups were comparable with regard to anthropometric variables (p>0.05). Both groups showed a female preponderance (52% vs 55%) with most patients being coloured (52% vs 55%).

The two groups included a similar spread of cardiac lesions except in group 1 most patients were treated for an AVSD (19%) and in group 2, TGA (34%).

## 5.2.2 Metabolic data

### 5.2.2.1 Lactate (mmol/L)

Preoperatively both groups had similar mean lactate levels (1.23mmol/L vs 1.07mmol/L). No patient with a preoperative lactate value exceeding 2mmol/L were considered for this study. Intraoperatively, the peak lactate levels did differ significantly ($p<0.0001$) but could be expected based on the criteria used to create the patient cohorts.

The reasons for the increase in lactate values during CPB can possible be explained by:

- During CPB pulsatile flow is converted to laminar flow patterns contributing to peripheral vasoconstriction and decreased peripheral tissue energy production. Furthermore, hypoperfusion of the intestinal mucosa stimulates the divergence of $O_2$ away from the splanchnic vascular bed, resulting in raised hepatic lactate production (Pojar *et al*., 2008; Chiolero *et al*., 2000).
- In addition, peripheral vasoconstriction associated with CPB causes the redistribution of circulating volume to the vital organs, compromising the microcirculation. This phenomenon is associated with peripheral arteriovenous shunting resulting in decreased perfusion to the skeletal muscles, which are an important lactate oxidizer. If decreased perfusion to the skeletal muscles persist it might result in serum lactate production (Trzeciak *et al*., 2005; Chiolero *et al*., 2000).
- During CPB, haemodilution reduces perfusion pressure and reduces the $O_2$ carrying capacity of blood. Therefore, in combination with the leftward shift of $O_2$ haemoglobin dissociation induced by hypothermia, this might limit $O_2$ delivery to the cells (Scaravilli *et al*., 2012).
- Hypothermia during CPB also contributes to vasoconstriction leading to further hypoperfusion at microcirculatory level and decreased splanchnic perfusion.

All the derangements stated above may contribute to increased lactate levels during CPB even in the presence of normal oxygenation and circulation (Jones *et al*., 2009).

From ICU admission till 48hr postoperatively, group 2 presented with significantly higher mean lactate values compared to group 1. Although at 48hr both groups had mean lactate levels less than 2mmol/L. These findings are supported by Kliegel *et al* (2004) concluding that if hyperlactatemia persists beyond 48 hours it seemed to be a predictor of poor outcome. With decreased splanchnic circulation and peripheral tissue/muscle perfusion, a build-up of lactate in the tissue occurs. During the postoperative period, a washout of lactate tends to occur. Postoperatively all the factors contributing to decreased blood flow to non-vital organs are eliminated as the patient is returned to normothermic temperatures and pulsatile flow is restored, which allows for peripheral tissue and gut mucosa to be perfused again returning lactate levels to normal.

#### 5.2.2.2 Haematocrit (%)

Haematocrit is a marker of haemoconcentration and blood viscosity, especially in children. In many cases, especially in paediatrics, hypovolemia and secondary haemoconcentration play a significant role in disturbed microcirculation (Marics *et al.,* 2015). No statistical differences were seen between the two groups preoperatively, intraoperatively or postoperatively. The lowest mean haematocrit values were recorded intraoperatively for both groups (group 1, 27.71%; group 2, 26.64%). This could be attributed to haemodilution caused by the priming of the heart-lung machine circuit and the administration of cardioplegia (Ranucci *et al*., 2006). Similar findings were reported by Abrahams *et al*., (2010).

### 5.2.3 Aortic cross-clamp time (min), CPB time (min) and oesophageal temperature (°C)

Both the aortic cross-clamp time (group 1, mean 125.3min, range 78-212min; group 2, mean 144.5min, range 99-261min; p=0.0106) and CPB time (group 1, mean 178.1min, range 102-342min; group 2, mean 221.4min, range 119-418min, p=0007) were longer in group 2 and showed a statistical significant difference when compared to group 1. This suggests that high blood lactate levels are more likely to occur with longer aortic cross-clamp and CPB times but are still dependent on other pre- and intraoperative factors. Similar results were reported by Demers *et al.* (2000), patients with lactate levels of

4mmol/L or higher had significantly longer CPB times and aortic cross-clamp times. Furthermore, an association was found between the duration of CPB and the magnitude of hyperlactatemia in the early postoperative period by Bakanov *et al.* (2009).

Both groups were cooled down intraoperatively therefore reflecting low oesophageal temperatures (group 1, mean 28°C, range 19.7-32°C; group 2 mean 25.5°C, range 18.8-32°C). A weak statistical significant difference was reported between the 2 groups with group 2 reflecting lower mean oesophageal temperatures (p=0045).

### 5.2.4 Postoperative complications and clinical outcomes

Postoperative complications were reported for both group 1 and 2 but only wound/sternal dehiscence (group 1, 3.8%; group 2, 20.5%; p=0.0208) and sternum left open (group 1, 11.5%; group 2, 34.1%; p=0.0157) showed statistical significant differences between the two (2) groups. Özker *et al.* (2012) stated that delayed sternal closure after cardiac surgery is a therapeutic option in the treatment of severely impaired heart in paediatric cardiac surgery. Postoperative wound infection and the severity thereof ranges from a superficial wound infection (which involves only skin or subcutaneous tissue) to fulminate mediastinitis with subsequent involvement of the sternum (sternal dehiscence and osteomyelitis) and organ tissues outside the incision (Mangram *et al.,* 1999). Several reasons could contribute to the development of wound/sternal dehiscence in children e.g. children with asplenia or had a cardiac transplant, those requiring β-adrenergic drugs, obstructive respiratory problems, concomitant infections at other sites and poor tissue oxygenation on the site of injury (Tortoriello *et al.,* 2003).

Postoperative complications that showed high recorded percentages for both lactate groups were acidosis (group 1, 28.8%; group 2, 34.1%), infection/SIRS (group 1, 46.2%; group 2, 63.6%) and acute renal failure (group 1, 23.1%; group 2, 22.7%).

Morbidity associated with CPB, also referred to as “post-pump syndrome” ranges from mild capillary leakage followed by intravascular volume depletion, generalized oedema, circulatory compromise, altered microcirculation and ultimately multi organ system

failure (Durandy, 2014; Warren *et al.*, 2009; Siegel *et al.*, 1996). The occurrence of "post-pump syndrome' has been attributed to the exposure of blood cells to foreign surfaces (CPB circuit) thus initiating the release of inflammatory mediators that may further contribute to lung, myocardium, kidney, liver, intestine and brain impairment (Durandy, 2014; Warren *et al.*, 2009).

The acidosis seen in both group 1 and 2 could be secondary to tissue hypoperfusion, which occurs despite the use of hypothermia to reduce metabolic demands and the maintenance of normal mixed venous oxygen saturations during CPB (Siegel *et al.*, 1996). SIRS is a frequent complication observed in children after open-heart surgery and has been associated with both CPB and surgical trauma (Boehne *et al.*, 2017). A higher incidence of SIRS is also reported with younger age or lower body weight (Guvener *et al.*, 2015; Soares *et al.*, 2010). According to literature the occurrence of acute kidney failure after paediatric open-heart surgery varies from 1.6% to 52%. This corresponds with our results as cardiac surgery with CPB is commonly perceived as a risk factor for decline in renal function (Krastins *et al.*, 2012).

No statistical significant differences were reported between group 1 and 2 for inotropic support time (p=0.2434), intubation time (p=0.1604), number of days spend in ICU (p=0.1646) and mortality (p=0.6805). Similar results were found by Lindsay *et al.* (2013). However, patients in group 2 experienced longer need for inotropic support (mean±SD 137.4±92 vs 106.7±150.2). The SD is extremely high in both groups therefore if you look at the median values for group 1 it is 76.5 vs 94.0 in group 2. The longer need for inotropic support in group 2 also had a longer intubation time (mean 95.2min vs 70.3min) and the remained longer in ICU (8.96 days vs 6.8 days) compared to the patients in group 1. The mortality rate in group 2 (18%) was also higher when compared to group 1 (14%). The longer need for inotropic support in group 2 could be ascribed to prolonged aortic cross-clamp, reperfusion injury, myocardial stunning, technical problems during surgery, cardioplegia and pre-existing congestive cardiac failure. Furthermore, pulmonary hypertension is a frequent problem encountered by paediatric patients suffering from CHD. Patients with pulmonary hypertension can develop right ventricular dysfunction due to an increase in the afterload of the right ventricle. In this situation pulmonary vasodilators or inotropes with pulmonary vasodilating properties

(inodilators) are frequently used to facilitate separation from CPB (Choudhury and Saxena, 2003).

The peak intraoperative lactate cut-off value of 4mmol/L may be too low to show an association between hyperlactatemia and postoperative complications and clinical outcomes. Furthermore, it might be of more value to evaluate the time that the patient was exposed to the elevated lactate levels rather than looking at a single peak intraoperative lactate value. In our practice, persistent high levels of lactate intraoperatively (>2.5mmol/L) prompts therapeutic intervention to increase tissue perfusion both intra- and postoperatively. The therapeutic intervention reduces the time that the patient is exposed to elevated lactate levels and may be the reason why an association could not be made between postoperative complications and outcomes and high intraoperative lactate levels (≥4mmol/L). In this study, the sample size was small, and a larger study population could bring forward differences not possible to show with relatively small numbers of patients.

### 5.2.5 Cardioplegic solutions

During the study two (2) different types of cardioplegic solutions were administered based on the preference of the cardiothoracic surgeon performing the open-heart surgery. In group 1 most patients received St Thomas II cardioplegia (75%, n=39) and in group 2 most patients received Bretschneider custodiol cardioplegic solution (55%, n=24). A statistical significant difference was recorded between the two (2) groups with regard to the cardioplegic solution used (p=0.0036).

Bretschneider custodiol cardioplegia is used by some centres for myocardial protection in complex cardiac surgeries as well as for organ preservation in transplant surgery. This type of cardioplegia is attractive for cardiac surgeons because it is administered as a single dose and is claimed to offer myocardial protection for up to three (3) hours (Gebhard *et al.*, 1984; Bretschneider, 1980), allowing performance of complex procedures without interruption (Edelman *et al.*, 2013). On the other hand, St Thomas II cardioplegic solution has also been a popular cardioplegic solution among cardiac surgeons but must be administered repeatedly at short intervals during surgery. An

increase in myocardial acidosis between the dosages have been reported, affecting postoperative outcome adversely (Khuri *et al*., 2005; Graffigna *et al*., 2002).

Most patients that received Bretschneider custodiol cardioplegia presented with the cardiac lesion, transposition of the great arteries (55%, n=22) and most patients that received St Thomas II cardioplegia presented with an AVSD (19%, n=10). Therefore, for the more complex and longer surgeries Bretschneider custodiol cardioplegia was used.

To summarize, in this study patients presenting with peak intraoperative lactate levels of 4mmol/L or higher in general did not display more postoperative complications or poorer clinical outcomes when compared to patients with peak intraoperative lactate values of <4mmol/L.

## 5.3 St Thomas II versus Bretschneider custodiol cardioplegia

The ninety-six (96) patients were then divided based on the cardioplegic solution used during cardiac surgery irrespective of their intraoperative lactate values. Two (2) cohorts were created, CPS 1 (patients receiving St Thomas II cardioplegia, n=59) and CPS 2 (patients receiving Bretschneider custodiol cardioplegic solution, n=37) and the demographic, anthropometric, cardiac lesions, intraoperative and postoperative complications and outcomes were compared between the two (2) groups.

### 5.3.1 Preoperative demographics, anthropometrics and cardiac lesions

The patients receiving Bretschneider custodiol cardioplegia (CPS 2) were younger (median 8.35 months' vs 19.00 months) weigh less (median 6.24kg vs 8.30kg) and were shorter (median 50.00cm vs 76.00cm) compared to the patients receiving St Thomas II cardioplegia (CPS 1). All these variables showed statistical significant differences between the two (2) groups ($p<0.05$). In both CPS groups, most patients were female (CPS 1, 54%; CPS 2, 51%) coloured (CPS 1, 51%: CPS 2, 57%) patients.

The predominant cardiac lesions in CPS 1 were AVSD (n=12, 20%) and in CPS 2, TGAs (n=20, 54%). From these results it seemed that Bretschneider custodial cardioplegia was the cardioplegia of choice when performing more complex cardiac surgeries that usually requires longer bypass times.

### 5.3.2 Metabolic data

#### 5.3.2.1 Lactate (mmol/L)

Intraoperatively, both CPS groups showed an increase in serum lactate values from baseline. The mean intraoperative lactate value for CPS 1 was 3.28mmol/L and for CPS 2 was 4.21mmol/L, showing a statistical significant difference between the groups (p=0.0332). Upon admission to ICU, the mean lactate values of both CPS groups already started to decrease (2.80mmol/L vs 3.40mmol/L) and gradually decreased further till both groups reported a mean lactate value below 2mmol/L at 48hr postoperatively (1.37mmol/L vs. 1.61mmol/L).

Cardioplegic arrest and CPB during cardiac surgery are associated with ischemic/hypoxic stress seen in cardiac and non-cardiac tissues as previously explained. A consequence of ischemic/hypoxic stress (anaerobic metabolism) associated with cardioplegic arrest and CPB is the accumulation of lactate in cardiac as well as peripheral and visceral tissues (Ascione and Angelini, 2003). Therefore, the intraoperative increase in lactate in this study is likely to be due in part to myocardial (and probably pulmonary) lactate that had accumulated during the cardioplegic arrest and CPB. However, limited literature is available about changes in blood lactate levels in children with CHD receiving cardiac surgery with CPB. Bretschneider custodiol cardioplegia is supposed to provide good buffering capacity and enhances anaerobic energy production during ischemic cardioplegic arrest (Ackemann *et al*., 2002; Morishita, 1999).

Furthermore, evidence suggests that hyperlactatemia observed following cardiac surgery may correlate with the duration of CPB (Inoue *et al*., 2001). In this study patients receiving Bretschneider custodiol cardioplegia had a much longer bypass time (mean 215.38min) than the patients receiving St Thomas II solution (mean 186.95min).

### 5.3.2.2 Haematocrit (%)

The haematocrit values showed no statistical significant differences ($p>0.05$) between CPS 1 and CPS 2 for any of the recorded time points. Intraoperatively, a decrease in the mean haematocrit values were recorded for both groups from baseline (CPS1, baseline 37.97%, intraoperative 26.76%; CPS 2, baseline 40.46%, intraoperative 27.95%). As previously explained the reason for the decrease could be attributed to haemodilution caused by the priming of the heart-lung machine circuit and the administration of cardioplegia (Ranucci *et al*., 2006).

### 5.3.2.3 Sodium (mmol/L)

The mean sodium values irrespective of the cardioplegic solution used, recorded intraoperatively (CPS 1, 133.63mmol/L; CPS2, 126.89mmol/L) fell outside the normal range of 135-145mmol/L (https://www.ucsfbenioffchildrens.org/tests/003481.html). The mean sodium values differ statistically between CPS 1 and CPS 2 intraoperatively (CPS 1, 133.63mmol/L; CPS2, 126.89mmol/L; $p<0.0001$) and after CPB upon admission to ICU (CPS 1, 139.58mmol/L; CPS 2, 137.41; $p=0.0108$). In both cases lower sodium values were recorded for patients that received Bretschneider custodiol cardioplegic solution (CPS 2). St Thomas II cardioplegia is an extracellular crystalloid cardioplegia and have sodium and calcium concentrations that mimics the concentrations found in plasma, whereas intracellular solutions, such as Bretschneider custodiol, have low sodium and calcium concentrations to mimic the intracellular milieu (Kotani *et al*., 2013). Therefore, Bretschneider custodiol solution can cause hyponatremia and haemodilution because of its low sodium concentration (15mmol/L) and relatively large volume of administration (50mL/kg) if it is drawn into the CPB circuit. When considering small intravascular and CPB priming volume, the risk of acute hyponatremia and normalization may be increased in paediatric patients (Kim *et al*., 2011).

As in this study, Lindner *et al*. (2012) and Kim *et al*. (2011) also reported that hyponatremia was more frequently seen in the paediatric population after the administration of intracellular cardioplegic solutions.

The sodium values recorded at the other time-points were comparable between the groups with no statistical significant differences (p>0.05).

#### 5.3.2.4 Potassium (mmol/L)

The potassium values at all the recorded time points for both CPS 1 and CPS 2 fell within the normal reference range of 3.5-5.5mmol/L and in considerable young or premature infants as high as 6.5mmol/L (Verive, 2016). A rise in intraoperative potassium levels was seen for both St Thomas II (Pre-CPB, 4.04mmol/L, Intra-CPB-low 5.11mmol/L) and Bretschneider custodiol cardioplegic solution (Pre-CPB, 4.02mmol/L, Intra-CPB-low 5.04mmol/L). The only statistical difference in mean potassium values between CPS 1 and CPS 2 was recorded 24hr (CPS 1, 4.80mmol/L; CPS 2, 4.35mmol/L; p=0.0005) and 72hr (CPS 1, 3.95mmol/L; CPS 2, 4.28mmol/L; p=0.0492) post-CPB, however, although there are statistical differences between the two groups the results remain within the normal reference range.

St Thomas II cardioplegic solution has a low sodium ion concentration. Low extracellular sodium concentration leads to cardiac arrest by depriving substrate for the fast sodium upstroke of the action potential, supported by a slight elevation of the extracellular potassium concentration (Gebhard *et al*., 1983) preventing further myocardial cell swelling by reducing sodium-potassium exchange pump activity during hypothermia (Shaffer *et al*., 1998). In a study conducted by Aldemir *et al*., 2014 they also reported a rise in potassium intraoperatively (4.39mmol/L) just after the unclamping of the aorta and even speculated that the higher serum potassium levels just after unclamping of the aorta was a favoured condition for lower ventricular fibrillation incidence.

### 5.3.3 Aortic cross-clamp (min), CPB time (min) and oesophageal temperature (°C)

In both CPS groups, the mean aortic cross-clamp time (CPS 1, 129.90min; CPS 2, 140.86min) and oesophageal temperature (CPS 1, 27.44°C; CPS 2, 25.87°C) were similar, and these variables were not statistically different between the two (2) groups (p>0.05). However, a statistical significant difference was seen between CPS 1 and CPS 2 for the

total bypass time (p=0.0328). Patients receiving Bretschneider custodiol cardioplegia (215.38min) had a much longer mean bypass time than the patients receiving St Thomas II cardioplegia (186.95min).

The statistical significance in bypass time between the two (2) CPS groups could be that Bretschneider custodiol cardioplegia was preferred by surgeons performing more complex surgeries. Most patients that received Bretschneider custodiol cardioplegia had TGAs (34%) whilst most patients receiving St Thomas II cardioplegia solution presented with AVSDs (20%). According to Vianna *et al*. (2013) 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.

### 5.3.4 Postoperative complications and clinical outcomes

No statistical significant differences were calculated for any of the postoperative complications or clinical outcome variables between the CPS 1 and CPS 2 groups except for phrenic or recurrent laryngeal nerve (RLN) injury (p=0.0199) and new onset seizures (p=0.0199). Patients receiving Bretschneider custodiol cardioplegia had a higher incidence of both phrenic or recurrent laryngeal nerve injury (10.8% vs 0.0%) and new onset seizures (10.8% vs 0.0%) compared to the children that received St Thomas II cardioplegic solution.

Nerve injuries after thoracic and cardiovascular surgery generally involve the brachial plexus, phrenic nerve, recurrent laryngeal, and facial nerve. Nerve injuries can also be the result of increased procedure duration causing prolonged periods of nerve compression (Setty *et al*., 2014). In this study, both the aortic cross-clamp time (140.86min vs 129.90min) and the total bypass time (215.38min vs 186.95min) were longer in the CPS 2 group that presented with the nerve damage.

Injury to the RLN can be a severe complication in cardiac surgery because it causes airway compromise by vocal cord paralysis (VCP) also referred to as cardiovocal syndrome (Alfares *et al*., 2016). The incidence of VCP following cardiac surgery ranges widely from 1.7% to 67% (Dewan *et al*., 2012), however, most studies indicate the rate is less than 9% that corresponds well with the 10.8% (CPS 2) recorded in this study. Infants, weighing

less than 1500g, are premature or younger, also have a higher risk of developing RLN paralysis (Mulpuru *et al*., 2008). In this study, a statistical significant difference was recorded for both weight ($p<0.0004$) and age ($p<0.0001$) between the two (2) CPS groups with the CPS 2 group being much younger and weighing much less than the CPS 1 group.

The two most common mechanisms of injury are direct trauma either to the recurrent laryngeal nerve (RLN) during the operation or indirect injury to the nerve from intubation (Otani *et al*., 1998). Aside from direct injury eight (8) mechanisms for RLN injury has been identified: central venous catheterization, hyperextension of the neck, traumatic endotracheal intubation, endotracheal tube trauma, faulty insertion of the nasogastric tube, sternotomy, traction on the heart, and hypothermic injury from ice slush (Hamdan *et al*., 2002). Furthermore, higher rates of RLN injury is also indicated during aortic arch procedures, due to the proximity to the surgical plane of dissection (Dewan *et al*., 2012).

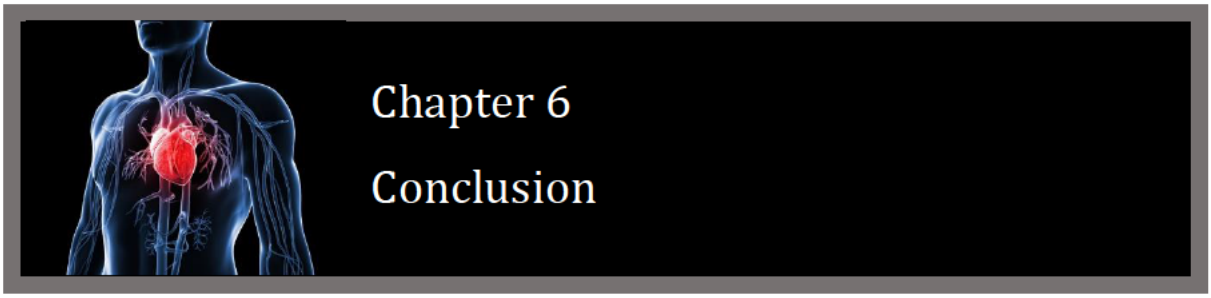
Phrenic nerve injury results in paralysis of the diaphragm and impairs respiratory function. According to Mok *et al*. (1991) phrenic nerve paralysis causes severe respiratory embarrassment in neonates but seems to cause fewer clinical or physiological abnormalities in children more than one (1) year old, unless associated respiratory muscles is compromised. In this study, the children that presented with increased phrenic and RLN injury (CPS 2) were much younger (median age 8.35 months) compared to the children with no incidence (CPS 1) (median age 19.00 months). The children in the CPS 2 group also experienced more respiratory insufficiency requiring mechanical ventilation >7 days postoperatively or reintubation (32.4%) compared to the children in the CPS 1 group (16.9%). This could be the reason why the children in the CPS 2 group were longer intubated (mean 91.8hr vs 75.7hr) and remained longer in ICU (8.3 days' vs 7.4 days) compared to the children in CPS 1. However, note that these variables were not statistically significant between the two (2) groups.

New onset seizures after paediatric cardiac operations have been described by several authors (Kim *et al*., 2011; Hsia *et al*., 2006; Bellinger *et al*., 1995). Bretschneider custodiol cardioplegia is known for its low sodium concentrations (15mmol/L) and relatively large administration volume (50mL/kg) and can therefore cause both hyponatremia and

haemodilution. Hyponatremia can lead to seizures in children and during anaesthesia can cause cerebral oedema and can affect the blood-brain barrier (Castilla-Guerra *et al*., 2006). Furthermore, the abrupt normalization of hyponatremia can cause even more detrimental effects on the central nervous system (McManus *et al*., 1995). All the children that presented with new onset seizures in this study received Bretschneider custodiol cardioplegia (CPS 2).

The clinical outcomes showed no statistical differences for inotropic support (p=0.7532), intubation times (p=0.5417), length of ICU stay (p=0.3845) and mortality (p>0.9999) between the patients that received Bretschneider custodiol cardioplegia and those receiving St Thomas II cardioplegia (p>0.05). These results were confirmed by literature (Di Eusanio *et al.,* 2013; Gaudino *et al.,* 2013; Shrestha *et al.,* 2014; Viana *et al.,* 2013; Braathen *et al.,* 2011; Scrascia *et al.,* 2011; Demmy *et al.,* 2008; Martin *et al.,* 2008; Salvador *et al.,* 2008; Minami *et al.,* 2005; Wiesenack *et al.,* 2004; Careaga *et al.,* 2001; Beyersdorf *et al.,* 1990; Gallandat Huet *et al.,* 1988).

Therefore, in this study patients receiving Bretschneider custodiol cardioplegia presented with phrenic and recurrent laryngeal nerve damage and new onset seizures that is not seen in patients receiving St Thomas II cardioplegia. For any of the other postoperative variables recorded no differences were seen when comparing CPS 1 with CPS 2.




## 6.1 Introduction

Hyperlactatemia during and after cardiopulmonary bypass surgery has been linked to increases morbidity and mortality in children undergoing surgery to repair complex congenital heart diseases (Cheung *et al.,* 2005; Munoz *et al.,* 2000). However, no specific peak lactate value has been identified as a consistent indicator of adverse clinical outcomes. The proposed predictive peak lactate levels range from 3-8mmol/L (Yilmaz *et al.*, 2011; Toraman *et al.*, 2004; Demers *et al.*, 2000). Demers *et al.* (2000) showed that a blood lactate level exceeding 4mmol/L or higher during CPB identifies with increased risk of postoperative morbidity and mortality. Based on this, a peak intraoperative lactate value exceeding 4mmol/L was chosen as the cut-off value to select a group of patients with predicted worse clinical outcomes in our study.

Hyperlactatemia intraoperatively could be due to type A or type B lactic acidosis. Type A results from an imbalance between tissue oxygen supply and demand due to ischemia, global hypoxia, respiratory failure, regional hypoperfusion and limb/mesenteric ischemia. Lactate production results from cellular metabolism of pyruvate into lactate under anaerobic conditions. Therefore, type A is related to total $O_2$ debt and the magnitude of tissue hypoperfusion. Type B lactic acidosis is due to delayed clearance of lactate, renal dysfunction, catecholamine release and accelerated aerobic glycolysis. The metabolic response to surgery itself may impair oxygen delivery and extraction at cellular level.

Cardiac surgery is characterised by dramatic changes in microvascular control with profound changes in cardiac output distribution. This results in a redistribution of perfusion, with some tissues experiencing substantial decreased $O_2$ transport while

others are being over-perfused. Therefore, an increase or change in lactate levels during CPB surgery may be a marker of regional hypoperfusion due to the redistribution of blood flow.

## 6.2 Peak intraoperative lactate values as a predictor of postoperative outcomes

Postoperative complications were reported for both lactate groups but limited statistical significant differences were recorded between patients with peak intraoperative lactate levels ≥4mmol/L versus those with lactate levels <4mmol/L. In this study, assessing lactate levels at a single point intraoperatively did not correlate with postoperative complications or mortality. Reason being, the absolute peak intraoperative lactate value of 4mmol/L was probably too low to demonstrate an association between hyperlactatemia as a predictor for increased postoperative clinical outcomes and complications. In a study conducted by Valenza *et al.* (2005) a peak intraoperative lactate level >5mmol/L was associated with a 75% sensitivity and 84% specificity for postoperative complications. In addition, in our unit any intraoperative increase in lactate levels above 2.5mmol/L prompts the need for therapeutic interventions.

Patients with intraoperative peak lactate levels ≥4mmol/L had statistically significant longer bypass times, aortic cross-clamp times and oesophageal temperatures compared to patients with peak lactate levels <4mmol/L.

Evaluating serial lactate values intraoperatively and assessing the duration of time that the patient is exposed to an increased lactate level might be a much better predictor of postoperative outcome. Therefore, a recovery period that describes not only magnitude but also duration and trend of hyperlactatemia over time might be more useful in predicting outcome.

## 6.3 Cardioplegia as a predictor of postoperative outcomes

Cardioplegia provides an additional level of myocardial protection during paediatric cardiac surgery. The majority of cardioplegic solutions exert their protective effects through mechanical arrest of the heart by depolarizing or hyperpolarizing the myocardial cell membranes (Martin and Benk, 2006).

Patients that received Bretschneider custodiol cardioplegia had higher peak intraoperative lactate values compared to those receiving St Thomas II solution. A possible reason for this is that the bypass time of patients receiving Bretschneider custodiol was statistically longer compared to those patients receiving St Thomas II solution. In literature extended bypass times is associated with increased intraoperative lactate values (Shah *et al.*, 2015; Shinde *et al.*, 2005; Mizock and Falk, 2002; Demers *et al.*, 2000). However, at 48 hours postoperatively both groups had lactate levels below 2mmol/L.

There have been concerns about hyponatremia following the rapid high-volume administration of low sodium Bretschneider custodiol cardioplegia solution which could result in hyponatremia (Ji *et al.,* 2012; Kim *et al.,* 2011). In this study, a similar response was found with the patients receiving Bretschneider custodiol cardioplegia that was not seen in patients receiving St Thomas II solution.

Regarding postoperative complications, the only statistical difference between the two cardioplegia groups were for new onset seizures and phrenic or recurrent laryngeal nerve injury. Associations between these injuries and the use of Bretschneider custodiol cardioplegia has already been published (Kim *et al.*, 2011; Hsia *et al.*, 2006; Bellinger *et al.*, 1995; Castilla-Guerra *et al.*, 2006). No substantial differences were found between St Thomas II and Bretschneider custodiol cardioplegia regarding the other postoperative complications, clinical outcomes and mortality. Therefore, in this study no clear association could be made between the use of cardioplegic solutions as a predictor of postoperative outcome. Prospective studies about the use of cardioplegic solutions in paediatric children receiving CPB is extremely limited. The results of this study again

emphasize the need to perform randomized prospective studies where variables that can affect results can be limited.

## 6.4 Limitations

- The sample size of the patient population used in this study was small.
- The cardioplegia used during this study was based on the preference of the surgeons and therefore not standardized.
- The fact that it was a retrospective observational study.

## 6.5 Recommendations

- Randomized prospective study design to restrict variables that can limit results.
- Increase in sample size.
- Assign a higher absolute value for peak lactate during cardiopulmonary bypass.
- Evaluation and comparison of lactate levels over time "area under the curve" to summarize duration of lactate exposure.
- Logistic regression to indicate the predictor/s of postoperative outcomes.

# Chapter 7
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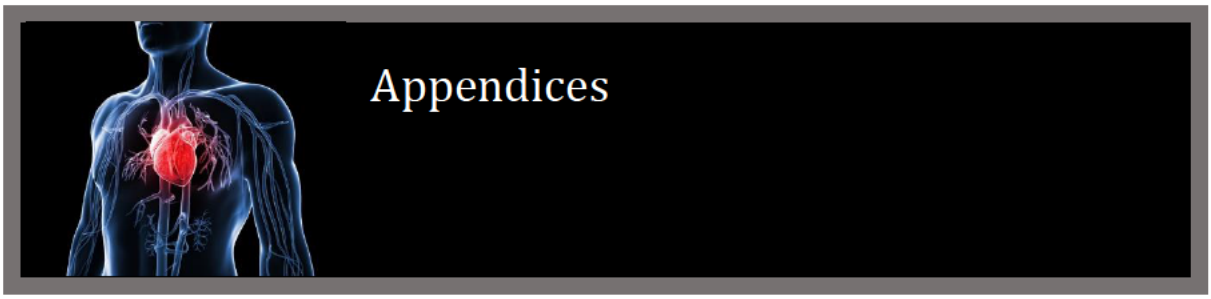


## Appendix A Ethical Approval

# Appendix A

# Ethical Approval

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

IRB nr 00006240
REC Reference nr 230408-011
IORG0005187
FWA00012784

16 February 2016

MR FJ PRETORIUS
FACULTY OF HEALTH AND ENVIRONMENTAL SCIENCES
CENTRAL UNIVERSITY OF TECHNOLOGY

Send per email: Johanpretorius8412@gmail.com; cc: lbotes@cut.ac.za

Dear Mr. Pretorius

**ECUFS NR 241/2015**
**MR FJ PRETORIUS**
**FACULTY OF HEALTH AND ENVIRONMENTAL SCIENCES, CUT**
**PROJECT TITLE: IMPACT OF PEAK INTRA-OPERATIVE LACTATE LEVELS ON POST-OPERATIVE OUTCOMES IN CONGENITAL SURGERY**

1. You are hereby kindly informed that, the Health Sciences Research Ethics Committee (HSREC) approved the above project after all conditions were met. This decision will be ratified at the meeting scheduled for 23 February 2016.

2. The Committee must be informed of any serious adverse event and/or termination of the study.

3. Any amendment, extension or other modifications to the protocol must be submitted to the HSREC for approval.

4. A progress report should be submitted within one year of approval of long term studies and a final report at completion of both short term and long term studies.

5. Kindly use the ECUFS NR as reference in correspondence to the HSREC Secretariat.

6. The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2006); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite), Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

Yours faithfully

DR SM LE GRANGE
CHAIR: HEALTH SCIENCES RESEARCH ETHICS COMMITTEE

Health Sciences Research Ethics Committee
Office of the Dean: Health Sciences
T: +27 (0)51 401 7795/7794 | F: +27 (0)51 444 4359 | E: ethicsfhs@ufs.ac.za
Block D, Dean's Division, Room D104 | P.O. Box/Posbus 339 (Internal Post Box G40) | Bloemfontein 9300 | South Africa
www.ufs.ac.za