“Investigation of acute systemic inflammatory response and myocardial injury after cardiac surgery in patients infected with human immunodeficiency virus using clinical and inflammatory markers”

Submitted in fulfillment of the requirements of the degree of Masters of Health Sciences in Clinical Technology; Faculty of Health Sciences at the Durban University of Technology.

(Clinical Technology: Cardiovascular Perfusion)

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March 2016

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AUTHORS DECLARATION

I Mawande Khayalethu Edson Gojo, hereby declare that this study represents the original work by myself, and has not been submitted in any form to another University. Where use was made of the work of others, it has been duly acknowledged in the text.

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DEDICATION

I dedicate this work to:

My late father Alfred Mzinjani Gojo, “many years have gone by without you but it still feels like it all happened yesterday. This work symbolizes your teaching and life advices”, *Ndiyakukhumbula tata*.

To my mother “in greatest moments of despair, you had faith in me and today here I am”, *enkosi mama*.

To my three little angels, Emihle, Sisanda and Zizipho even though I am hardly at home with you, your existence is my courage and strength.

To my wife, Ziyanda Dlembula, thank you for your support and midnight snacks to help me keep going.

ABSTRACT

Introduction: The immediate post-cardiopulmonary bypass (CPB) immune responses and organ injuries in immune- compromised patients remain poorly documented. We conducted a prospective clinical study to determine whether or not human immunodeficiency virus (HIV) seropositive patients generate higher acute systemic inflammatory response and suffer greater myocardial injury, compared to HIV seronegative patients.

Methodology: Sixty-one consecutive patients i.e. Thirty HIV seropositive patients and Thirty-one seronegative, undergoing elective cardiac valve(s) replacement were enrolled, over a period of nine months from a single center hospital, after informed consent was acquired. The C-reactive protein (CRP) and Erythrocyte sedimentation rate (ESR) were used as biomarkers of acute inflammatory response, and cardiac troponin I (cTnI) as a biomarker for measuring postoperative myocardial injury. Single tests were measured preoperatively and postoperatively, in both groups, and these were compared and correlated to perioperative events and CPB parameters.

Results: The mean age group was similar between the HIV seropositive and negative group (37.8 and 37.1 years, respectively). Preoperatively both groups had relatively equal CRP levels (p=0.388), ESR levels (p=0.817) and cTnI (p=0.489). The CPB events and durations were significantly different between the two groups, CPB duration (p=0.021). Other CPB events include, clamp aortic duration (p=0.026), CPB blood transfusion (p=0.013), CPB total urine output (p=0.035) and CPB peak lactate (p=0.040). Postoperatively we observed significant increased biomarkers level in both groups, with no significant difference between the groups: mean CRP (p=0.115), mean ESR (p=0.214) and cTnI (p=0.363). We observed a significant negative correlation between the mean change in CRP levels and mechanical ventilation (r=-0.548, p=0.002) in the seropositive group, but not in the uninfected group (r=0.025, p=0.893). The correlation between the difference in CRP and ICU stay was not significant between in both group (r=-0.231, p=0.229 and r=0.25, p=0.975, respectively). A significant positive correlation between postoperative cTnI and the inotropic support duration (r=0.384, p=0.040) was seen in the seropositive groups, but not in the negative group (r=0.092, p=0.622). Furthermore we observed a significant drop in CD4 cells postoperatively (p=<0.001) in the HIV seropositive group. Antiretroviral treatment appeared to influence the degree of change in CD4 cells postoperatively.

Conclusion: We conclude that HIV positive patients' postoperative reactions to cardiac surgery supported by CPB are similar to those of HIV seronegetive patients. We further report non-paralleling correlations between the biomarkers and perioperative events; however these do not seem to affect the overall outcomes between the two groups.

ACKNOWLEDGEMENTS

To the Lord almighty, indeed you deserve all the glory and honor. I pray and thank you for your everyday protection and wisdom to prosper; your name shall forever be praised.

Just like a forensic detective, who dealt with a cold long-forgotten case, that no one believe it could be solved. Dr. R Prakaschandra, you came in and took my dusty proposal file that was neglected by others but you believed in it. Today here I am, full of knowledge and understanding of the research field, all because you. I wish to thank you for being an excellent mentor and teacher. You truly understand what hard work and dedication can bring to one's life**.** *THANK YOU.*

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Abbreviation	Full name
ACC	American College of Cardiology
AIDS	Acquired Immunodeficiency Syndrome
AR	Aortic regurgitation
ART	Antiretroviral therapy
ATP	Adenosine triphosphate
AVR	Aortic valve replacement
CABG	Coronary artery bypass graft
CART	Combined antiretroviral therapy
CI	Confidence interval
CK-MB	Creatine Kinase-MB
CPB	Cardiopulmonary bypass
CRP	C-reactive protein
CTL	Cytotoxic T lymphocytes
cTnI	Cardiac troponin I
DC	Dendritic cells
DNA	Deoxyribonucleic acid
DVR	Double valve replacement
ESC	European society of cardiology
ESR	Erythrocyte sedimentation rate
gp	glycoprotein
HAART	Highly active antiretroviral treatment
HIV	Human Immunodeficiency Virus/
ICU	Intensive care unit
IL	Interleukin
IQR	Inter-quartile range
MHC	Major histocompatibility complex
MR	Mitral regurgitation
MVR	Mitral valve replacement
NK	Natural killer cells

NNRTI	Non-nucleoside reverse transcriptase inhibitors
NRTI	Nucleoside reverse transcriptase inhibitors
NYHA	New York Heart Association
PCT	Procalcitonin
PI	Protease inhibitors
PVL	Plasma viral load
PVR	Pulmonary vascular resistance
RNA	Ribonucleic acid
ROC	Receiver-operator characteristic
SIRS	Systemic inflammatory response syndrome
TLRs	Toll-like receptors
TNF	Tumor necrosis factor
UNAIDS)	Joint United Nations Programme on HIV/AIDS
WBC	White blood cells
WHO	World Health Organization

CHAPTER ONE – INTRODUCTION

Since the first Human Immunodeficiency Virus/ Acquired Immunodeficiency Syndrome (HIV/AIDS) cases were reported in the United States in June 1981, the number of cases and deaths among persons with AIDS increased rapidly during the 1980s, followed by substantial declines in new cases and deaths in the late 1990s (Alejandro, Jose and Emili 1993).

According to the Joint United Nations Programme on HIV/AIDS (UNAIDS) in 2014, there were about thirty-five million people living with HIV globally. Since the start of the pandemic, around seventy-eight million people have become infected with HIV and around thirty-nine million people have died of AIDS-related illnesses. In Sub-Saharan Africa there were about twenty-five million people living with HIV in 2014, making it the leading subcontinent with infected people in the world. South Africa has the highest prevalence of HIV/AIDS compared to any other country in the world with estimations of about five and half million people living with HIV (UNAIDS, 2014).

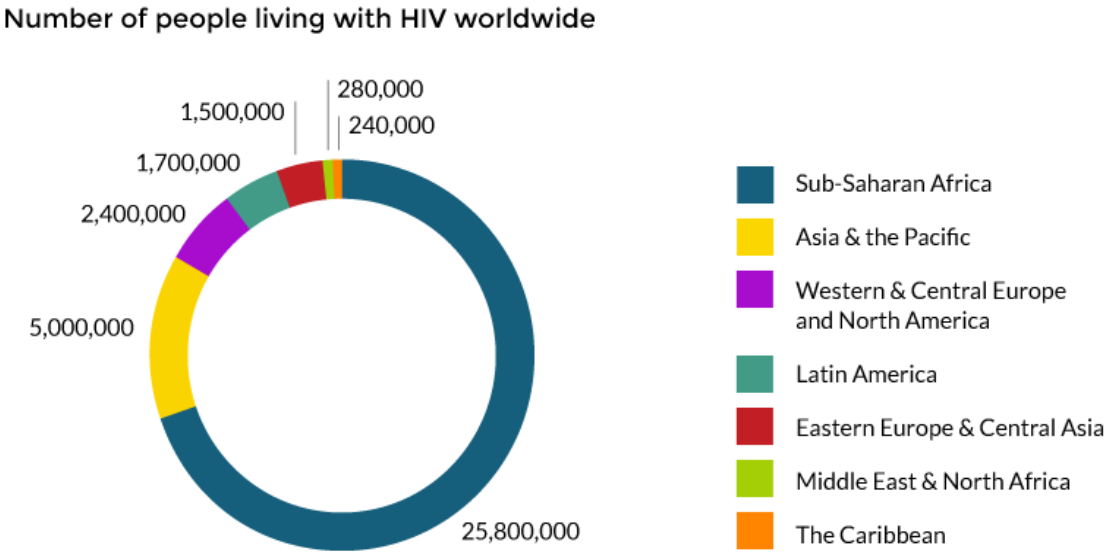


Figure 1.1: Global HIV and AIDS statistics 2014. www.avert.org. Retrieved 06/04/2015.

People living with HIV are also prone to any other conditions which may not be as a result of the HIV infection, but due to various factors that cause ailments and diseases amongst all human being. Some of these conditions may require lifestyle changes, medical intervention or even surgical corrective procedures. Cardiac

surgery is no exception, since HIV positive people may also require open heart surgery supported by the cardiopulmonary bypass (CPB) machine. Open cardiac surgery employs use of sophisticated mechanical devices to support the patient's haemodynamics allowing for the heart to be stopped and opened or positioned and twisted to exposed any area to operate on without haemodynamic alterations.

The first successful heart operation was conducted by Dr Rehn in 1896, when he repaired a stab heart wound suffered by a twenty-two year-old named Wilhelm Justus (Blatchford & Rehn. 1985). However this was a closed heart repair, giving rise to the famous Latin medical term "nolitangere" which means "do not touch the heart". This continued to be taught to medical students as a base fact as fears of fatal consequences of interrupting blood circulation restricted open heart surgical operations (Gravlee, Davis, Kurusz and Utley. 2000).

The conceptual idea of cardiopulmonary bypass (CPB) was born in 1930 by Dr John Heysham Gibbon after he helplessly watched a female patient die in an attempted pulmonary thrombo-embolism operation (Philip and Christopher. 2004). The design and application of the CPB machine was fraught with various challenges, but a breakthrough was accomplished in 1952 after a lengthy period of laboratory research on dogs, with Dr F. John Lewis performing the first successful open heart surgery in a five year old female (Cooley. 1987).

The principle of the CPB machine is to drain blood from the venous circulation of the patient, into an artificial oxygenator for blood gaseous exchange, and actively pump oxygenated blood back to the systemic circulation of the patient (Eugene, Hessel and Aaron.2000). Although this machine has simplified cardiac surgery by allowing the heart to be stopped, the technology also causes adverse effects on a patient's physiological mechanisms and cognitive functions as illustrated in Figure 1.2. These include complications such as inflammatory systemic responses, myocardial injury, and damage to other major organs such kidneys and brain (Steidl, 2011, Jesse, Castillo, Delgade, Ramirez and Urdaneta. 2003) resulting in increased morbidity and mortality (Laffey, Boylan and Cheng, 2002). Cardiac surgery utilizing CPB is therefore often independently related to perioperative morbidity and mortality (Murphy and Angelini. 2004).

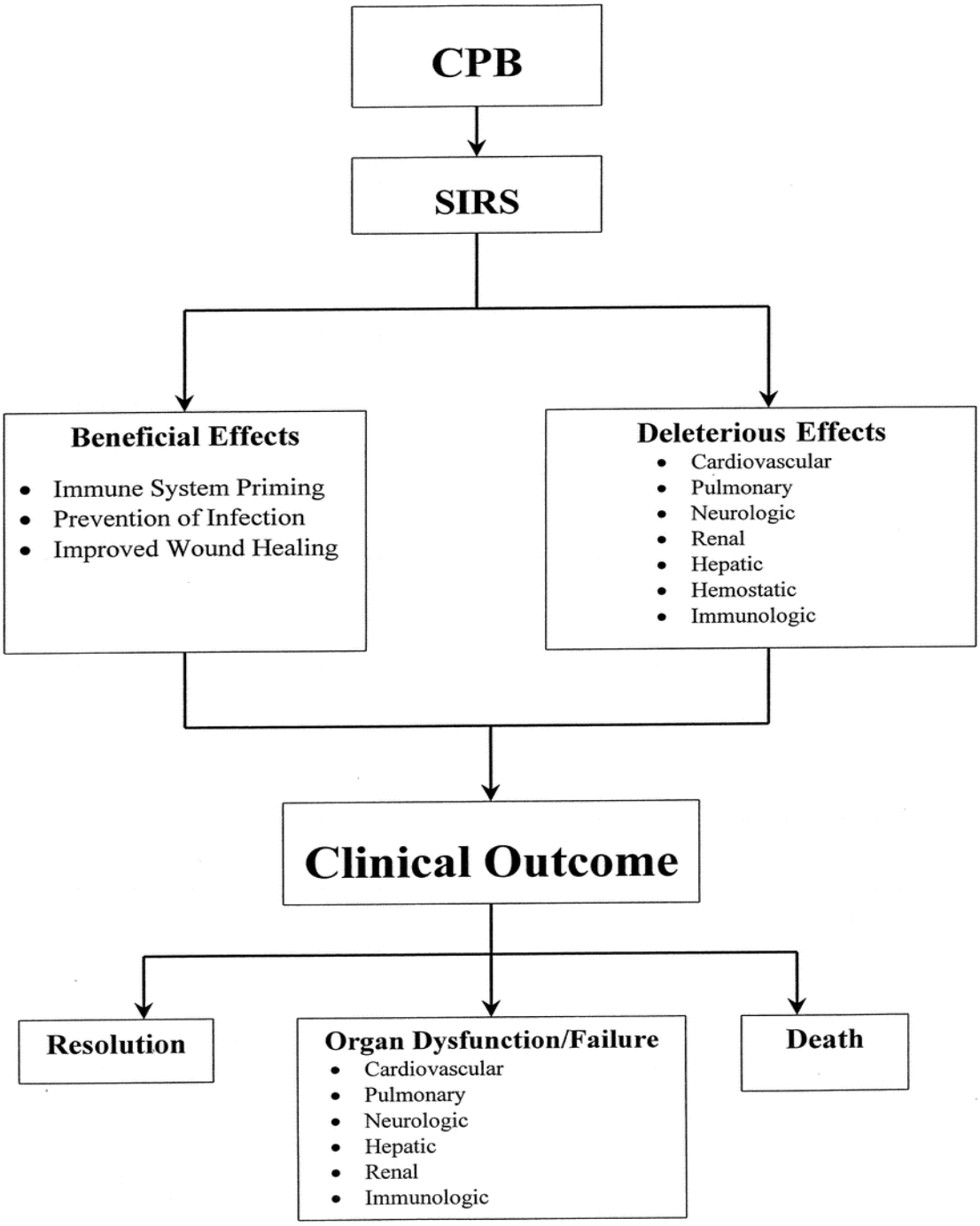


Figure 1.2: Schematic diagram of the balance between beneficial and adverse effects and the resultant clinical sequelae of the inflammatory response following cardiac surgery, (Laffey, et al. 2002).

Complex-associated inflammatory response during CPB is thought to be attributed to blood's exposure to abnormal shear forces from roller pumps and blood contact with artificial surfaces of the bypass circuit (Cremer, Martin and Redi. 1996, Day and Taylor. 2005). Immune system activation i.e. coagulation as well as fibrinolytic systems activation, with consequent degranulation of leukocytes and release of

cytotoxic enzymes, complement system, inflammatory mediators such as tumor necrosis factor (TNF), various interleukins, platelets and endothelial cells are activated during CPB (Hunt, Parratt and Segal. 1998, Zimmermann, Simon and Seeburger. 2003). These are also considered as major contributors to cardiopulmonary bypass perioperative adverse effects (Jesse et.al, 2003).

Today, although open heart surgery and other cardiovascular surgeries are performed with very minimal complications, CPB remains an extracorporeal circuit which trigger various immunological responses.

In the era of the human immunodeficiency virus (HIV) pandemic, there have been various concerns about the operative risks, infections and benefits of cardiac surgery in patients infected with the HIV, as they are known to already have a compromised immune system and chronic inflammation (Kesieme, Ekpe and Delia. 2011). This led to cardiac surgery departments setting a minimum acceptable CD4 T-cell count level ranging between 250 and 400 cells per cubic millimetre or use of undetectable viral load for HIV positive patients to undergo elective corrective cardiac surgery. Acquired Immunodeficiency syndrome (AIDS) is diagnosed when CD4 T-cell level drops below 200 cells per cubic millimetre of blood or when opportunistic infections arise (Kortenbout, Mtshali and Van Dyk. 2009).

In the early years after the pandemic had surfaced, cardiac surgery operations were not conducted in patients with AIDS as their survival was very short, (Alejandro, Jose and Saura, 1993). Following the introduction of highly active antiretroviral treatment (HAART), the lifespan of HIV positive patients have increased dramatically. In addition, recent research studies suggest that little difference exists with regards to surgical outcomes and duration of hospital stay between HIV positive patients and negative patients undergoing cardiac surgery (Filsoufi, Salzberg, von Harbou, Neibart and Adams, 2006).

Many studies that have been conducted to investigate the outcomes of cardiac surgery in HIV seropositive patients were retrospective studies, and mostly addressing the patients' outcomes in terms of morbidity, mortality and hospital stay (Michael et. al, 2014, Gregory et.al, 2003, Blyth et. al, 2006). There is a very limited information published prospectively on the HIV disease profile in correlation with alterations and immune system activation during and after cardiac surgery supported

by CPB. Depletion of the immune system cells and immune alterations usually do not result in clinical adverse events depending on patient's preoperative clinical wellbeing and the state of the immune system and hence are only evident upon laboratory testing, (Markewitz, Lante, Franke, Marohl, Kuhlmann and Weinhold, 2001). For this purpose, more readily available, standardized methods for immunologic monitoring and organ injury related clinical biomarker appear highly desirable and merit further investigation

This study was designed in order to ascertain the immune alterations and activation among HIV positive patients and to compare these parameters to a group of HIV negative also undergoing cardiac surgery on CPB. This study also sought to identify preoperative risk and perioperative complications to determine whether clinical relevant events correlate to alterations of immune responses and organ injuries based on laboratory tests.

The aim of the study was to investigate the severity of acute systemic inflammatory response and myocardial injury after cardiac surgery in patients infected with human immunodeficiency virus in comparison with HIV negative patients, using C-reactive protein (CRP), Erythrocyte sedimentation rate (ESR) and Cardiac troponin I (cTnI) biomarkers. Amongst HIV positive patients, CD4+ Tcells level count were measured prospectively before and after the operation to investigate any alterations and their significance. Consecutive patients undergoing elective cardiac valvular replacements were recruited as participants.

CHAPTER TWO: STUDY BACKGROUND AND LITERATURE REVIEW

2.1 STUDY BACKGROUND

2.1.1 CARDIOPULMONARY BYPASS

2.1.1.1 Physiological principle

The cardiopulmonary bypass is an extracorporeal circulation maintaining full support of the normal physiological circulation by means of artificial devices (Philip et al, 2004). The primary principle of the cardiopulmonary bypass machine is to drain blood from the venous circulation i.e. superior and inferior vena cava of the patient, into an artificial oxygenator for blood gaseous exchange, and pump oxygenated blood back to the systemic circulation i.e. aorta of the patient (Eugene et al, 2000).

This allows for the heart to be stopped and emptied, allowing surgeons to open any desired heart chamber, and conveniently conduct surgical heart repair procedures safely. Cardiac surgery in the absence of cardiopulmonary bypass is deemed impossible (Jonathan and Ralph, 2004). There are four main physiological functions which are fully or partially performed by the cardiopulmonary bypass extracorporeal circulation are: maintenance of blood flow (function of the heart), gaseous exchange which allows ventilation of the patient (function of the lungs), blood-endothelial interface as a result of continuous blood flow hence preventing blood vessel collapse and reticulo-endothelial function which is also known as macrophage system that is part of innate immune defence system (Jonathan et.al, 2004). Cardiopulmonary bypass consists of various functional components that are interconnected to form a circulatory circuit, illustrated in figure 2.1.

2.1.1.2 Cardiopulmonary bypass circuitry components

The venous reservoir component serves as the right atrium as it receives deoxygenated blood from the superior and inferior vena cava (Jonathan et.al, 2004). It allows for monitoring volume imbalances between venous return and arterial blood flow to the patient, and it ranges in blood capacities from neonates to adults volumes. There are two main types: soft reservoir which is made of a plastic bag material and rigid reservoir which is made of a transparent hard material (Philip et al, 2004). Rigid reservoirs are integrated with cardiotomy reservoirs and defoaming layer coated with silicone compound which allows for filtering of blood suctioned from the surgical field (Eugene et al, 2000).

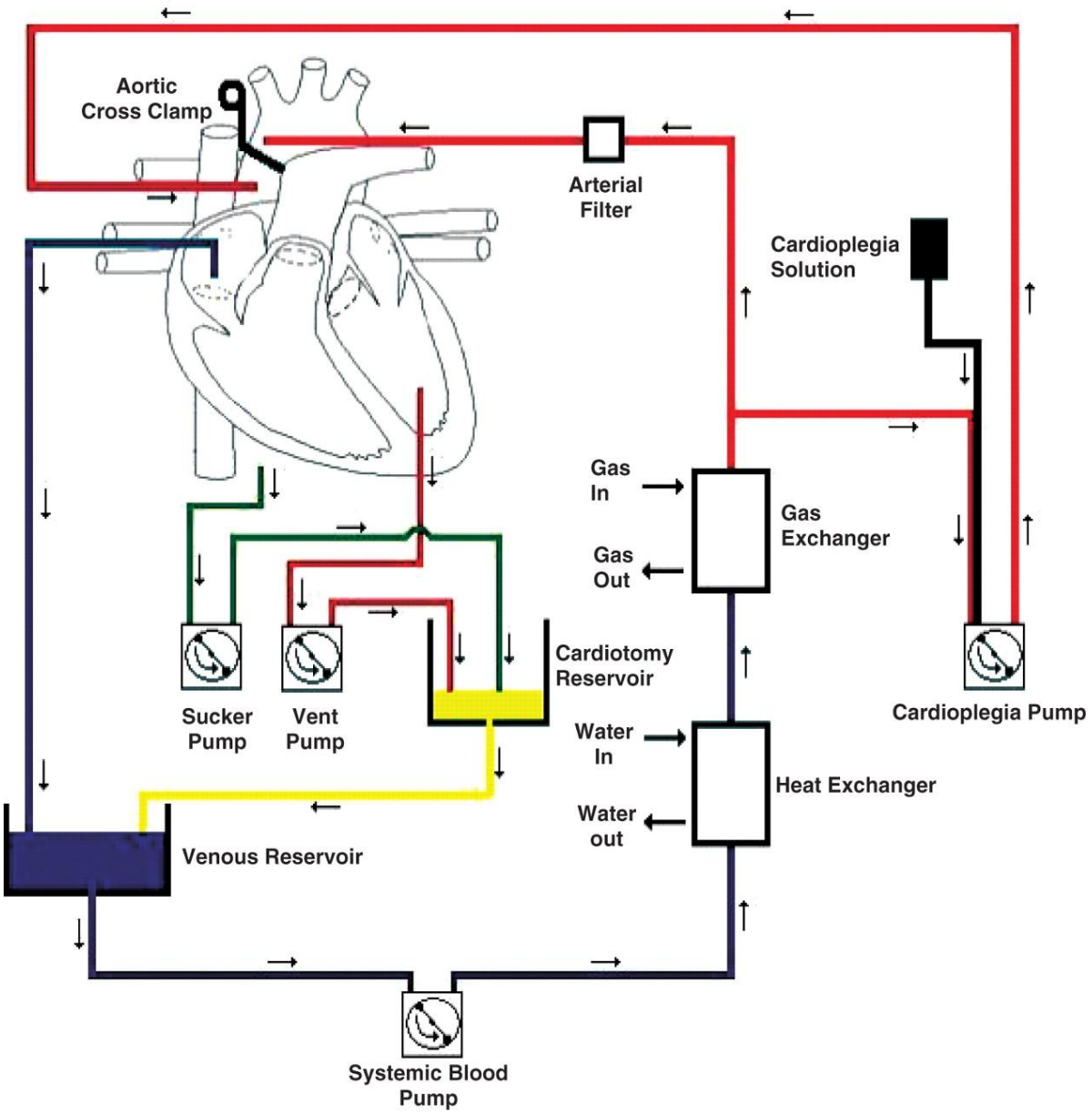


Figure 2.1: Diagrammatic representation of Cardiopulmonary bypass extracorporeal circuit. (Machin and Allsager. 2006)

The pumps serve as the ventricles by providing adequate blood flow movement within the circuit and back to the patient (Jonathan et.al, 2004). There are two types of blood pumps namely centrifugal and roller pumps. Roller pumps are the most widely used due to simplicity. Roller pumps are also used as a cardiotomy blood sucker and vent pump to suction blood from the surgical field. There is also the cardioplegia roller pump which is used to administer cardioplegia solution (Eugene et al, 2000).

Oxygenators serve as an artificial lung for gaseous exchange (Jonathan et.al, 2004). There two types namely the bubble and membrane oxygenator. The membrane oxygenator is made of either silicone or polypropylene; it is the most widely used due to its efficacy and minimal incidents of embolic events (Philip et al, 2004). Gas exchange is driven by diffusion through the membrane according to the gas partial pressure difference.

Heat exchangers allow for thermoregulation of the patient. Water is used to regulate the patient's blood temperature by flowing counter currently to blood. Blood and water are separated by either an aluminium or stainless steel material which allows for heat transfer (Kane, Gerard and Mark, 2000). In the current design of oxygenators, heat exchangers are integrated within oxygenators.

Arterial filters are used within the cardiopulmonary bypass circuit to filter or trap gross and microembolic material (Jonathan et.al, 2004). Arterial filters are used to filter blood just before it returns to the patient. There are two types of filters namely: depth and screen filters. Screen filters are the mostly used and are usually made of woven polymer threads that have a defined pore size and filters by interception. Arterial filter pore size ranges around 35micrometer (Eugene et al, 2000).

Plastic tubing and polycarbonate connectors system connect different functional components of the cardiopulmonary bypass circuit to one another forming a bridge for blood and from and to the patient. Polyvinyl chloride and latex tubing are the currently mostly used types of tubing (Philip et al, 2004).

2.1.1.3 Cardiopulmonary bypass biocompatibility

Human blood cells and proteins interface only with the blood vessel endothelium, which is adapted to allow maintenance of fluidity of blood and the integrity of the vascular system concurrently (Henry and Nina, 2000). This is achieved by anti-coagulants and procoagulants produced by endothelial cells (Henry and Nina, 2000). Blood contact with foreign surface area such as biomaterial, basement membrane or cell membrane lead to activation of platelets, blood coagulation and leukocytes to a variable degree (Francesco, 2014). No biomaterial has been found to be as thrombo-resistant as endothelium is (Holger and Wurzinger, 1984).

The cardiopulmonary bypass circuit functional components and tubing are lined with heparin-based biocompatible surfaces; however biomaterials are relative not

absolute phenomena and they still trigger immune response to a certain degree (Francesco, 2014). Studies have shown variable results with some suggesting a reduction in complement activation and pro-inflammatory cytokine release however this is not consistently found (Belboul and al-Khaja, 1997). Hence, when blood is exposed to foreign surfaces, immune response activation occurs as a natural response of the body's immunity response (Henry and Nina, 2000). This generates the systemic inflammatory response syndrome which is characterised by leukocytosis, increased capillary permeability, and accumulation of interstitial fluid which may lead to organ dysfunction and hemodynamic instability, (Laffey, Boylan, and Cheng, 2002 and Butler, Chong, Baigrie, Pillai, Westaby and Rocker, 1992). Cardiac surgery and cardiopulmonary bypass combined, trigger defence reactions illustrated in figure 2.2 below and these reactions may be so intense that relatively all cells in the body are affected (Philip et al, 2004).

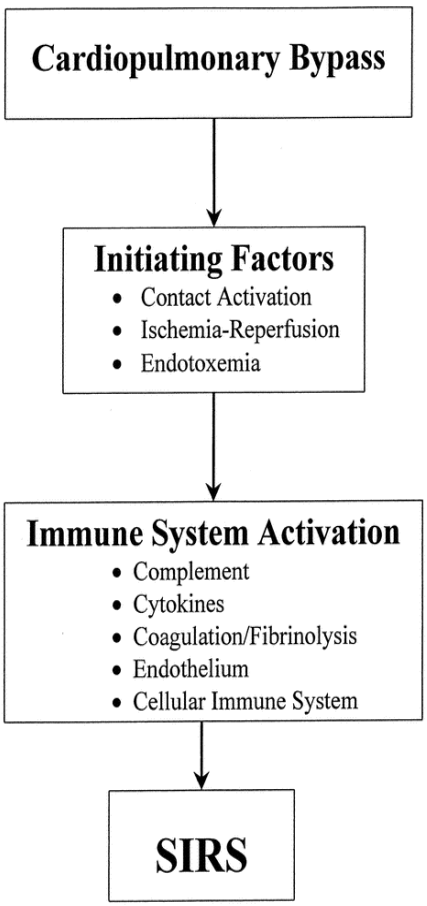


Figure 2.2: Schematic diagram of the sequence of events by which cardiopulmonary bypass (CPB) may lead to the development of systemic inflammatory response syndrome, (Laffey et al. 2002).

In addition, biomaterial properties such as mechanical properties, durability and function, physical and chemical characteristics are determinants of the degree of intrinsic surface activity when in contact with blood (Henry and Nina, 2000). These material are easily contaminated, mobile and very reactive (Rather, Hoffman, and Schoen, 1996). Biomaterials may initiate biological reactions that involve defensive systems in the human body, such as coagulation, complement system, fibrinolytic, kallikrein and kinin systems (Philip et al, 2004).

Despite the progress in technology in the design of the CPB circuit, and improvements in therapeutic option, perioperative complications on many of the body's organs and systems still occur, giving rise to the high morbidity and mortality rate in patients undergoing surgery on CPB (Steidl, 2011).

2.1.1.4 Effects of CPB on pulmonary physiological functions

Lung injury is due to collapse and pleural disruption as well as due to the inflammatory response mediated by contact of blood components during CPB, (Rochelle, and Botti, 2004). Severity may vary from microscopic changes associated with minimal or no clinical manifestation to a fulminating capillary leak syndrome and acute respiratory failure depending on CPB duration and on the patients underlying pulmonary reserve, (Jonathan, Robert and Daniel, 2000). During open heart surgery, the lungs are not perfused and are bypassed usually allowing them to collapse to functional residual capacity during aortic cross-clamping initiating the creation of abnormal physiological changes associated with pulmonary complication known as atelectasis (Jonathan et al, 2000).

Cardiopulmonary bypass affects the lung parenchyma. It causes an alteration in pulmonary compliance most commonly related to an increase in lung water. This can further lead to a requirement for increased ventilator support and a diminished ability of the lungs to perform their function in gas exchange, (Jaggers, Neal, Smith, Ungerleider and Lawson, 1999). Cardiopulmonary bypass also affects the vascular component-stroma of the lungs, resulting in changes in pulmonary vascular resistance (PVR), which in turn affects the function of the right ventricle (Jaggers et al, 1999).

2.1.1.5 Effects of CPB on myocardial function

Approximately twenty percent of cardiac surgical patients develop myocardial dysfunction in the perioperative period, resulting in an inability of the heart to maintain sufficient blood at normal end-diastolic pressures (Savaris, Polanczyk and Clausel, 2001). Cardiac failure may be related to inadequate myocardial protection, reperfusion injury, ischemia, infarction, incomplete revascularization, metabolic, uncorrected pathology, mechanical abnormalities, conduction issues, pulmonary hypertension and right ventricular failure (Paul, Roekaerts, John and Heijmans, 2012).

Myocardial injury is defined as the disruption of normal cardiac myocyte membrane integrity resulting in the loss of intracellular constituents including detectable levels of a variety of biologically active cytosolic and structural proteins, such as troponins, into the extracellular space, illustrated in figure 2.3 below, (uptodate.com). In the events of myocardial damage or injury, cardiac enzymes, which are proteins that are found in the myocardium, are released into the bloodstream (Suleimon, Zacharowski, and Angelini, 2008).

Figure 2.3: Depiction of intracellular constituencies leaking into extracellular due to damage. Httpgomerblog.comwp-contentuploads20150434269232_m: retrieved 12/06/15

In addition calcium influx and altered intracellular calcium hemostasis during reperfusion contributes to post ischemic myocardial injury and functional impairment, (Savaris et al, 2001). Neutrophils and neutrophil derived products, oxygen radicals generated by neutrophils, myocytes and vascular endothelium are potentially toxic to cells contributing to the development of myocardial oedema (Jakob, Russell, Vinod and Andrew, 2000).

Multiple mechanisms have been proposed to explain the findings of myocardial injury after cardiac surgery for example from cardiac manipulation, inadequate myocardial protection, and intraoperative defibrillation, (Asim and Mohammed, 2009). Intraoperative myocardial injury may result in postoperative myocardial sub-endocardial necrosis and metabolic and post ischemic functional depression.

Myocardial injury during cardiac surgery may occur before, during, or after cardiopulmonary bypass. Injury before CPB may result from severe hypotension, ventricular fibrillation, cardiogenic shock, or from coronary artery spasm. Injury during CPB may result from misdistribution of cardio-protective solution, but even under adequate cardioplegia delivery myocardial injury may still occur due to other factors like myocardial distension. Post cardiopulmonary bypass injury may result from post ischemic reperfusion (Laffey et al, 2002).

Cardiopulmonary bypass and cardioplegic diastolic arrest reduces cardiac work by fifty percent (50%) or more and myocardial oxygen demand is further reduced by the principle of hypothermia to minimize basal energy requirements. Ventricle venting causes a reduction in oxygen supply-demand mismatch thereby lowering myocardial injury risks (Phillip et al, 2004). Imbalance between myocardial oxygen demand and supply postoperatively determines the optimal cardiac function (De Boer, Pinto, and van Veldhuisen, 2003). Sufficient coronary blood flow at the release of aortic cross-clamping allows washout of aerobic and anaerobic metabolites. Metabolites like lactate, hydrogen ions and carbon dioxide which may be injurious if they accumulate in myocardial tissue for a longer period of time even during delayed intermittent cardioplegia administration may lead to ischaemic dysfunction and metabolic abnormalities (Jakob et al, 2000).

The heart may also be damaged due to inflammatory response causing aggravation to the heart, or due to the heart being operated on and manipulated causing postoperative arrhythmias. Cardiac surgery with cardiopulmonary bypass has been

found to release a greater amount of troponin I within the first seventy-two hours postoperative compared with patients who undergo cardiac surgery without CPB (Khan, De Souza, Mister, Flather, Clague and Davies, 2004).

2.1.1.6 Effects of CPB on renal function

Post cardiac surgery renal impairment poses a risk of increased intensive care unit stay, resulting in a lengthy total hospital length of stay (Mitchell and Mark, 2006). Mortality associated with renal impairment postoperatively after CPB is believed to be more than fifty percent (Simon and Julie, 2000). Preoperative renal function, cardiopulmonary bypass duration, low cardiac output, use of intra-aortic balloon counter pulsation and advanced age are predictive factors of renal dysfunction postoperatively after cardiac surgery with CPB (Mitchell and Mark, 2006).

Glomerular filtration rate has been proven to be the determinant of renal function (Sear, 2005). A reduction in the creatinine clearance that occurs below normal the range illustrates that the kidneys are not functioning properly in their process of the glomerular filtration of urine. In comparison between cardiac surgeries that employs CPB and one without CPB, a significant decrease in glomerular filtration rate has been demonstrated by a decrease in creatinine clearance in surgery with CPB (Ascione, Lloyd, Underwood, Gomes, and Angelini, 1999).

Albumin-to-creatinine ratio increase and an increase in N-acetyl glucosaminidase activity in the CPB groups also demonstrate renal dysfunction. Cardiac surgery with cardiopulmonary bypass has clinically been associated with severe cases of acute kidney injury when serum creatinine was ≥50% or ≥0.3mg/dl within 48 hours (Massoudy, Wagner, Thielmann, Herold and Kottenberg-Assenmacher, 2008).

2.1.1.7 Effects of CPB on vascular function

Cardiopulmonary bypass blood flow alterations may have complications on both systemic and pulmonary hemodynamics along with hormonal and metabolic changes (Uozumi, Manabe, Kawashima, Hamanaka, Monden, and Matsumo, 1972).

Increased peripheral systemic vascular resistance has been associated with cardiopulmonary bypass; most studies have aligned this phenomenon with non-pulsatile blood flow, as pulsatility is thought to reduce activation of the renin-angiotensin system (Jonathan et al, 2004). Clinically increased peripheral vascular

resistance is of great concern especially postoperatively due to its effect on other haemodynamic parameters, as it increases left ventricular workload with subsequent compromising of sub-endothelial perfusion (Taylor, Bian, and Morton, 1979).

2.1.1.8 Effects of CPB on neurological function

Damage to the brain is most commonly caused by cerebral emboli (Patel, Deodhar, Grayson, Pullan and Keenan, 2002). Atherosclerotic plaque, air, fat, and platelet aggregates are the main contributors of brain damage during CPB (Roach, Kanchuger, Mangano, Newman, Nussmeier and Wolman, 1996).

Although membrane oxygenators and arterial line filters help reduce the risks of possible causes of injury by filtering oxygenated blood return to the patient, neurological adverse effects still occur because of CPB (Carrascal, Guerrero, Maroto, Cortina, Rodríguez and Renes, 1999).

Hemodynamic fluctuations, cerebral hyperthermia after CPB and systemic inflammatory response have been associated with postoperative cerebral injury. Hypoperfusion with the ischemia/reperfusion cycle to the brain may also be another cause of damage (Hogue, Palin, and Arrowsmith, 2006).

2.1.1.9 Role of heamodilution during CPB

The heart-lung machine is primed using clear fluids which can either be colloid or crystalloid and heparin to prevent blood clotting (John and Piet, 2006). Priming of the cardiopulmonary bypass circuit with clear fluid solutions leads to haemodilution, which is an increase in the volume of blood plasma, resulting in a reduced concentration of red blood cells or Haematocrit (John and Piet, 2006).

Sudden haemodilution affects blood viscosity at the initiation of bypass causes a decrease in systemic vascular resistance appears to cause significant hypotension (Philip and Christopher, 2004). Decreased blood viscosity as a result of haemodilution has also been associated with physiological advantages of improving regional blood flow. Haemodilution has been associated with altered pharmacokinetic and pharmacodynamics properties of drugs during CPB, predominantly by alteration in protein binding through dilution of plasma protein (John and Martin, 2000).

Karkouti, Beattie, Wijeysundera, Rao, Chan, Dattilo,Djaiani, Ivanov, Karskia and David (2005) conducted an observational study which sought to determine whether the degree of hemodilution during cardiopulmonary bypass is independently related to perioperative acute renal failure necessitating dialysis support. The independent relationship was assessed between the degree of hemodilution during cardiopulmonary bypass, as measured by nadir hematocrit concentration, and acute renal failure necessitating dialysis support. Multivariate logistic regression was used to control for variables known to be associated with perioperative renal failure and anemia. Karkouti et al, 2005 observed that 9080 patients included in the analysis, 1.5% (n 134) had acute renal failure necessitating dialysis support. There was an independent, nonlinear relationship between nadir hematocrit concentration during cardiopulmonary bypass and acute renal failure necessitating dialysis support. Moderate hemodilution (nadir hematocrit concentration, 21%-25%) was associated with the lowest risk of acute renal failure necessitating dialysis support; the risk increased as nadir haematocrit concentration deviated from this range in either direction (P .005). Compared with moderate hemodilution, the adjusted odds ratio for acute renal failure necessitating dialysis support with severe hemodilution (nadir hematocrit concentration 21%) was 2.34 (95% confidence interval, 1.47-3.71), and for mild hemodilution (nadir hematocrit concentration 25%) it was 1.88 (95% confidence interval, 1.02-3.46). They concluded that given that there is an independent association between the degree of hemodilution during cardiopulmonary bypass and perioperative acute renal failure necessitating dialysis support, patient outcomes may be improved if the nadir hematocrit concentration during cardiopulmonary bypass is kept within the identified optimal range, (Karkouti et al, 2005).

2.1.1.10 Role of hypothermia during CPB

Reduction of metabolic rate thereby reducing oxygen demand has been a major cardio-protective mechanism of hypothermia. Vent Hoffs law states that myocardial oxygen consumption in the arrested heart decreases by fifty percent for every 10degrees Celsius reduction in temperature. Hypothermia and cardiac arrest combined reduce myocardial oxygen consumption by ninety-seven percent when profound cooling of 4degrees Celsius is achieved (Laurie, 2000).

Vladimir, Vladimir Sergey, Dmitry, Gleb, Denis, Igor, Anna, Vladimir and Alexander (2014) conducted a study with the aim to test the hypothesis that normothermic

cardiopulmonary bypass is as effective as hypothermic CPB in terms of cardiac protection (cTnI level) and outcome in patients with valvular heart disease. One hundred and forty (140) patients who had valvular heart disease, with /without coronary artery disease were surgically treated under CPB. The primary endpoint was the dynamics of troponin I. The secondary endpoints were ventilation time, the need for inotropic support, intensive care unit (ICU) and hospital stay durations, complications and mortality. There were no significant intergroup differences in dynamics of troponin I. Ventilation time was significantly lower in the hypothermic group (p=0.01).

Their conclusion was that normothermic CPB in patients with valvular heart disease was as effective as hypothermic perfusion, in terms of myocardial protection after the surgery assessed by cTnI release (Vladimir et al, 2014).

2.1.1.11 Immune system cells depletion after CPB

Cardiopulmonary bypass is associated with both functional changes and number in both cellular and humoral constituents of the adaptive immune system (Misoph, Babin-Ebell, Schwender, Grossmann, Keller and Eiert, 1997). These changes have been partially related to postoperative morbidity and mortality related to infection due to a loss of T and B cells and immunoglobulin consumption. Immunosuppression has been directly related to the magnitude and duration of the surgical procedure and to the volume of transfused blood (Hisatomi, Kobayashi, Moriyama, Shimokawa, Toyohira and Taira, 1997 and Roth, Golub and Grimm, 1974).

Clinical prevalence of infection after cardiac surgery supported by CPB, suggests that prolonged operating time and duration of CPB are significantly correlated to the incidence of infections (Ulicny and Hiratzka, 1991). This supports that the quantitative and qualitative reduction of humoral and cell-mediated immune mechanisms after CPB, which may lead to adverse effects on clinical outcomes and contribute to additional injuries in a patient with a down-regulated immune system in the early postoperative period (Philip and Kenneth, 2002).

Serum levels of immunoglobulins and complement are markedly reduced while leukocyte counts fall with the onset of CPB including all components of humoral immunity as a consequence of the hemodilution (Asimakopoulos, Kohn, Stefanou, Haskard and Landis, 2000, Kress, Gehrsitz and Elert, 1987).

Markewitz et al, 2001 reported a decrease of T lymphocytes and T helper (TH) cells (CD4+) but found that suppressor/cytotoxic T cells and B cells appear to be nearly unaffected. The type-1 TH cell mediated immune response appear to be depressed following cardiac surgery when using cytokine measurements of Inteleukin-2 and Interleukin-12 which are important for the activation of the type-1 TH-cells (Markewitz, Lante, Franke, Marohl, Kuhlmann and Weinhold, 2001). Immuno suppresion has been associated with post bypass complications such as sepsis especially in paediatrics.

Tetsuro, Shigeki, Munetaka, Yukihiro, Takahiro, Hideki and Hisataka (2003) conducted a study to investigate the effects of cardiac surgery with CPB on antigen-specific immunity. Twenty patients who underwent elective cardiac surgery using CPB were randomly divided into two groups: group A (n ¼ 10) and group B (n ¼ 10) with and without steroid administration, respectively. Group C patients underwent off-pump CABG (n ¼ 8). Peripheral blood mononuclear cells (PBMCs) were taken before and after surgery. Proliferation responses to pure protein derivative antigen were measured. The effects of CPB and steroid on T cell response and antigen-presentation were assessed by cross-stimulation between the preoperative and the postoperative PBMCs. Antigen-specific T cell responses decreased to about 5% of the preoperative values immediately after surgery with CPB, regardless of steroid administration. The T cell response in group B was significantly higher than that in group A. The results showed that CPB mainly impaired T cell responses, and steroid administration enhanced impairment of T cell response and antigen-presentation. They concluded that Open-heart surgery with CPB severely impaired antigen-specific immunity, (Tetsuro et al, 2003).

2.1.1.12 Cardiopulmonary bypass and Human immunodeficiency virus

Since the first open heart operation was performed on a patient known to be HIV positive, issues like the compromised immune system, limited survival and increased risk to the anaesthetic and surgical team of acquiring HIV infection have been the major concerns in offering cardiac surgery to patients with AIDS (Agaskar, Ghorpade, Athan and Mohajeri, 2003).

With concomitant highly active antiretroviral therapy, intermediate HIV and cardiac status appear to be favourable (Deneve et al, 2010). Various studies have found that

CD4+ counts can be reliably used to predict the outcomes of patients with HIV/AIDS after surgical procedures, the lower the CD4+ count, the higher the risks of post-operative infective complications, increased length of hospital stay, and mortality (Deneve et al., 2010).

Cardiac patients who are HIV positive have been associated with immunodepression, poor general condition, high number of associated diseases and infections, high rates of infectious valve endocarditis, frequent recurrence of infection after surgery, unsatisfactory long-term results and increased chance of transmission of HIV-1 to the surgeon and clinical staff (Cipriano, Miguel, Pedro, Mario-Vicente and Betancor, 2000).

The routine use of increasingly intensive antiretroviral therapies in HIV-1 infected patients has led directly to dramatic declines in morbidity and mortality among HIV-1-infected patients with advanced immunodeficiency of CD4+ count <100 cells/mm3 (Palella, Delaney, Moorman, Loveless, Fuhrer and Satten, 1998). Due to the increased life expectancy that is being reported for medically treated patients with HIV-1 infection, this disease is considered to be a chronic illness today.

Although there are reports of declining morbidity and mortality in HIV positive patients undergoing cardiac surgery even in patients with AIDS (Palella et al, 1998), the use of cardiopulmonary bypass remains a risk factor of immune system alterations (Asimakopoulos et al, 2000). However it is still unclear whether HIV progresses due to CPB and also whether HIV positive patients generate severe CPB induced immune system alterations compared to HIV negative patients (Blyth, Buckels, Sewsunker, Khan, and Mathivha, 2006).

2.1.2 HUMAN IMMUNODEFICIENCY VIRUS

2.1.2.1 Introduction

Human immunodeficiency virus (HIV) is a single-stranded RNA virus of the lentivirus subfamily of the retrovirus family. Two subtypes have been identified, HIV-1 and HIV-2. Human immunodeficiency virus, like other retroviruses contains the enzyme reverse transcriptase that enables viral RNA to be transcribed to DNA, which then becomes incorporated into the host cell genome and is able to replicate freely (www.wikipedia.com). HIV preferentially infects T-helper lymphocytes (CD4 T cells) and leads to their progressive quantitative and qualitative destruction, making the host more susceptible to opportunistic infections and malignancies. AIDS is diagnosed when CD4 T-cell level drops below 200 cells per cubic millimetre of blood or when opportunistic infections arise (Kortenbout, Mtshali and Van Dyk, 2009).

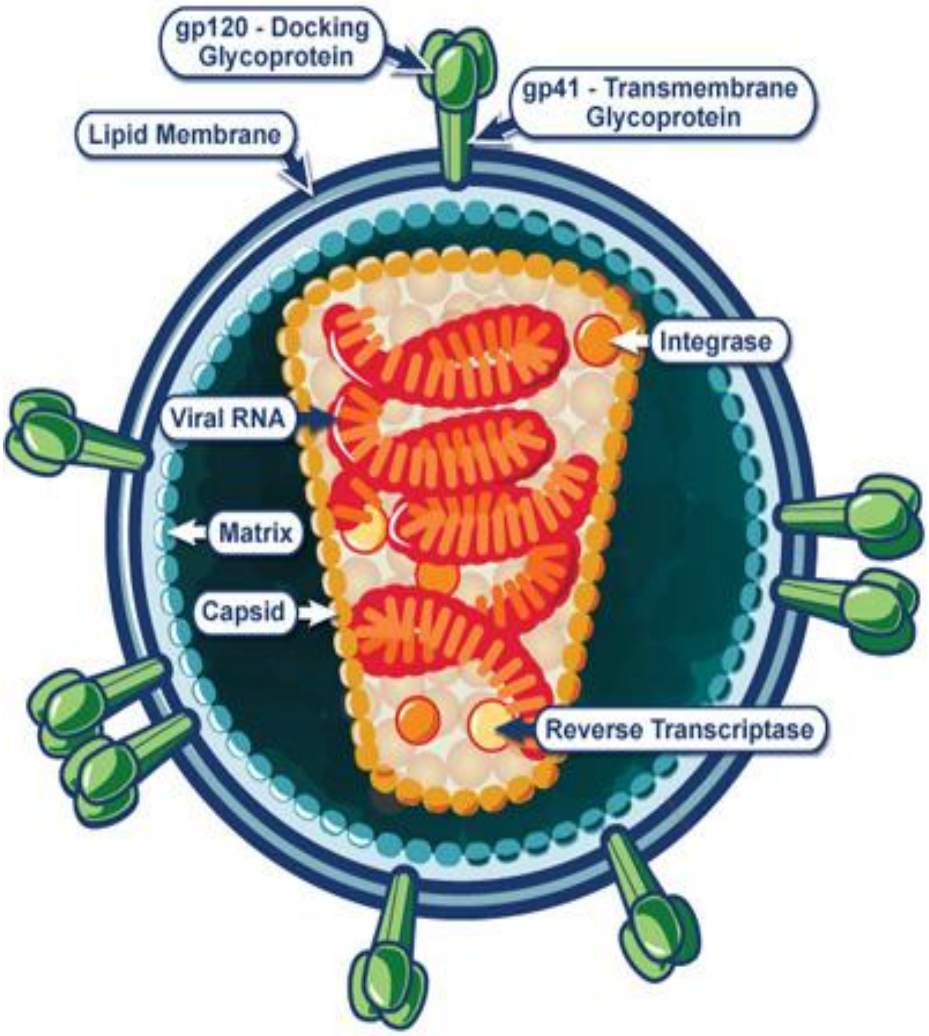


Figure 2.4: Structure of HIV
//www.niaid.nih.gov/topics/HIVAIDS/Understanding/Biology/Pages/structure.aspx

Human immunodeficiency virus is spherical in shape and has a diameter of 1/10,000 of a millimetre (figure 2.4). The outer coat of the virus, known as the viral envelope (Env), is composed of two layers of fatty molecules called lipids, taken from the membrane of a human cell when a newly formed virus particle buds from the cell. Embedded throughout the viral envelope are proteins from the host cell, as well as 72 copies on average of a complex HIV protein known as Env. Env copies protrude through the surface of the virus particle called a virion. Env consists of a cap made of glycoprotein 120 (gp120), and a stem consisting of glycoprotein 41 (gp41) that anchor the structure in the viral envelope (National institute of allergy and infectious diseases).

2.1.2.2 HIV and the immune system

Viruses are obligatory intracellular microbes that can cause tissue injury in two main ways: viral replication which may lead to cytopathic effects in infected cells and the host immune response can kill infected cells even if the viruses themselves are not cytopathic, (Abbas, Lichtman and Pillai. 2014). The immune system protects the host from infections by either eliminating the invading pathogens or by reducing the negative impact of infections on host fitness (Medzhitov, Schneider, and Soares, 2012).

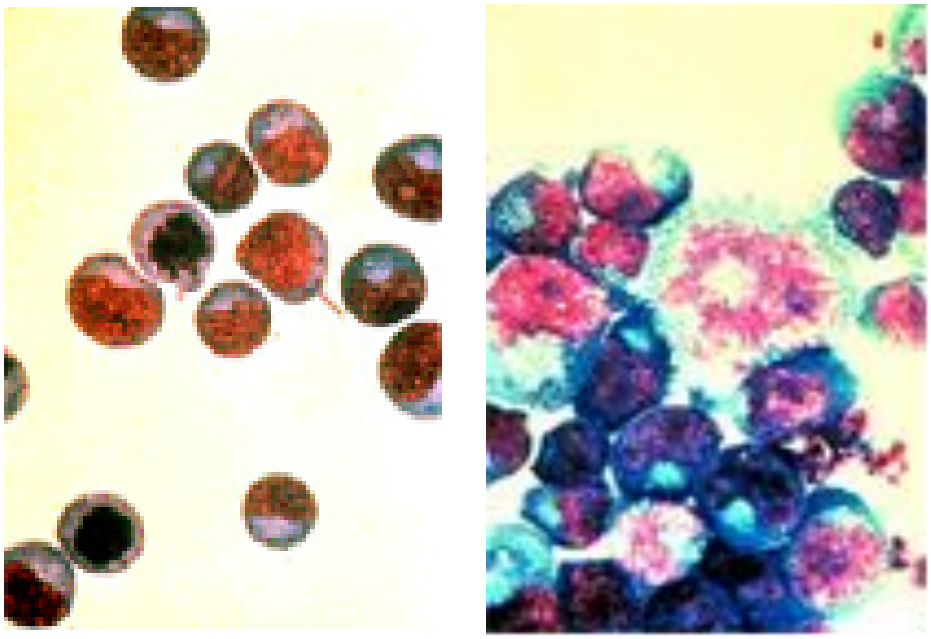
The pathogenesis of HIV centres on the struggle between HIV replication and the immune responses of the patient, via cell-mediated and immune-mediated reactions. The HIV viral burden directly and indirectly mediates CD4+ T-cell destruction. The HIV destructs CD4+ cells; CD4+ progenitor cells in bone marrow, the thymus, and peripheral lymphoid organs; as well as CD4+ cells within the nervous system, such as microglia. Destruction of these immunologic mediates lead to failure of T-cell production and eventual immune suppression (Lwasaki, 2012).

At the onset of an infection viruses develop different strategies to avoid the attack from the innate immune system. The human immunodeficiency virus (HIV) is able to overcome innate and adaptive immune responses in infected individuals and thereby reducing the immunity of the host.

Innate immune response is the primary line defence response against viruses. Viruses are detected by the innate immune system primarily by recognition of viral nucleic acids. Toll-like receptors (TLRs) expressed in the endosomes, which detect

nucleic acids of the genomes associated with the virions. Innate defense against HIV-1 is via complement system activation that together with interferons, cytokines and chemokines stimulate innate immune cells, such as dendritic cells (DCs), natural killer (NK) cells, natural killer T (NKT) cells, monocytes, or macrophages. These factors act in concert until the adaptive immunity is established. Innate immunity controls the infection process in the acute phase (Wilfried, Cornelia and Wilflingseder, 2011).

The HIV specifically targets cells of the immune system i.e. helper T cells, macrophages, and dendritic cells. The protein that HIV-1 binds to when it infects a cell is CD4, which is the co-receptor protein found in large numbers on the surface of helper T cells. This protein is also expressed on macrophages and dendritic cells (Lauren. 2012). An attack on these cells, by the AIDS virus disrupts their function, kills the cells, or makes them targets for killing by Cytotoxic T lymphocytes that recognize them as being virus-infected. Figure 2.5 below illustrates the difference between normal T cells and HIV infected T cells.



(A) **Normal T cells**. (B) **HIV infected T cells.**

Figure 2.5: Differentiation between normal and HIV infected T cells (National institute of allergy and infectious disease). www.niaid.com. Retrieved 09/06/15

Early in the course of viral infection, the principal defense mechanism is humoral immunity. Antibodies block viral binding to and entry into cells, and promote viral elimination by opsonization and phagocytosis, and by activating the complement system. Antibodies also block the spread of viruses that are released from infected cells and thus, antibodies prevent cell-to-cell spread of infection.

Once viruses become established inside cells they are inaccessible to antibodies. The principal mechanism of defense against established viral infections is the Cytotoxic T lymphocytes (CTL) response. The CTLs are mostly CD8+ kill infected cells and thus eliminate the reservoir of infection. Cytotoxic T lymphocytes may also be responsible for tissue injury and disease in HIV positive patients (Abbas et al, 2014)

T cells are lymphocytes that develop in the thymus and people who are not infected with HIV and in generally good health have an estimated 800 to 1,200 CD4+ T cells per cubic millimetre of blood. These cells then develop their T-cell antigen receptors and differentiate into the two major peripheral T-cell subsets, one of which expresses the CD4+ helper cells marker and the other CD8+ cytotoxic cells.

T helper cells play a central role in the initiation and regulation of the acquired immune response. T helper cells recognize antigen presented on the surface of antigen presenting cells in association with class II molecules encoded by the major histocompatibility complex (MHC). T-cell activation requires other specific costimulatory signals generated by the antigen presenting cell. Cytotoxic T cells recognize antigen presented on the surface of antigen presenting cells in association with class I molecules encoded by the MHC. Cytotoxic T cells are capable of destroying virus-infected target cells (Philip et al, 2002).

2.1.2.3 Pathogenesis of HIV

Host cells infected with HIV have a shortened life span as a result of the virus's using them as "factories" to produce multiple copies of new HIV. Thus, HIV continuously uses new host cells to replicate itself. As many as 10 million to 10 billion virions are produced daily. In the first 24 h after exposure, HIV attacks or is captured by dendritic cells in the mucous membranes and skin.

Within 5 days after exposure, these infected cells make their way to the lymph nodes and eventually to the peripheral blood, where viral replication becomes rapid. CD4+ lymphocytes that are recruited to respond to viral antigen migrate to the lymph nodes. These become activated and then proliferate via complex interaction of cytokines released in the microenvironment of the lymph nodes. This sequence of events makes the CD4+ cells more susceptible to HIV infection.

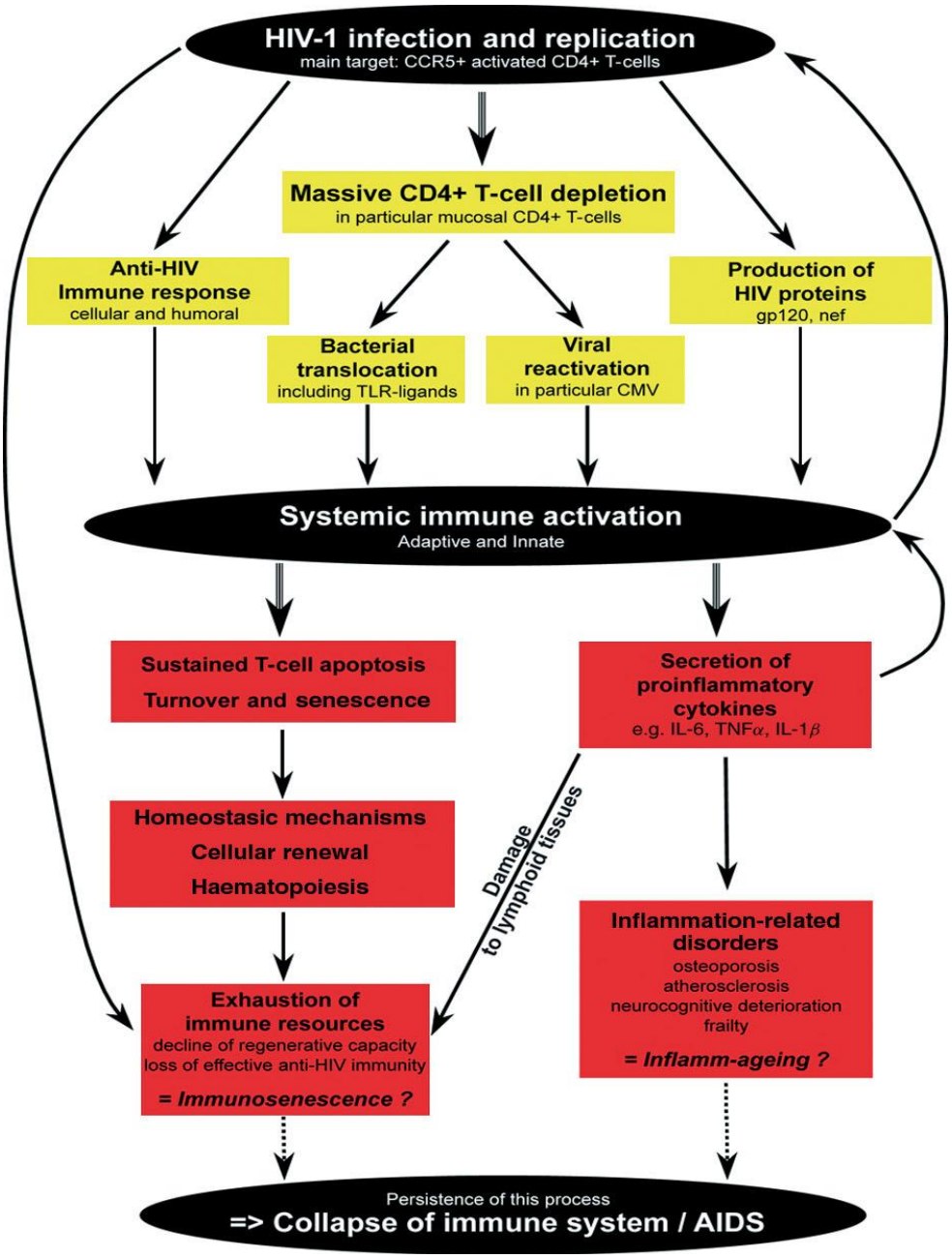


Figure 2.6: A model of HIV pathogenesis. Causes and consequences of immune activation are in yellow or red, respectively. Hypothetical consequences of immune activation that make a parallel with human ageing are in italic (Appay and Sauce, 2008)

The pathogenesis of HIV infection involves dynamic interactions between the virus and the host immune system which result in immune activation throughout the course of infection. The degree of activation of the immune system can be monitored by measuring the serum levels of a variety of molecules such as viral load and CD4 cells.

The most characteristic feature of HIV/AIDS is a selective depletion of the CD4+ T-helper-inducer subset of T cells which lead to impaired immune response against HIV and other antigens (Boasso, Shearer, and Chougnet, 2009), as depicted in figure 2, 7 in comparison with immune impairment caused by other chronic infections. The degree of CD4+ T-cell depletion is currently the single most important laboratory finding taken into consideration when recommendations are made regarding therapy with antiretroviral drugs, (Tsoukas and Bernard, 1994). The most useful assay in determining the level of immunodysfunction in HIV infection is the phenotypic analysis of the patient's lymphocytes, since this virus targets and destroys CD4+ T cells, (Nicholson and Jones, 1989).

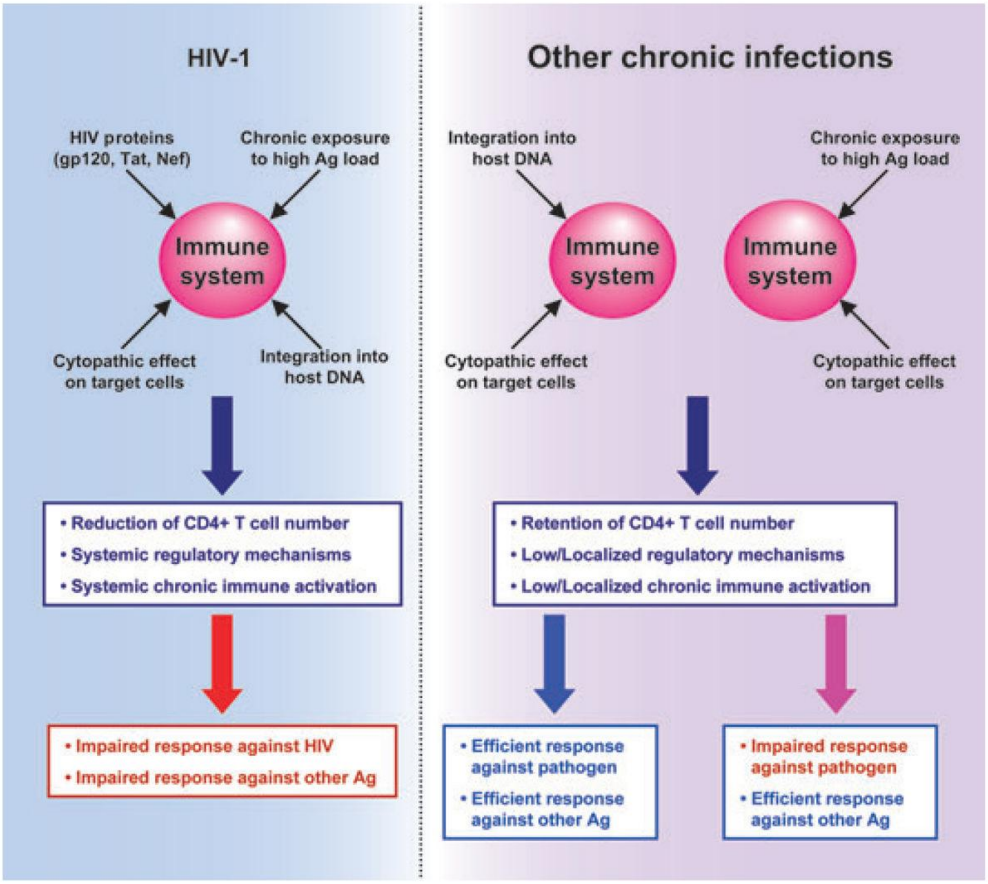


Figure 2.7: Impairment of immune function by human immunodeficiency virus (HIV) In contrast to other chronic infections (Boasso et al, 2009).

The HIV viral load measures how much HIV is in blood and it clinically determines HIV virulence. The HIV viral load ranges from undetectable and may increase up to millions of copies per ml, with fewer than 50 copies deemed as undetectable. Figure 2.8 illustrates the relationship between CD4 cells count vs. viral load in a time graph.

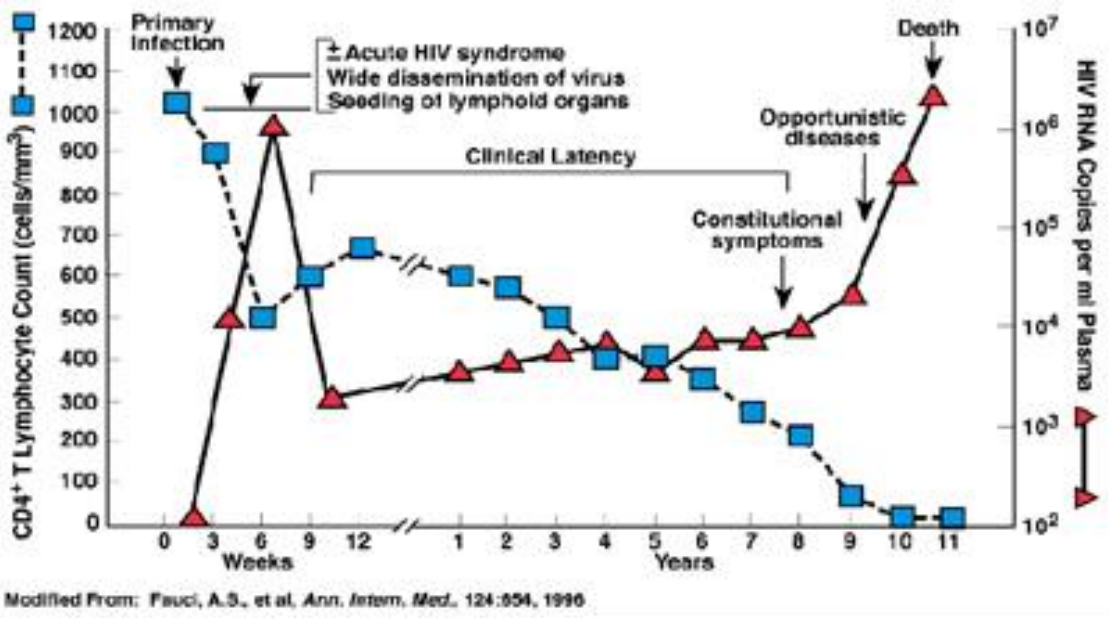


Figure 2.8: The relationship between the levels of HIV (viral load) and CD4+ T cell counts over the average course of untreated HIV infection (National institute of allergy and infectious disease). www.niaid.com. Retrieved 09/06/15

2.1.2.4 Inflammation in HIV

The HIV virus is known to suppress the immune functioning but it is reported that it can cause excessive immune activation and inflammation (Anne, Diane and Judith, 2010). This may seem to be a conflict of theories but the answer to this paradox lies in the complexity of the immune response. Various studies have been conducted to address this dilemma. Acute HIV infection causes a rapid and intense release of a variety of cytokines, interferona, interferon-g, inducible protein 10, tumor necrosis factor, IL-6, IL-10, and IL-15 (Stacey, Norris, Qin, Haygreen, Taylor, Heitman, Lebedeva, DeCamp, Li and Grove, 2009)

The HIV gene products have also been suggested to directly induce the activation of lymphocytes and macrophages, and the production of proinflammatory cytokines and chemokines as well as high levels of proinflammatory cytokines, such as tumor necrosis factor alpha (TNFα), interleukin 6 (IL-6) and interleukin 1 beta (IL-1β) in both plasma and lymph nodes, are also observed from the early stages of HIV-1 infection

(Lafeuillade, Poizot-Martin, Quilichini, Gastaut, Kaplanski and Farnarier, 1991). Antigenic stimulation during HIV-1 infection may be induced by other viruses, such as cytomegalovirus (CMV) and Epstein barr virus (EBV), and this is believed to indirectly cause immune activation and inflammation (Abbas et al, 2014).

The HIV virus has also been reported to establish itself in the gut associated lymphoid tissue in the gastrointestinal tract; in the body's largest source of HIV-susceptible CD4 T-cells, at the earliest stages of infection. It then infects these T-cells and damages the epithelial lining of the intestines which become more permeable and allows bacteria that naturally reside in the gut to escape through a process known as microbial translocation. These bacteria and the substances they produce enter the bloodstream causing a strong systemic inflammatory immune response (Jason, David, Timothy, Tedi, Guido, Srinivas, Zachary, Ethan, Olivier, Daniel, Bruce, Beningo, Leia, Alan, Jeffrey, Frederick, Loius, Micheal, Steven, and Daniel, 2006).

Systemic inflammation has been linked to a failure to normalise CD4 cells in treated HIV infection. Interleukin 6 (IL-6) is an inflammatory cytokine and also a biomarker of disease progression in treated HIV infection. Furthermore it is not conclusive that inflammatory mediators to CD4 cells cause immune restoration failure (Carey, Joseph, Nicholas, Scott, Benjamin, Doug, Davide, Andrea, Jeffrey, Ari, Jeffrey, John, Jacob, Timothy, Benigno and Michael, 2014).

2.1.2.5 Antiretroviral therapy

Highly active antiretroviral treatment (HAART) protocols are constructed using agents selected from two or three antiviral drug classes. These classes are based on their mechanisms of action in suppressing HIV replication. The three main classes include the nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs) Beth, Elaine, Weibin, Philip, William and Huiping, 2011).

Table 2.1: ARVs for Treatment of HIV Infection.

NRTIs	NNRTIs	PIs	FUSION NHIBITORS
zidovudine (ZDV, AZT)	nevirapine (NVP)	nelfinavir (NFV)	enfuvirtide (ENF)
lamivudine (3TC)	efavirenz (EFV, EFZ)	ritonavir (RTV)	
stavudine (d4T)	delavirdine (DLV)	saquinavir (SQV)	
didanosine (ddI)		indinavir (IDV)	
abacavir (ABC)		lopinavir/ritonavir (LPV/r)	
tenofovir (TDF)		atazanavir (ATV)	
emtricitabine (FTC)		amprenavir (APV)	
zalcitabine (ddC)		fos-amprenavir (fos-APV)	

Nucleoside reverse transcriptase inhibitors and non-nucleoside reverse transcriptase inhibitors suppress HIV replication by inhibiting the action of HIV reverse transcriptase, while PIs inhibit the HIV protease enzyme. The choice of the combination to be used depends on considerations of drug potency, tolerability, potential for adherence, and resistance (Beth et al, 2011). Antiretroviral drugs are established to achieve reduction in morbidity including morbidity from opportunistic infections and prolong life of HIV infected individuals, to improve quality of life of infected persons, achieve rapid and sustained suppression of viral load, enhance immunity by increasing CD4+ cell count and to reduce the risk of transmission of HIV to infants and sexual partners.

2.2 LITERATURE REVIEW

2.2.1 Introduction

Previously patients infected with HIV/AIDS were denied major cardiac surgery in certain hospitals due to poor understanding of the pathophysiology of the disease as well as fear of transmission to the surgical team. Perceived poor surgical outcomes with prolonged wound healing and increased risk of post-operative infections due to compromised immunological conditions discouraged surgical interventions (Raghuram, Kumar, Balamurugam, Arulmurugan, and Sivakami, 2006, Frater, Sisto and Condit, 1989). Patients infected with HIV/AIDS have been associated with immune system activation and alteration due to both defence mechanisms and the virus itself attacking immune cells. Activated immunological mechanisms lead to complete body inflammatory syndrome. The introduction of HAART has changed the natural history of HIV/AIDS from a morbid disease to a chronic disease with improved life expectancy and promising surgical outcomes even in patients with an AIDS state of disease.

Patients infected with HIV and diagnosed with valvular heart disease (VHD) have been associated with development of infective endocarditis (Valencia and Miro, 2004). Infective endocarditis is an inflammation and scarring of myocardial inner tissues such as cardiac valves. Immune system weakness is associated as the risk factor of developing infective endocarditis in HIV positive patients (Levy, Simon and Rios, 1989). Disorders of cardiac valves in both HIV seropositive and negative patients are commonly due to infective endocarditis or rheumatic fever which is an inflammatory disease that mostly affect connective tissues including the heart giving rise to rheumatic valvular heart disease.

Surgical intervention is regarded as the most beneficial treatment of diseased cardiac valves. This treatment involves open heart surgery to replace or repair the diseased heart valve (s), hence require the employment of CPB. Patients infected with HIV undergoing surgical corrective procedures for valvular insufficiency may be expected to induce higher postoperative inflammatory response and myocardial damage/injury compared to HIV seronegetive patients. This may be due to pre-operative immune paresis, HIV induced inflammation; rheumatic valvular disease induced myocardial scarring and inflammation in HIV patients and CPB immune activation, immune cells alterations, systemic inflammatory response and multifactorial cardiac surgery related myocardial injury.

Very limited literature is published regarding this area of research, this study seek to review and investigate immune alterations and activation among HIV positive and compare these parameters to a group of HIV negative also undergoing cardiac valvular surgery on CPB focusing mainly on the systemic inflammatory response and myocardial injury.

2.2.2 C- reactive protein and systemic inflammatory response

Systemic inflammatory response syndrome (SIRS) remains the outmost impactful adverse effect of cardiopulmonary bypass, and it is characterized clinically by the body producing at least two of the following characteristics: respiratory rate >20 breaths per minute or PaCO2 < 32 mmHg, leukocytes >12,000, temperatures >38°C or <36°C and heart rates >90 beats per minute, (Laffey et al, 2002). These clinical manifestations are observed postoperatively and studies have concluded that they cannot be used independently to diagnose inflammatory response, as confirmatory laboratory tests may be required (Kirklin and McGraffin, 1987). In many cases patients who undergo cardiac surgery supported by cardiopulmonary bypass experience few to no clinical identifiable adverse sequel and convalesce normally (Kirklin and McGraffin, 1987). This may not be necessarily due to cardiopulmonary perfection or specific drugs aimed at abolishing the inflammatory response but probably due the individual's innate ability to compensate for the damaging effects (Philip et al, 2004).

Systemic inflammatory response during extracorporeal circulation involves complex interaction of systems and cellular elements in the body. The biochemical events and pathways are a complex interaction with regulatory and counter-regulatory effects. Activation of all defence systems triggering the inflammatory cascade finally results in activation of several types of cells.

The complement proteins react sequentially and mediate a number of the immune responses. Activated systems may give rise to the activation of platelets, leukocytes and erythrocytes destruction which may lead to the release of destructive enzymes, oxygen free radicals, endotoxins and anaphylactic reactions. These biological reactions of systemic inflammatory response may ultimately affect the heart, lungs, brain, kidneys and other organs of the body (Philip et al, 2004) which may eventually lead to mortality as illustrated in figure 2.9 below. Systemic inflammation causes the

rise in transaminases, urea, creatinine, and amylase, which each indicate failure of certain body organs following surgery (Cremer, Martin, Redl, Bahrami, Abraham, Graeter, Haverich, Schlag, and Borst, 1996). The neutrophils are considered to be the most important cells causing the inflammatory response to heart surgery, (Bechtel, Mühlenbein, Sievers and Misfeld, 2007).

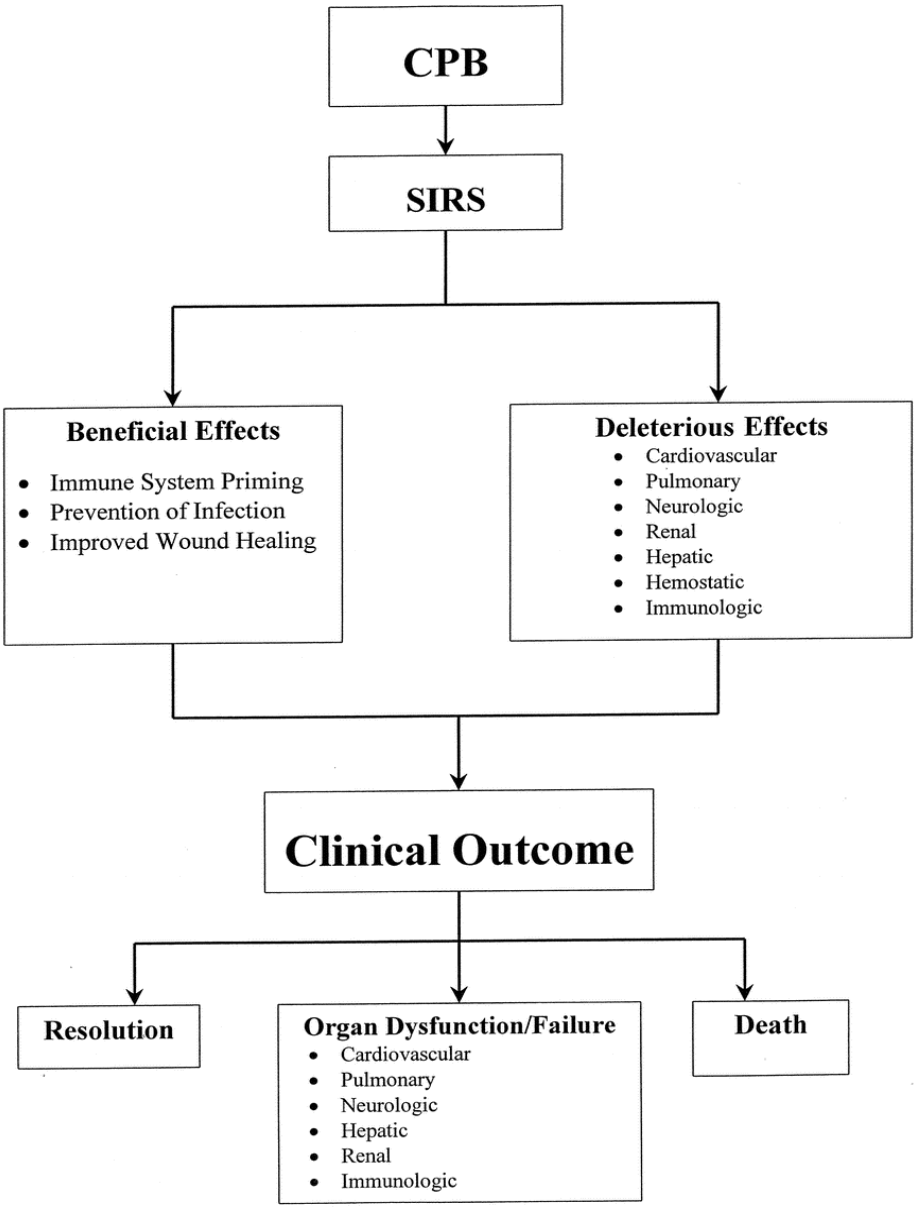


Figure 2.9: Schematic diagram of the balance between beneficial and adverse effects and the resultant clinical sequelae of the inflammatory response following cardiac surgery, (Laffey, et al. 2002).

Postoperative acute respiratory distress syndrome, total body oedema, pulmonary hypertension, coagulation abnormalities, haemodynamic instability and myocardial dysfunction are characterized post bypass effects occurring as a result of

inflammatory reactions (Shinji, 2003). These abnormalities may lead to morbidity and or mortality requiring prolonged positive inotropic support postoperatively, prolonged postoperative ventilation period, renal dysfunction, postoperative bleeding, acute increase in body temperature and subsequently neurological injury (Seghaye, Duchateau, Grabitz, Nitsch, Marcus, Messmer and von Bernuth, 1994).

Mara, Elena, Guglielmo, Alfredo, Elisabetta, Maria, Salvatore and Alessandro (2008) screened 737 consecutive patients after cardiac surgery to evaluate CRP levels in cardiac surgery patients without clinical or laboratory signs of infection. Patients with fever (> 37.28C), elevated white blood cell count (> 11 000/ml), neutrophilia (> 70%), or any inflammatory, infective or malignant disease were excluded. CRP levels were measured on admission and at discharge and the values were related to the following variables: age, sex, diabetes mellitus, renal failure, type of surgery, postoperative atrial fibrillation, pericardial or pleural effusion, and length of hospital stay. Follow-up (mean: 23± 8.5 months) was available for 175 patients (94%). They found that in the 187 patients enrolled in the study, the CRP values were significantly elevated (median: 4.23 mg/dl, interquartiles range: 2.68–6.64) independent of any variable analysed. At discharge, CRP levels were significantly reduced compared with values on admission (median: 1.55 mg/dl, interquartiles range: 0.84–2.37, $P < 0.001$). They concluded that early after cardiac surgery, in patients without clinical or laboratory signs of acute infection, CRP levels are significantly elevated and do not correlate with clinical variables. Furthermore they stated that findings suggest a systemic inflammatory response to surgery-related stress (Mara et al, 2008).

The recommended diagnosis of SIRS is a combination of both clinical evaluation and laboratory blood tests for parameters such as CRP. A study was conducted to investigate how use of CRP as a marker to confirm the presence of early sepsis might reduce the false positive rate inherent in the defining SIRS criteria; conclusion was made that CRP indeed has validity for confirming the presence of SIRS with progression to sepsis even when clinical features are incomplete or equivocal, (Pancer, Engelman, Hoque, Alam, Rucinski and Bernstein, 2011).

C-reactive protein (CRP) is a protein found in the blood which rises in response to inflammation in the innate state, i.e. CRP is an acute-phase-protein. It is produced by hepatocytes, predominantly under transcriptional control by the cytokine Interleukin-6 (IL-6) in response to factors released by macrophages as depicted in figure 2.10 below.

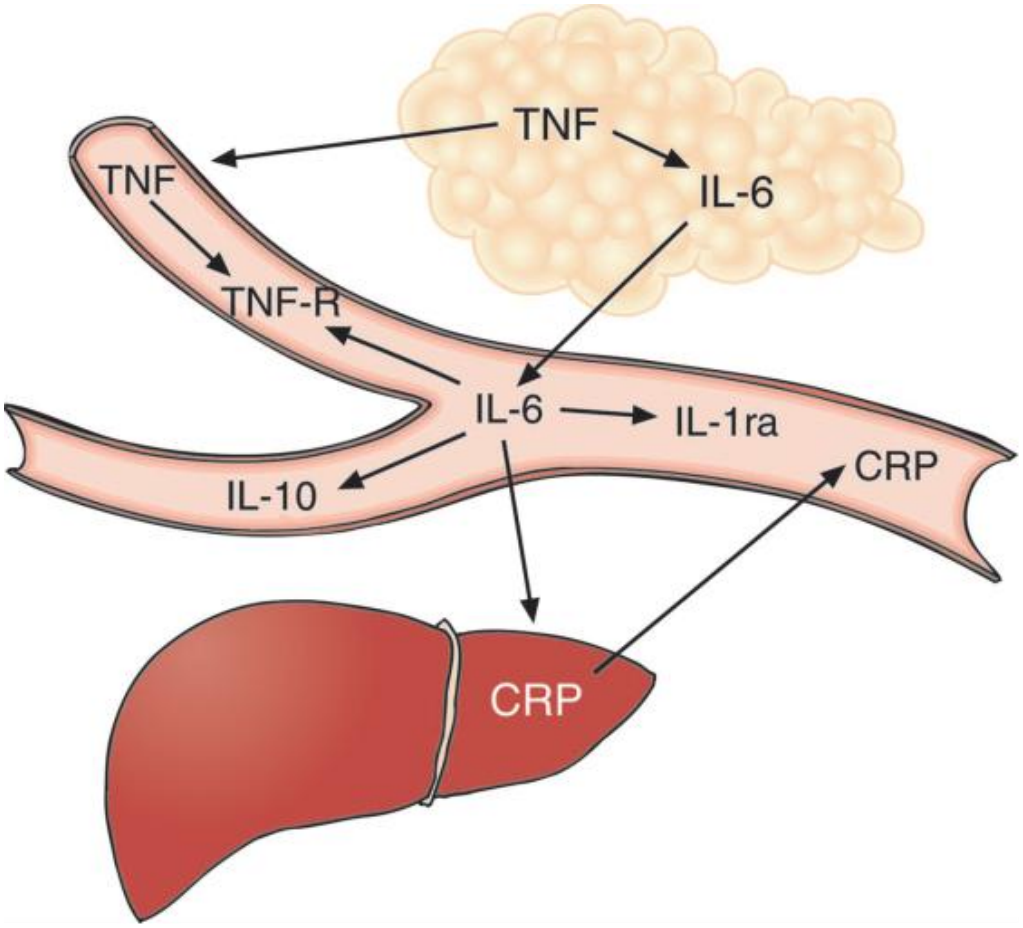


Figure 2.10: Chronic low-grade systemic inflammation. Stimulates the production of IL-6 in adipose tissue and blood mononuclear cells, IL-6 enhances the systemic levels of C-reactive protein, (Anne and Bente, 2005).

It normally measures at concentrations of less than 10 mg/L in the blood and reach peak level after surgery between 24 and 48hours as illustrated in figure 2.11. The normal range of CRP varies amongst different laboratory units, According to the American Heart Association the most widely used range is: <0,8mg/L is regarded as normal, <1,00mg/L as low, between 1,00mg/L – 3,00mg/L as average and >3,00mg/L as high. C-reactive protein is a sensitive but nonspecific, marker of inflammatory response that has clinical use in patients suspected of disturbances of immune system and it has been recommended as an important marker of inflammatory response to myocardial injury (Iimar, Paulo, Orlando and Alcides, 2003).

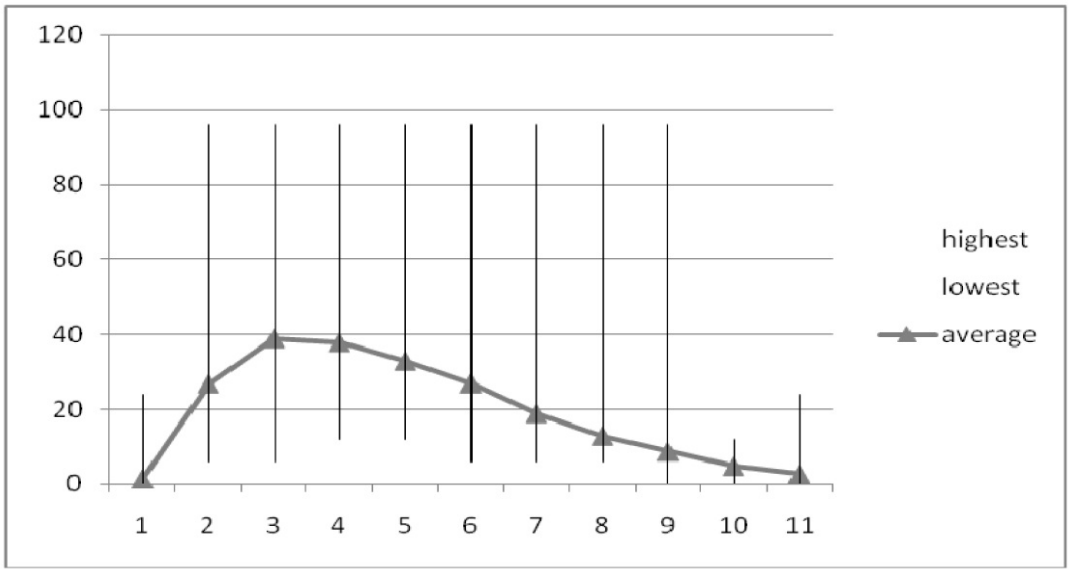


Figure 2.11: The CRP level between day 1 and day 11, reaching peak level on day 3. http://www.scopemed.org/journal.php?jid=20. Retrieved 10/10/15.

Plasma concentrations are increased in infective, inflammatory, and ischaemic disease (Gabay and Kushner 1999). Aouifi, Piriou, Blanc, Bouvier, Bastien, Chiari, Rousson, Evens and Lehot (1999) conducted a study to investigate the effects of CPB on serum procalcitonin and CRP concentrations. Serum procalcitonin and CRP concentrations were measured before operation, at the end of surgery and daily until postoperative day eight. They found that procalcitonin and CRP serum levels increased postoperatively regardless of the type of surgery.

There is a positive correlation between CRP levels and inflammation in patients with chronic rheumatic valvular disease. A study was conducted by Zehra, O¨ zgu¨l, Telat, Ahmet, Kerim, Ahmet, Erdem and Sinan (2002) to determine the role of inflammation detected by high sensitivity CRP (hs-CRP) levels in the progression of chronic rheumatic valve disease. A total of 113 patients with chronic rheumatic valve disease (81 women, 32 men; mean age 40"14 years, range 13–70), 51 patients with prosthetic valve(s) (31 women, 20 men; mean age 48"13 years, range 21–71) and 102 healthy subjects (68 women, 34 men, mean age 41"12 years, range 25–73), as a control group, were assessed. Hs-CRP was determined using latex-enhanced immunonephelometric assays on a BN II analyzer (Behring). Levels of hs-CRP were significantly higher in patients with chronic rheumatic heart disease than in patients with prosthetic valve(s) and healthy subjects (0.62"0.64 vs. 0.35"0.41 vs. 0.24"0.18 mgyl, P-0.01 and P-0.001 respectively as illustrated in Fig 2.12 below.

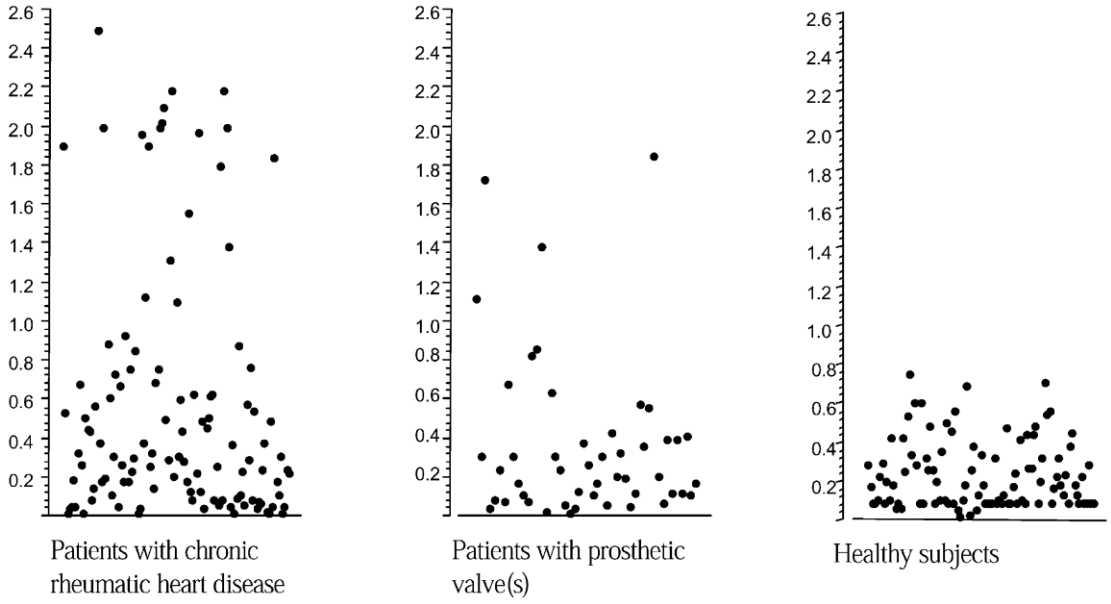


Figure 2.12: Individual values of levels of C-reactive protein (mg/dl) in patients and in healthy subjects, (Zehra, et al, 2002).

They concluded that hs-CRP is increased in chronic rheumatic heart disease, and that this may indicate that inflammatory response still persists in the chronic phase (Zehra et al, 2002). They further found no correlation between CRP and age, sex or functional capacity.

Shinji (2003) conducted a study to elucidate the duration of SIRS and the mechanisms that lead to the protraction of SIRS in patients who are operated on under CPB. The duration of SIRS in 13 patients with SIRS was studied. Two groups were divided according to the duration to investigate the meaning of the duration of SIRS. The perioperative parameters which significantly correlated with the duration of SIRS, including the kinetics of cytokines and white blood cells (WBC) counts were investigated. In patients with SIRS extending for a period greater than 12 hours (group A), the duration of CPB, interleukin-6 (IL-6), interleukin-8 (IL-8) and WBC count after aortic declamping were significantly longer and higher than those in patients with SIRS lasting less than 12 hours (group B). The duration of SIRS significantly correlated with the highest level of IL-6 ($r=0.724$, $p=0.0038$) and the duration of CPB ($r=0.626$, $p=0.0201$). The conclusion was that the duration of CPB and cytokinemia, with high IL-6 levels, during this short time frame until just after cardiac surgery might play an important role in the development of the SIRS (Shinji, 2003).

2.2.3 C-reactive protein and HIV

In some studies HIV appears to independently increase the risk of cardiovascular disease via elevated cytokine levels, chronic vascular inflammation, and endothelial dysfunction, (Ross, Rizk and O'Riordan, 2009).

The CRP levels increase with infection and there exists a negative correlation between CRP and CD4 count in patients infected with HIV (Melchior, Niyongabo, Henzel, Durack-Bown, Henri and Boulier, 1999). Studies have associated low values of CRP to predict longer survival within HIV-infected individuals (Grützmeier and Sandström, 1999); this is evident in patients taking ARVs with a decrease in CRP levels as an indicator of good treatment response.

Mahdad and Robert (2005) conducted a study to investigate clinical value of CRP measurements in HIV-positive patients. C reactive protein was measured in 109 HIV-1 antibody-positive patients admitted to hospital for investigation. In 67 patients with intercurrent infection CRP levels were 2.2–483.5mg/ and in 42 patients with alternative non-infection diagnoses CRP levels were 0.5–108.6 (median¼5.9) mg/dL. Whereas in those with infections, elevated CRP levels fell in response to specific therapy, values remained abnormal in those with non-infection diagnoses. They concluded that CRP appears useful for diagnosis and monitoring of intercurrent infection in HIV-1 antibody-positive patients. They also found that in HIV-1 antibody-positive patients without intercurrent infection, CRP values higher than in the general population possibly reflect a sustained acute-phase response as a consequence of HIV infection, (Mahdad and Robert, 2005).

Bryan, Richey, Larry, Wendy, Frank, Barbara, Stephen and Gange (2006) conducted a study by obtaining a single measurement of CRP from 513 HIV-infected men in the multicenter AIDS cohort study to examine the association between CRP and immune suppression and progression to AIDS. The cross-sectional associations between log10 CRP was correlated inversely with CD4 lymphocyte counts (r=−0.17; P=.001) and directly with log10 HIV RNA levels (r=0.20; P .001). Levels of CRP of more than 2.3 mg/L were associated with a decreased time to the development of AIDS (relative time to AIDS, 0.36; P .001) compared with individuals with CRP levels of 1.2 mg/L or less, which remained significant after adjustment for CD4 lymphocyte counts and HIV RNA and hemoglobin concentrations. Levels of CRP significantly increased over time with mean slopes of 8.5% (95% confidence interval, 4.9%-12.2%) and 4.5%

(95% confidence interval CI, 2.1%-6.9%) per year for individuals with and without progression to AIDS, respectively. Individuals had a geometric mean CRP level of 2.5 mg/L in the 6-month interval before progression to AIDS, which was an increase from a nadir of 1.0 mg/L at 6.5 years before progression to AIDS. They concluded that levels of CRP were associated with HIV disease progression independent of CD4 lymphocyte counts and HIV RNA levels. They further found that regardless of progression to AIDS, HIV-infected individuals had a significant increase in CRP over time. This may have implications for cardiovascular disease among HIV-infected individuals (Bryan et al, 2006).

Redd, Eaton, Kong, Laeyendecker, Lutalo, Wawer, Gray, Serwadda and Quinn, (2010) tested longitudinal serum samples of HIV-1 seroconverters in three HIV-1 disease progression groups: long-term nonprogressors, standard progressors, and rapid progressors for levels of C-reactive protein (CRP), as a marker for immune activation. CRP levels significantly increased in the standard progressors group (P, 0.0001) but not in the rapid progressors group or the long-term nonprogressors group. They concluded that increased immune activation i.e CRP is significantly associated with HIV-1 disease progression but not microbial translocation.

Postoperative CPB related inflammatory responses are associated with morbidity in almost all cardiac surgery patients, in the cases of HIV positive patients this postoperative risk factor may be expected to increase higher than in non HIV patients due to pre-existing inflammation.

2.2.4 HIV progression and CPB

Standard methods used to monitor HIV disease progression and therapy response are clinical assessment, CD4+ T lymphocyte count measurement, and plasma viral load (PVL) quantification. Sanjim, Preena, Arun, Hitender, Sanjeev, Anuradha and Richa (2013) conducted a study to evaluate use of CD4+ cell count to quantify HIV disease progression. Newly diagnosed HIV seropositive subjects (n = 130) were categorized into three study groups: CD4 counts <200 cells/µl (group A, 43 subjects); 200-500 cells/µl (group B, 44 subjects); and >500 cells/µl (group C, 43 subjects). At recruitment, PVL estimation was performed for group A subjects only, who were then initiated on highly active antiretroviral therapy (HAART) and were followed up after six months for evaluation of response to HAART by measuring the CD4 counts and PVL. Groups B and C were followed up after six months to monitor disease

progression by measuring only CD4 counts. They found that among group A subjects, a rise in the median CD4 counts after six months of HAART was observed. At baseline, PVL ranged from 2636 to >750,000 copies/ml with a median PVL at baseline of 165,000 copies/ml. At follow-up, 90% of the study subjects had undetectable levels of viraemia. Among group B and C subjects, a fall in the CD4 counts at follow-up was observed. Among group A subjects, a rise in the median CD4 counts after six months of HAART was observed. At baseline, PVL ranged from 2636 to >750,000 copies/ml with a median PVL at baseline of 165,000 copies/ml. At follow-up, 90% of the study subjects had undetectable levels of viraemia. Among group B and C subjects, a fall in the CD4 counts at follow-up was observed. They concluded that CD4 count is a powerful tool to determine response to antiretroviral therapy (ART) and monitor disease progression in HIV/AIDS. PVL is important to assess response to ART, especially in immunovirologic discordant responses (Sanjim et al, 2013).

In the past cardiac surgery in general, and particularly when supported by CPB has been associated with the progression of HIV infection (Yee, 1991). Aris, Pomar and Saura 1993, conducted a study to prove the hypothesis that cardiopulmonary bypass may accelerate the development of acquired immunodeficiency syndrome (AIDS) in the human immunodeficiency virus carrier. 40 patients positive for human immunodeficiency virus that underwent cardiac operations between 1986 and 1992 were analysed, especially in regard to the progression to AIDS. Thirty-four patients (85% were intravenous drug abusers; in 4 (10%) transmission of infection was sexual, and in 2 (5%) it was through a contaminated blood transfusion. Heart valve operations were performed in 38 patients (95%), mostly for endocarditis in drug addicts. Findings showed that hospital mortality was 20% (8 patients). The 32 survivors were followed up to a mean of 21 months (range, 4 months to 6 years). Four patients (12.5%) experienced progression to AIDS during the follow-up period. Actuarial progression to AIDS was 5% (25%) at 1 year, 20% (210%) at 2 years, and 40% (*19%) at 5 years. There were 8 late deaths (5 due to recurrent endocarditis, 2 due to AIDS, and 1 due to overdose). Actuarial survival was 79% (+8%) at 1 year, 60% (211%) at 2 years, and 48% (214%) at 5 years. They concluded that their findings indicate that progression to AIDS in the patient positive for human immunodeficiency virus is not accelerated by the use of cardiopulmonary bypass (Aris et al, 1993).

Recent data since the introduction of highly active anti-retroviral treatment (HAART) does not support the ideas that implicate progression of HIV during or after CPB as past studies have found (Imanaka, Takamoto, Kimura, Morisawa, Ohtsuka and Suematsu, 1999). One study found that HIV infected patients are at greater risks of postoperative morbidity compared to HIV negative patients and this is evident by prolonged hospital length stay (Jiménez-Expósito, Mestres, Claramonte, Cartañá, Josa, Pomar, Mulet and Miró, 2006). King, Perkal and Rosenthal (2015) found that patients undergoing surgery with preoperative CD4+ count greater than 200 cells/mm3 have an almost two-fold increased risk of death, while patients with preoperative CD4+ count from 50 to 199cells/mm3 have an almost three-fold increased risk of death and patients with CD4+ count less than 50cells/mm3 – a six-fold increased risk of death. They further noted correlation between CD4+ cells in HIV patients and HIV negative patient age, stating that an HIV-positive person with a CD4+ count greater than 200cells/mm3 had the same post-surgical risk of death as an HIV-negative person who was 16 years older. An HIV-positive person with a CD4+ count from 50 to 199cells/mm3 had the same post-surgical risk of death of an HIV-negative person who was 25 years older. An HIV-positive person with a CD4+ count less than 50 cells/mm3 had the same post-surgical risk of death as an HIV-negative person who was 47 years older (King et al, 2015).

Gregory, Alexander, Benator, and Gharagozloo (2003) conducted a retrospective review of 37 consecutive patients at two integrated centers from 1994 to 2000. Standard database and follow-up information included opportunistic infections, CD4 count, viral load, New York Heart Association status, and angina status. Risk to operating room personnel was also reviewed. Median age was 41 years; 34 of 37 patients were male. Operations performed were coronary artery bypass graft ([CABG] 27), aortic valve replacement ([AVR] 4), AVR/CABG (2), AVR/mitral valve repair (1), mitral valve repair (1), excision of atrial masses (1), and tricuspid valve repair (1). Complications included death in 1 of 37 (2.7%), sepsis in 2 of 37 (5.4%), deep sternal infection in 1 of 37 (2.7%), bleeding in 2 of 37 (5.4%), prolonged ventilation in 2 of 37 (5.4%), and readmission in 8 of 37 (21.6%). Actuarial freedom from a composite end point of angina, death, myocardial infarction, repeat revascularization, and congestive heart failure was 81% at 3 years with no late deaths. Preoperative and follow-up CD4 counts and viral loads were not significantly different at a mean follow-up of 28 months. No patients progressed from HIV positive status to AIDS during the study period. Six “needle stick” injuries requiring antiretroviral prophylaxis occurred in 5 caregivers without seroconversion. Their

conclusion was that in selected patients infected with HIV, risks and outcomes of cardiac surgery are acceptable, with concomitant highly active antiretroviral therapy, intermediate HIV and cardiac status appears to be favourable and that needle stick injuries occur at a rate mandating optimal reduction of patient viral loads preoperatively (Gregory et al, 2003).

Blyth et al (2006) reviewed records of 49 patients, 17 males and 32 females, aged between 17 and 67 years undergoing surgery with CPB over a nine-year period to determine the outcomes, risk-to-benefit ratio and, if possible, the effect of surgery with CPB on the progression of their HIV disease. Forty-eight underwent cardiac surgery and one aortic dissection repair. They found that four HIV-infected patients underwent surgery with good early outcome. Thereafter an absolute CD4 cell count greater than 400microliter and the absence of the stigmata of AIDS in patients fulfilling the normal criteria for surgery allowed cardiac surgery using CPB. Fifty operations were performed. Three patients with CD4 counts of 37, 868 and 1245microliter died early, giving a 30-day mortality of 6% for 50 procedures. Six patients with active infective endocarditis underwent emergency surgery. Three of these, one with a pre- and two with only post-operative counts all below 250 microliter, died within three months. Sixteen complications occurred in the remaining 46 patients (34.7%). Pre-operative CD4 cell counts taken in 42 patients averaged 685microliter. Pre- and post-operative counts known in eight showed variations, as did repeated counts in those awaiting surgery. Forty-one patients left hospital in the New York Heart Association (NYHA) class I, five in class II and one in class III. Prior to surgery, the majority (38) were in class III and seven were in class IV. Follow up ranging from two to 70 months averaged 23.1 months. Eight late deaths occurred, three related to AIDS. They then concluded that according to their findings surgery seems to be worthwhile in selected HIV infected patients. Furthermore they found that early outcome paralleled that in the uninfected, giving a low risk-to-benefit ratio. Emergency surgery in patients with active infective endocarditis and significant immunocompromise met with high mortality. In their results they could not show that CPB accelerated progression to AIDS even though progression to or toward AIDS was seen in five patients, in three according to cell counts and in two on clinical grounds, (Blyth et al, 2006).

Asako et al, (2008) reported cardiac surgery in three patients infected with the human immunodeficiency virus when they compared preoperative and postoperative CD4+ cells: **Case 1:** A 64-year-old man who had history of catheter ablation due to Wolff-

Parkinson-White syndrome in 1993 complained of palpitation in May 2005. Left ventriculography demonstrated mitral regurgitation (MR) and mitral stenosis, which were operative indications, and left atrial thrombus. His C-reactive protein (CRP) was 1.7 mg/dl. Although his blood cultures were negative, infectious endocarditis was suspected. During his preoperative cardiac examination he was diagnosed with HIV infection. His preoperative CD4+ T-lymphocyte count was 329 /mm3. He was not receiving HAART. In September 2005, mitral valve replacement (MVR) was performed using conventional CPB. An aortic cannula was inserted; venous cannulation was performed with bicaval cannulation; CPB was established; and pulmonary vein venting was placed. The perfusate temperature was 32°C. The aorta was cross-clamped, the cold cardioplegia solution was infused into the aortic root, and cardiac arrest and myocardial protection were undertaken. MVR was performed using an Edwards- MIRA 27-mm prosthetic mechanical valve. The aortic cross-clamp time was 79 min, and the bypass time was 110 min. Cefotiam hydrochloride (1 g) was given during the operation, which was continued at 2g/day for 7 postoperative days (PODs). The postoperative course was uneventful. The histological findings in the resected mitral valve proved to be infectious endocarditis. The CD4+ T-lymphocyte count on POD 13 was 377/mm3. The patient was discharged on POD 17. **Case 2:** A 64-year-old man was diagnosed with HIV infection in April 2002 and received HAART from August 2002. He was followed for aortic stenosis from 2004, and from May 2005 he felt short of breath. In January 2006, an echocardiogram demonstrated calcification of the aortic valve. His maximum pressure gradient between the aorta and left ventricle was 119 mmHg, and aortic valve area was 0.36 cm2. His preoperative CD4+ T-lymphocyte count was 396/mm3. In March 2006, aortic valve replacement was performed using a St. Jude 19-mm prosthetic mechanical valve. CPB was established similarly to that in case 1. The aortic cross-clamp time was 128 min, and the bypass time was 86 min. The patient's postoperative period was uneventful. The postoperative antibiotic was also same as in case 1, and HAART was restarted from POD 1. His CD4+ T lymphocyte count on the POD 19 was 294/mm3, and he was discharged on POD 22. **Case 3**: A 46-year-old man, who was diagnosed with aortic regurgitation (AR) and MR due to infectious endocarditis, was transferred to our hospital in March 2007. Echocardiography demonstrated vegetations attached to the aortic and mitral valves, severe deformation of the aortic valve, severe AR, and moderate MR. The patient was diagnosed with HIV infection and syphilis during his preoperative examination. Computed tomography demonstrated an ascending aortic aneurysm, which was suspected to be a syphilitic aneurysm. His preoperative CD4+ T-lymphocyte count

was 158/mm3, and the HIV RNA viral load was 3000 copies/ml. The patient was not receiving HAART. In April 2007, MVR, AVR, and replacement of the ascending aorta were performed. Right femoral arterial and right brachiocephalic arterial cannulas were inserted; venous cannulation was undertaken with bicaval cannulation; CPB was established, and pulmonary vein venting was placed. While the perfusate temperature was cooling, MVR was performed using an Edwards- MIRA 25-mm prosthetic mechanical valve; then AVR was performed using a St. Jude 19-mm prosthetic mechanical valve. The perfusate temperature was maintained at 22°C, selective cerebral perfusion was started and open distal anastomosis performed. The aortic cross-clamp time was 136 min, bypass time was 193 min, and open distal time was 18 min. The postoperative antibiotic was the same as in cases 1 and 2. His CD4+ T-lymphocyte count on POD 14 was 105/mm3. The patient's postoperative course was for the most part uneventful, and he was discharged on POD 37. His CD4+ T-lymphocyte count was 125/mm3, and the viral load was 130copies/ml at that time. The results show that two out of three had reduced postoperative CD4+ T-lymphocyte counts compared with their preoperative count. Preoperative CD4+ T-lymphocyte count decreased from 396/mm3 and 158/mm3 to 294/mm3 and 105/mm3 postoperative respectively. Although there were changes in cell mediated cells all patients had no postoperative complications. They concluded that HIV infected patients can undergo open heart surgery using CPB if their viral loads are not high even if their CD4+ T lymphocytec counts are low (Asako, Masahiro and Masatoshi, 2008).

Michael, Nicholas, Douglas, Johnston, Stephanie, Wayne, Colleen and Edward (2014) conducted a study to investigate outcomes of patients with human immunodeficiency virus infection undergoing cardiovascular surgery in the United States. They recruited 5,621,817 patients who underwent coronary artery bypass graft (CABG), valve, aortic, or other cardiovascular surgery between 1998 and 2009 from the Nationwide Inpatient Sample. Of these, 9771 (0.17%) patients were seropositive for HIV. Using multivariable logistic regression modeling and 1:1 propensity-score matching, they determined the influence of HIV infection on outcomes. They found that the percentage of HIV+ patients undergoing cardiovascular surgery increased significantly from 0.09% to 0.23% between 1998 and 2009. HIV+ patients were more often male, black, younger than 55 years of age, and on Medicaid, and they were more likely to undergo valve and other cardiovascular surgeries, but less likely to have CABG. Among propensity-matched pairs, patients with HIV were at no increased risk for in-patient mortality. HIV+

patients were more likely to receive a blood transfusion and have any postoperative complication. Patients with HIV were less likely to have a postoperative stroke. Rates of pneumonia, renal complications, and wound infection were similar between the groups. The median length of stay and mean total cost were not different between the groups. Factors that predicted in-hospital death in HIV+ patients included metastatic cancer, coagulopathy, renal failure, and aortic, other, or combined surgical procedure. Risk-adjusted outcomes for patients with and without HIV among propensity-matched pairs are tabulated below

Variable	HIV (n ¼ 1633)	No HIV (n ¼ 1633)	P
Median length of stay, [15th, 85th percentiles]	8 [5, 20]	7 [4, 18]	.060
Total charges, median US$	77,661	77,290	.006
Total cost, median US$	32,413	31,125	.700
Hospital mortality, n (%)			
Overall	100 (6.1)	102 (6.2)	.915
Pericardial surgeries	(17.0)	(16.3)	.905
Nonpericardial surgeries	(3.4)	(4.8)	.068
Complications, n (%)			
Any complication	597 (36.6)	541 (33.1)	.038
Stroke	20 (1.2)	45 (2.8)	.001
Blood transfusion	382 (23.4)	334 (20.5)	.047
Renal complication	145 (8.9)	151 (9.2)	.791
Wound infection	24 (1.5)	31 (1.9)	.313
Pneumonia	156 (9.6)	129 (7.9)	.086
Discharge disposition, n (%)			.801
Home health care	381 (23.3)	368 (22.5)	
Inpatient facility	20 (1.2)	23 (1.4)	
Other transfer	283 (17.3)	267 (16.4)	
Routine/home transfer	946 (57.9)	973 (59.6)	

They concluded that cardiovascular surgery can be performed safely on patients with HIV with no increased hospital mortality and only minimal increased need for blood transfusion (Michael et al, 2014).

Karpelowsky, Leva, Kelley, Numanoglu, Rode and Millar (2011) conducted a study to investigate factors associated with the development of complications in HIV-infected children undergoing surgery. HIV-infected children younger than 60 months undergoing surgery at a tertiary referral paediatric hospital from July 2004 to July 2008 were recruited. Children were followed postoperatively for the development of complications, length of stay, and mortality. Eighty-two HIV-infected children, with a

median age of 11.5 months (interquartile range, 6-24 months), were enrolled. Most (68; 82.9%) had World Health Organization (WHO) stage 3 or 4 HIV disease, 72 (88%) had centers for Disease Control and Prevention stage 2 or 3 disease, and 60 (73%) were taking highly active antiretroviral therapy. Half (41; 50%) were underweight, 37 (45.1%) underwent emergency surgery, 28 (34.2%) required major surgery, and 40 (48.7%) had surgical site contamination at the time of surgery. The median length of hospital stay was 4 days (interquartile range, 2-14 days), and in-hospital mortality was 6 (7%). Thirty-four (42%) children developed 37 complications. On univariate analysis, malnutrition, HIV stage, or type of surgery was not associated with development of complications. In contrast, young age (6 vs. 13.5 months; P = .0004), low hemoglobin (9.6 vs. 10.5 g/dL; P = .04), or having a major procedure (14 [42%] vs. 9 [18%]; P = .03; relative risk, 2.2 [1.2-4.8]) was associated with complications. On logistic regression, younger age (odds ratio = 4.3; P = .004; 95% confidence interval, 1.6-11.9) and major surgery (odds ratio = 6.8; P = .001; 95% confidence interval, 1.5-31.4) were associated with development of a complication. Conclusion was that young age and major surgery were the main predicators of complications in HIV-infected children undergoing surgery (Karpelowsky et al, 2011).

2.2.5 Cardiac troponin I and cardiac surgery

Cardiac troponins (cTn) are cardiac regulatory proteins that control the calcium-mediated interaction of actin and myosin, and are the preferred biomarkers for myocardial injury as they are highly sensitive and specific for the diagnoses of myocardial necrosis. Disruption of normal cardiac myocyte membrane integrity results in the loss of intracellular constituents including detectable levels of a variety of biologically active cytosolic and structural proteins, such as troponins into the extracellular space. Elevation of troponins serum levels are detected within 3 to 12 hours from the onset of acute myocardial damage, peak at 24 to 48 hours as illustrated in figure 2.13, and return to baseline over 5 to 14 days (Kumar & Canon, 2009).

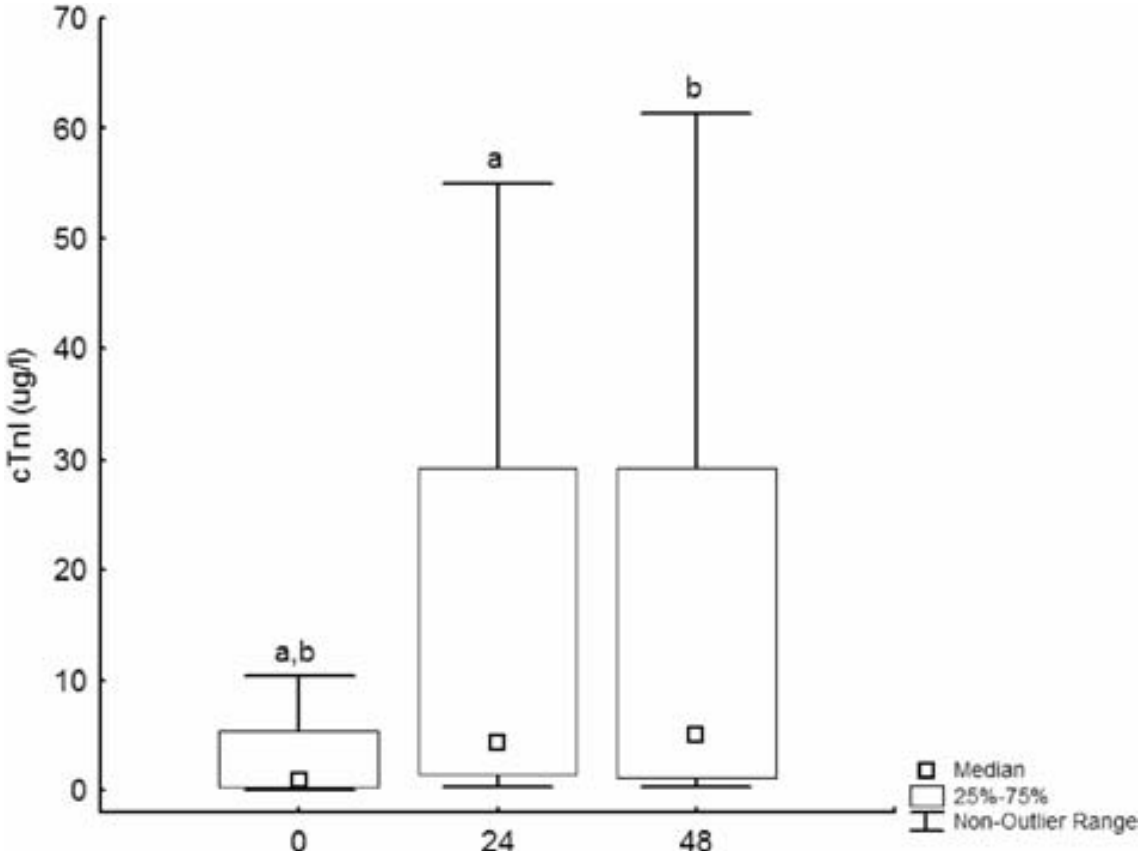


Figure 2.13: cTnI concentration over time in hours, (Iwan, Alan, Neal and Christophe 2006).

Cardiac troponin I is a preferred biomarker for myocardial injury as it has the highest sensitivity and specificity for the diagnoses of acute myocardial infarction (Kumar & Canon, 2009). Cardiac troponin levels are normally so low, that they cannot be detected with most blood tests, however Troponin I is usually considered normal when less than 10microgram per litre is detected.

Increased troponins are observed after almost all cardiac surgery. The clinical significance of this elevation is controversial. Yvette, Henri and Luc (2010) conducted a study to evaluate if troponin I (cTnI) measured 1 h after cardiac surgery provides additional information to identify patients at risk for hospital mortality. Nine hundred and thirty-eight patients undergoing cardiac surgery between October 2006 and June 2008 were evaluated; included 688 isolated CABGs and 250 valvular (qCABG) operations, and cTnI levels were measured 1 h (cTnI) after surgery. To assess the value of cTnI as a predictor for hospital mortality, receiver-operator characteristic (ROC) curves were used. The median cTnI level was 1.3 microgram per litre (mg/l), 75% inter-quartile range (IQR) 0.68–2.59 mg/l. Ten patients (1.1%) died, cTnI release of the dead, median: 6.8 mg/l was significantly higher than the measured values in the group of survivors, median: 1.3 mg/l (P-0.001). Regression analysis

showed a significant correlation between cTnI and hospital mortality (P-0.001). The ROC indicates a cTnI level of 4.25 mg/l with a ROC of 0.80 as optimal cut-off point for predicting hospital mortality, with a sensitivity of 70% and a specificity of 89%. Addition of type of surgery, isolated CABG vs. valve surgery, acute vs. elective surgery and EuroSCORE class did not improve the ROCs. In the validation set, the median cTnI level was 1.17 mg/l. Fifty-six patients had a cTnI level) 4.25 mg/l. Of the 579 patients, 11 patients (1.8%) died, six of them had a cTnI level) 4.25 mg/l. Their conclusion was that postoperative cTnI level, measured within the first hour after cardiac surgery, can identify a subgroup of patients with increased risk for hospital mortality furthermore said that patients may benefit from better monitoring, eventually with specific diagnostic and therapeutic interventions (Yvette et al, 2010).

Literature reports conflicting if not confusing findings with regards to raised plasma troponin, which is a diagnostic marker for myocardial infarction but also found to rise after cardiac surgery, leading to difficulties in diagnosing postoperative myocardial infarction. Dan, Muhammad, Michael, Amir, David and Arik (2006) conducted a study to ascertain whether the same processes influence troponin elevation in both conditions (myocardial infarction and cardiac surgery), a literature search was performed from 70 studies, for plasma troponin elimination curves after myocardial infarction, myocardial infarction with reperfusion, and cardiac surgery. 11 curves using the Stratus immunoassay kit were analysed: 5 post-cardiac surgery (412 patients), 2 after myocardial infarction with reperfusion (169 patients), and 4 after myocardial infarction (640 patients). For each group, a new plot was formulated from the mean troponin level at each time interval. While the up-slope of the cardiac surgery curve was much steeper than that of myocardial infarction, resembling that of myocardial infarction with reperfusion, its down-slope was significantly more gentle than that of both other groups (-0.91 vs. -5.31, $t = 3.47$, $df = 8$, $p < 0.01$. The findings suggested that postoperative troponin elevation involves enhanced cell permeability as seen after ischemia reperfusion rather than permanent cellular damage. The gentler down-slope may point to surgery-induced impaired troponin removal from the circulation (Dan et al, 2006).

2.2.6 Myocardial injury in HIV

In patients infected with HIV cardiovascular abnormalities are frequent but clinically discrete. Dilated cardiomyopathy and myocarditis which is an acute or chronic inflammatory process that affects the myocardium in response to the action of

various infectious, chemical or physical agents have a well-recognized association with HIV infection and AIDS (Aziz, Doddi and Penupolu, 2010). Previous studies have suggested that about 10 percent of HIV people develop myocarditis, either because HIV directly invades the heart muscle or because the patient's weakened immune system makes the heart muscle more susceptible to attack by other infectious agents, especially toxoplasmosis [Grange,1990 and Matturi, 1990).

Myocarditis may lead to valvular tissue scarring and damage causing valve incompetency that may require surgical repair. Patients with HIV may not only be coming for cardiac surgical interventions due to HIV related myocardial damage but due to other various clinical causes such as rheumatic disease and coronary disease related risk factors. The prognosis of myocarditis in HIV patients combined with other non HIV related myocardial damaging disease may seem prone to increase perioperative myocardial injury compared to HIV negative patients with similar non HIV related diseases (Chiasson, Berenson, Li, Schwartz, Singh, and Forlenza. 1999).

Some theories suggest that HIV infects myocytes even though this is not abundant or highly multiplicative in these cells, (Lewis, 2000). Despite the paucity of evidence of direct myocyte involvement, HIV infection has been proven to have structural and functional injury to the heart as a whole. Ayaskanta, Sidhartha and Rabindra conducted a study to determine the prevalence and characteristics of cardiac manifestations in patients with HIV infection and to evaluate their correlation with CD4 count. 70 consecutive patients with HIV infection admitted to Post Graduate Department of Medicine from the period of July 2010 to August 2011 were studied. All cases of patients living with HIV/AIDS diagnosed after positive ELISA test for HIV infection were included, whereas those with congenital heart disease, rheumatic heart disease, hypertension and Ischemic heart disease were excluded from the study. CD4 count and 2D echocardiography along with routine investigations were done for all patients. The results found that male to female ratio was 2:1. Echocardiographic abnormalities were seen in 58% of patients. Reduced ejection fraction (below 50%) and fractional shortening below 30% were the most common cardiac abnormality (48.7%) followed by pericardial effusion (17.4%), pulmonary artery hypertension (11.4%), dilated cardiomyopathy (8.5%), diastolic dysfunction (8.5%) and regional wall motion abnormality (1.4%) respectively. Significant statistical positive correlation was observed between low CD4 count and echocardiographic abnormalities ($p < 0.0001$). Pericardial effusion was seen more in patients with CD4 count below 200 ($p < 0.001$). The maximum number of

echocardiographic abnormalities was seen in WHO clinical stage IV. They conclude that cardiac manifestations are frequent amongst patients living with HIV/AIDS in the Indian population but do not have detectable clinical manifestation. Furthermore, echocardiographic abnormalities have a strong correlation with low CD4 count and occur more in advanced stage of the disease, (Ayaskanta et al, 2012).

Patients infected with HIV are also associated with left ventricular dysfunction in both adults and children as a result of HIV related cardiomyopathy (Felker, Thompson and Har, 2000). Lipshultz, Fisher, Lai and Miller, (2003) reported that cardiomyopathy is strongly associated with a CD4 count of less than 100cells/ml. Further stated that ventricular diastolic dysfunction is relatively common in long-term survivors of HIV infection as per clinical and echocardiographic findings; left ventricular diastolic dysfunction may lead to systolic dysfunction (Lipshultz et al, 2003).

2.2.7 Sepsis in HIV+ patients

Joa˜o and Sigrid (2013) conducted a study to evaluate sepsis in AIDS patients assessing clinical, etiological and inflammatory characteristics. Patients with severe sepsis or septic shock associated or not with HIV infection, and admitted to intensive care unit (ICU) were enrolled in the research. Clinical, microbiological and inflammatory parameters were assessed, including C-reactive protein (CRP), procalcitonin (PCT), interleukin-6, interleukin-10 and TNF-a. Outcome measures were in-hospital and six-month mortality. 58 patients with severe sepsis/septic shock admitted to ICU, 36 HIV-positive and 22 HIV-negative. All HIV-positive patients met the criteria for AIDS (CDC/2008). The main foci of infection in HIV-positive patients were pulmonary and abdominal (p 0.001). Fungi and mycobacteria were identified in 44.4% and 16.7% of HIV-positive patients, respectively. In contrast, the main etiologies for sepsis in HIV-negative patients were Gram-negative bacilli (36.4%) and Gram-positive cocci (36.4%) (p.0.001). CRP and PCT admission concentrations were lower in HIV-positive patients (130 vs. 168 mg/dL p.0.005, and 1.19 vs. 4.06 ng/mL p.0.04, respectively), with a progressive decrease in surviving patients. Initial IL-10 concentrations were higher in HIV-positive patients (4.4 pg/mL vs. 1.0 pg/mL, p.0.005), with moderate accuracy for predicting death (area under receiver-operating characteristic curve 0.74). In-hospital and six-month mortality were higher in HIV-positive patients (55.6 vs. 27.3% p.0.03, and 58.3 vs. 27.3% p.0.02, respectively). They found that the course of sepsis was more severe in HIV-positive patients, with distinct clinical, etiological and inflammatory characteristics (Joa˜o and Sigrid, 2013).

Harrison, Lewis, and Lavy (2002) conducted a prospective, blind, controlled study on wound infection after implant surgery involving 41 procedures in patients infected with the human immunodeficiency virus (HIV) and 141 in HIV-negative patients. The wound infection was assessed using the asepsis wound score. The incidence of wound infection was comparable with that of the HIV-negative group ($p = 0.396$) in HIV positive patients, with no preoperative contamination. The preoperative CD4 cell count was found not to be predictive of the incidence of infection ($r = 0.16$). In HIV positive patients with preoperative contamination the incidence of infection increased markedly compared with that in HIV-negative patients ($p = 0.084$). This suggests that wound healing and infection in HIV positive patients may be dependent on contamination.

2.2.8 Valvular heart surgery and HIV

Tec, Diane, Peter, Mark, Marc, William, and Duke (2003) conducted a 10-year retrospective clinical review to investigate early and late results of cardiac Valve replacement in Human Immunodeficiency Virus–Infected Patients. Twenty-two HIV-infected patients underwent valve replacement between 1990 and 1999, with no operative or hospital mortality. Mean patient age was 37.6 years; fifteen were men. There were twelve aortic valve replacements, seven mitral valve replacements, and three double valve replacements. Mechanical valves were used in 11, bioprostheses in seven, and homografts in four. Follow-up information was available in 20 of 22 patients (84%). At mean follow-up of 5 years, they reported 10 late deaths, due to: intracerebral haemorrhage (2), heart failure (2), unknown cause (2), renal failure (1), AIDS (1), sepsis (1) and endocarditis (1). Out of the 20 patients with active preoperative endocarditis, 4 (20%) developed recurrent endocarditis; freedom from recurrent endocarditis was 83% at 1 year. Intravenous drug abuse was reported in 16 patients; survival among these patients was 94% at 1 month and 50% at 5 years. Recurrent endocarditis was only seen in patients with continued intravenous drug abuse. They concluded that cardiac valve replacement in HIV-infected patients has low operative risk, but late results are poor when HIV infection is associated with intravenous drug abuse, probably due to immunocompromise and continued high-risk behaviour, (Tec et al, 2003).

2.2.9 C-reactive protein and Infective endocarditis

Yuko, Mitsuharu, Yasuyuki, Hidekazu, and Shigefumi (2014) conducted a study to determine if preoperative time course changes in serum C-reactive protein (CRP) levels can predict clinical outcome of surgical intervention for active infective endocarditis. Surgically treated patients (n = 109) with active infective endocarditis were reviewed retrospectively. We divided the patients into 2 subgroups according to preoperative transition of increasing or decreasing serum CRP levels, and performed a comparative study. The increasing CRP group included 29 patients and the decreasing CRP group included 80 patients. There were more patients with methicillin-resistant Staphylococcus aureus and New York Heart Association functional class IV in the increasing CRP group. Hospital mortality was significantly higher in the increasing CRP group (34.5%) than that in the decreasing CRP group (5.0%) ($p<0,05$). In multivariate analysis, 3 significant risk factors of surgical outcome were identified: a tendency for increasing preoperative CRP levels (odds ratio [OR]: 18.15, 95% confidence interval [CI]: 1.03-320.78), nosocomial infective endocarditis (OR: 18.73, 95% CI: 1.57-223.60), and dialysis (OR: 1025.46, 95% CI: 2.89-363587.12). They found that the outcome of operations for patients with increasing preoperative CRP levels is poor. For treatment of active infective endocarditis, a better operative result is expected when preoperative CRP levels are decreasing (Yuko et al, 2014).

2.2.10 Lactate level as a risk factor during CPB

Lactate is the end product of anaerobic respiration and is normally cleared from the blood by the liver and kidneys. Lactic acidosis occurs when the physiological buffering systems are overloaded causing a PH of less than 7, 25 with plasma lactate greater than 5mmol/L. Hypoperfusion and hypoxia are some of the causes of increased lactate. This causes pyruvic acid to be preferentially converted to lactate during anaerobic respiration. Hyperlactataemia is defined as plasma lactate greater than 2mmol. Jean-Michel, Paul, Manuel, Patrick, Alain, Arrigo and Denis (2003) conducted a prospective and observational study to determine the respective frequencies, risk factors, and outcomes of no hyperlactatemia 9(NHL), immediate hyperlactatemia (IHL), or late hyperlactatemia (LHL) > 3mmol/L after cardiac surgery. Arterial blood gas levels and lactate concentrations were measured at ICU admission, 4 h after surgery, between 6 h and 16 h after surgery, and on day 1 in consecutive patients (n 325) undergoing CPB for cardiac surgery. Sixty-seven patients (20.6%) had an IHL on ICU admission, and 56 patients (17.2%) acquired

LHL during their ICU stay. ICU mortality was 1.5% for NHL, 3.6% for LHL, and 14.9% for IHL groups ($p < 0.0001$). The three groups differed significantly for elective surgery, type of operation, CPB duration, intraoperative mean arterial pressure, and intraoperative and postoperative use of vasopressor. Independent risk factors for IHL were non-elective surgery, CPB duration, and intraoperative use of vasopressor. Logistic regression identified hyperglycemia and epinephrine therapy for LHL as postoperative risk factors. Receiver operating characteristic curves showed that IHL more accurately predicted ICU mortality than LHL. They concluded that hyperlactatemia is common after cardiac surgery, and also found that a lactate threshold of 3mmol/L at ICU admission is able to identify a population at risk of morbidity and mortality after cardiac surgery, (Jean-Michel et al, 2003).

Tissue perfusion is at risk during CPB and in the immediate postoperative period. The duration of CPB, degree of hypothermia, duration of cooling and rewarming, pH management strategy and the haematocrit values are all potential factors that may contribute to tissue hypoperfusion during CPB (Munoz, Laussen and Palacio, 2000). This leads to an anaerobic condition in which oxidative phosphorylation is not possible and adenosine triphosphate (ATP) is produced from pyruvate, the latter being metabolised into lactate (Demers, Elkouri and Martineau, 2000).

Plasma lactate concentrations indicate a balance between lactate production by regional tissue beds and the ability of the liver to metabolise lactate via the Cori Cycle, gluconeogenesis, and the Krebs cycle. High NYHA class and longer duration of CPB is associated with a significant increase in lactate levels during perioperative period and that increased lactate levels are directly proportional to the duration of mechanical ventilation and inotropic support, (Shinde, Golam, Kumar and Patil, 2005).

Marco, Barbara, Giuseppe, Federica, Daniela and Maira (2006) conducted a study to determine which perfusion-related factors may be responsible for hyperlactatemia, with specific respect to hemodilution and oxygen delivery, and to verify the clinical impact of hyperlactatemia during CPB in terms of postoperative morbidity and mortality rate. During CPB, serial arterial blood gas analyses with blood lactate and glucose determinations were obtained. Hyperlactatemia was defined as a peak arterial blood lactate concentration exceeding 3mmol/l. Pre- and intraoperative factors were tested for independent association with the peak arterial lactate concentration and hyperlactatemia. The postoperative outcome of patients with or

without hyperlactatemia was compared. They found that factors independently associated with hyperlactatemia were the preoperative serum creatinine value, the presence of active endocarditis, the CPB duration, the lowest oxygen delivery during CPB, and the peak blood glucose level. Once corrected for other explanatory variables, hyperlactatemia during CPB remained significantly associated with an increased morbidity, related mainly to a postoperative low cardiac output syndrome, but not to mortality. They concluded that hyperlactatemia during CPB appears to be related mainly to a condition of insufficient oxygen delivery. During CPB, a careful coupling of pump flow and arterial oxygen content therefore seems mandatory to guarantee a sufficient oxygen supply to the peripheral tissues, (Marco et al 2006).

Hyperlactemia observed in HIV positive patients has been strongly associated with the type of antiretroviral medication that the patients are taking. Alexander, Bruno, Huldrych, Stefan and Rainer (2005) conducted a study to evaluate the risk factors for and outcome of hyperlactatemia in HIV-Infected persons taking combined antiretroviral therapy (CART) and whether or not there is a need for routine lactate monitoring in these immunocompromised patients. The incidences of, risk factors for, and courses of hyperlactatemia and lactic acidosis were prospectively assessed 3 groups: persons already receiving CART at baseline, treatment-naive persons who initiated CART during the observation period, and persons who received no CART before or during the observation period. A total of 22,678 lactate assessments were performed for 1566 persons; 662 (42.3%) had at least 1 lactate level measurement of 12.4mmol/L, and 49 (3.1%) had severe hyperlactatemia (lactate level of 15.0mmol/L). The incidence of hyperlactatemia was 227 cases (95% confidence interval, 210–245) and 59 cases (95% CI, 38–93) per 1000 person-years of follow-up among persons with and persons without CART, respectively. During the observation period, the incidence decreased from 459 cases (95% CI, 415–508) to 85 cases (95% CI, 76–107) per 1000 person-years of follow-up, respectively, because of changing CART prescription patterns. Severe hyperlactatemia occurred in treated persons only. In multivariable Cox proportional hazards models, significant risk factors for severe hyperlactatemia were regimens containing stavudine and didanosine (hazard ratio [HR], 6.65; 95% CI, and 2.70–16.3) and regimens containing efavirenz (HR, 2.85; 95% CI, 1.31–6.21). Lactic acidosis was diagnosed in 4 of 1566 persons, all of whom were receiving stavudine and didanosine.

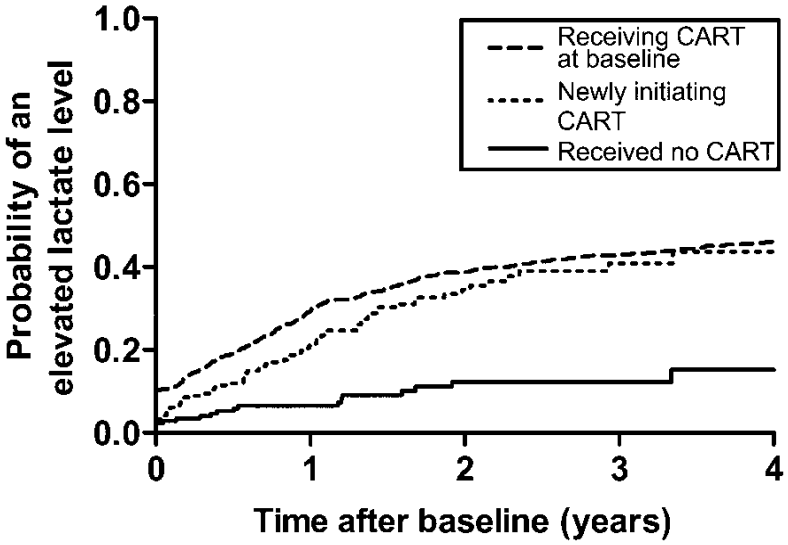


Figure 2.14: Probability of developing hyperlactatemia (Alexander, et al 2005).

The results show that hyperlactatemia was frequently observed in all 3 groups, but severe hyperlactatemia and lactic acidosis were rarely observed among persons who received CART. Furthermore, lactate monitoring appeared to be indicated primarily for persons receiving stavudine and didanosine and for persons who are symptomatic, (Alexander et al, 2005).

Other studies have associated hyperlactatemia with lipoatrophy, hyperlipidemia, and hyperglycemia in HIV patients further reporting that age, sex, or stage of infection with human immunodeficiency virus were not predictive of hyperlactatemia, (Boubaker, Flepp, Sudre, Furrer, Haensel, Hirschel, Boggian, Chave, Bernasconi, Egger, Opravil, Rickenbach, Francioli and Telenti, 1991).

2.2.11 Blood transfusion and HIV

The administration of allogenic blood products during cardiac surgery is a common practice; administration of packed red blood cells and other blood products are associated with increased morbidity and mortality in the non-HIV infected population undergoing cardiothoracic surgery (Marik and Corwin, 2008, Murphy, Reeves, Rogers, Rizvi, Culliford and Angelini, 2007). The adverse effects of transfusion are potentially more significant in HIV-infected patients (Hillyer, Lankford, Roback, Gillespie and Silberstein, 1999).

Michael et al, (2014) reported that HIV positive patients were more likely to receive a blood transfusion and have any postoperative complication compared to non-infected

patients undergoing similar type of cardiac surgery. It has been suggested that blood transfusions induce a second insult to the systemic inflammatory response that already after cardiac surgery exists. Reduction of the use of blood products in cardiac surgery can further decrease mortality (Bilgin and van de Watering, 2013).

2.2.12 Conclusion

Cardiac surgery in HIV positive patients has been reviewed retrospectively with positives outcomes showing very little difference when compared to the outcomes of cardiac surgery in HIV negative patients. However these studies have focused mainly on morbidity and mortality rates in these immunosuppressed patients. Very minimal prospective studies have been done or published to evaluate the immune activation and alterations of HIV cellular biomarkers and other cardiac surgery postoperative risk factors such as myocardial injury.

Amongst most cardiac surgery postoperative risk factors, it appears that people infected with HIV are already having some of these factors. These factors may be expected to rise excessively after surgery based on the baseline existence. This study focused mainly on inflammatory response, myocardial injury and immune HIV cells (CD4 cells) depletion or alterations.

CHAPTER THREE: MATERIALS AND METHODOLOGY

3.1 Introduction

The aim of the research study was to investigate acute systemic inflammatory response and myocardial injury after cardiac surgery in patients infected with Human immunodeficiency virus using C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) cardiac troponin I (cTnI) biomarkers and clinical assessments. The primary objective was to determine whether or not HIV positive patients undergoing cardiac surgery generate excessive acute systemic inflammatory response and myocardial damage compared to HIV negative patients using relevant biomarkers. The secondary objective was to determine if there are predisposing factors (viral load, CD4 count and anti-retroviral medication) that can increase or reduce the risks of cardiac surgery supported by CPB in HIV positive patients. Only patients diagnosed with valvular heart disease and who require surgical cardiac valve replacement were selected as participants of the research study.

The study was designed as a prospective clinical study to investigate the severity of acute systemic inflammatory response and myocardial injury after cardiac surgery in patients infected with human immunodeficiency. Sixty-one (61) participants were selected as participants from a single centre hospital, Inkosi Albert Luthuli Central Hospital (IALCH) and were divided into two groups i.e. thirty HIV positive patients and thirty-one HIV negative patients undergoing elective on-pump cardiac surgery. These HIV positive patients were recruited consecutively, and a relatively corresponding age-and-gender matched ‘control’ HIV negative patient was selected, after informed consent had been sought. After noting that no prospective similar study has been published, because most studies on HIV patients were retrospective studies, case reports and literature reviews, a biostatistician was consulted to verify the number of participants and data variables required to significantly test the hypothesis.

The sample size was confirmed as adequate when calculated for comparing the means of two normally distributed samples of equal size using a two-sided test with significance level alpha and power 1-beta. A biostatistician letter of consultation which includes statistical analysis approach to be employed is included as Appendix A. A total sample size of 600 measurements as data collection in the HIV positive group were collected, and a total of 540 measurements in the HIV negative group

were collected. The significant difference between the two groups is due to a single variable (CD4 cells count) which could not be measured in the HIV negative group; this will be regarded as a limitation in the study discussion. Apart from CD4 cells count, data sample collection paralleled between the two groups.

3.2 Selection criteria

Inclusion criteria:

a) HIV negative patients and HIV positive patients with CD4 count ≥ 200
b) Patients requiring the use of cardiopulmonary bypass machine to support physiological blood circulation for heart valvular replacement.
c) Above the age of 18 and below the age of 60 years, for standardization of adults cardiac surgery setup methodology.

Exclusion criteria:

a) Patients undergoing cardiac surgical intervention for the second time.
b) Patients under the age of 18 years and over the age of 60 years.
c) Patients not proficient to understand English or Zulu.
d) Combined Cardiac procedures, i.e. heart valve replacement and coronary artery bypass grafting.
e) Patients with any type of Hepatitis

3.3 Ethical considerations

Ethical approval was obtained from the Durban University of Technology Institutional Research and Ethics Committee (IREC) {Appendix C (1) & (2)}, Inkosi Albert Luthuli Central Hospital Clinical Manager Dr K E Letebele-Hartell (Appendix D), cardiothoracic surgery Head of Department: Dr R Madansein (Appendix E), and Kwazulu Natal (KZN) EThekwini Health District (Appendix F). Additional informing letters were sent to the cardiac surgery supporting departments, i.e. Anaesthetics and Nursing.

Patients who met the inclusion criteria were recruited from the cardiac ward and an informed consent form was provided in both English and Isizulu (Appendix B (1) & (2)) respectively to all patients participating in the study. Patients were verbally notified as to the purpose and the requirements of the study. Patients were informed that their right to participate in the study was entirely voluntary and that they were

entitled to withdraw at any point without affecting the medical treatment rendered to them. They were also informed that all information used in the study would remain confidential and that any data reported in scientific journals or published would not include information identifying them as a patient in the study.

Confidentiality and anonymity was prioritized, as the South African constitution allows and respects individual's privacy regarding their health statuses especially in HIV/AIDS. All patients who willingly agreed to participate in the study were asked to sign consent.

Two (2) witnesses were used when recruiting participants to ensure that the participants do not feel coerced and under duress to participate.

3.4 Methodology

3.4.1 Cardiopulmonary bypass

A Stockert S5 heart - lung machine (CPB) utilizing roller pump was used in all patients during data collection. Eurosets Admiral Oxygenator and tubing was the only oxygenator used during data collection. Admiral oxygenator internal surfaces are coated with Phosphorylcoline which is the predominant lipid head-group found in the outer layer of cell membranes. Phosphorylcoline has a natural affinity for water and binds water tightly around itself. As a result does not promote clots formation (www.eurosets.com, brochure admiral, 2014). Admiral oxygenators require a priming volume of 190 ml, has a contact surface area of 1.35meter square with maximum blood flow rate of 7,0litre/min. Total CPB circuits priming solution included 1450ml of Plasmalyte B, 5000i.u of heparin and 50ml of 20% Albusol. Standard protocol for CPB conduction was not modified; electrolytes and blood pH corrections were corrected as per the standard protocol to maintain normal ranges. Also, the use of adrenaline and other routine drugs were not prohibited nor limited during data collection.

Mistral cardioplegia delivery sets were used to administer cardioprotective solutions which was either cold blood cardioplegia delivered at the ratio of 4:1 blood to medsol cardioplegic solution at an average delivery pump rate of 240ml/min for the duration of four minutes induction and 2 minutes maintenance, or ST Thomas II crystalloid

cardioplegic solution which was delivered at a standard protocol of 20ml/kg induction and 10ml/kg maintenance.

Patients' temperatures were cooled down as per the standard unit protocol of hypothermia which for heart valvular surgery range between 28-32 degrees Celsius, and then rewarmed to core temperatures of 35 degrees Celsius before termination of CPB. Topical hypothermia which employs pouring ice cold normal saline on the heart was employed in all patients as a standard protocol during cardiac surgery.

3.4.2 Cardiac anaesthesia

Table 3.1 (as per IALCH protocol)

Pre-medication:	▪ Lorazepam 1-2mg orally
Anaesthetic induction:	▪ Fentanyl 3.5-7µg/kg ▪ Propofol 0.6-1.4mg/kg ▪ Pancuronium 8mg + ▪ Rocuronium 50mg
Anaesthetic maintenance:	▪ Fentanyl 100µg/hr ▪ Isoflurane 0.6-1% ▪ Midazolam 1mg/hr or boluses (1-3mg)
During CPB:	▪ Fentanyl 100µg/hr ▪ +/- Midazolam 1mg/hr
Post CPB:	▪ Fentanyl 100µg/hr ▪ Midazolam 1mg/hr ▪ +/-Pancuronium ▪ Inotropic support (Adrenaline)

3.4.3 Laboratory tests- C-reactive protein

ADVIA chemistry systems Wide Range C-reactive protein (wrCRP) method was used to test for CRP. This method measures CRP in serum and plasma by a latex-enhanced immune-tirbidimetric assay. It is based on the principle that the analyte concentration is a function of the intensity of scattered light caused by the latex aggregates. The latex particles coated with anti-CRP rapidly agglutinate in the presence of C-reactive protein-forming aggregates.

The wrCRP latex reagent is a suspension of uniform polystyrene latex particles coated with anti-CRP antibody. When serum containing CRP is mixed with the latex reagent, agglutination takes place resulting in an increase in the turbidity. This turbidity is measured at 571 nm. The CRP concentration in serum is determined from a calibration curve that is generated with calibrators

3.4.4 Laboratory test- CD4 cell count

HIV positive patients were tested for CD4 T-cell count using Panleucogating (PLG)/CD4 method which uses a sequential gating strategy to identify all CD45+ leucocytes in order to measure the CD4% of lymphocyte and absolute CD4 count. Absolute CD4 counts are derived by single platform analyses that incorporate the use of FlowCount beads with a pre-defined concentration.

3.4.5 Laboratory test- Troponin I

The cTi laboratory test uses the ADVIA Centaur TnI-Ultra assay which is a three-site sandwich immunoassay using direct chemiluminometric technology. An ancillary reagent is included to reduce nonspecific binding. The binary lite reagent includes a polyclonal goat anti-troponin I antibody labelled with acridinium ester and 2 biotinylated mouse monoclonal anti-troponin I antibodies. The solid phase reagent is magnetic latex particles conjugated with streptavidin. All reagents are contained within the ReadyPack.

The antibodies in the binary lite reagent bind to troponin I in the sample. The biotin contained in the immune complex then binds to the streptavidin-labelled magnetic particles. The system then automatically dispenses 100 microliter of sample into a cuvette, 100microliter of binary lite reagent plus 50 microliter of ancillary reagent and incubates for 2,75 minutes at 37 degrees Celsius. It then separates; aspirates and washes the cuvettes with wash 1. Then again dispenses 300microliter each of acid

reagent and base reagent to initiate the chemiliminescent reaction. It then reports results according to the selected option.

3.4.6 Data samples collection and time frames

On the eve of the operation each participant was identified and recruited and asked to sign the consent if willing to participate in the research study.
On the day of the operation upon arrival in operation room, routine invasive and non-invasive heamodynamic monitoring devices such as peripheral drip line, electrocardiogram electrode, pulse oximeter, invasive blood pressure, central venous pressure, urine catheter and temperature monitoring cable were inserted and/or placed on the patient.

Preoperative samples

Patient demographics such as gender, age, type of surgery, cardiac ejection fraction, New York Heart Association (NYHA) classification and current medication were recorded on the data sheet.

After all monitoring devices were placed on the patients just before initiation of anaesthesia, arterial blood samples were taken from the radial or femoral invasive arterial catheter. Blood samples were collected by the researcher for laboratory tests using appropriate recommended sample collection method and test tubes for each of the tests i.e. C-reactive protein, Erythrocyte sedimentation rate, Troponin I and CD4 cell count (HIV positive patients only). These variable tests served as baselines.

Intraoperative samples

Intraoperative samples included: myocardial protection technique employed for each case, blood products transfused, peak-lactate level, total urine output, aortic cross-clamp duration and CPB duration.

Postoperative samples

Postoperative samples included clinical assessments such as: duration on mechanical ventilation, duration on positive inotropic support and duration in the intensive care unit, all measured in days.

On the second postoperative day (48hours) blood samples were taken by the researcher for postoperative laboratory tests i.e. C-reactive protein, Erythrocyte

sedimentation rate, Troponin I and CD4 cell count (HIV positive patients only). These samples were taken according to each test standard recommended time that it reach peak levels at, and in this study all variables under study are categorised as reaching after 48hours of surgery.

Patient follow up only lasted until all postoperative samples and clinical assessments were collected meaning until the patient was extubated, weaned off inotropes and transferred out of intensive care.

A data sheet (Appendix G) was used to record all preoperative, intraoperative and postoperative data variables of each participant. Microsoft excel was used to record variables and related demographics for statistical analysis. These were then transferred to SPSS version 23 for further analysis.

Table 3.2 Summary of data collection and time frames

DAY ONE	
Eve of the operation	▪ Recruitment ▪ Informed consent signing
DAY TWO	
Preoperative **Intraoperative**	▪ Demographics, ▪ Indication for surgery ▪ Preoperative assessments ▪ Laboratory tests ▪ CPB duration ▪ Cross-clamp duration ▪ Urine output ▪ Peak lactate ▪ Myocardial preservation ▪ CPB events
DAY FOUR	
Postoperative	▪ Clinical assessments ▪ Laboratory tests

3.5. Data analysis techniques

All numerical variables were tested for distribution using the Kolmogorov Smirnov test. Data were expressed as mean and SD (for normally distributed data) and as median and the interquartile ranges (IQ 25-75%) if not normally distributed. Variables which showed large variability and nonparametric distribution were log transformed. Demographic data was shown using descriptive statistics.

In order to test whether there is a difference in the measured markers for systemic inflammatory response for HIV positive patients compared to HIV negative patients, a two sample t-test for independent groups was used.

To investigate whether the risk of myocardial injury in the HIV positive group is larger than the risk for the HIV negative group, a z-test for two proportions was used. (The z-test is based on the normal distribution and is a test for the equality of two proportions, in this case the risk of myocardial injury or inflammatory response).

In order to test for the change in troponin and C-reactive protein levels before surgery (base line) and after surgery (24 hours after surgery and the 48 hours after surgery) for the two groups, a longitudinal model with group, time and a group time interaction was fitted to determine whether there are group differences, time differences and whether there is an interaction effect.

Preoperative categorization of cardiac troponin I, was used to group patients as per baseline levels range.

The statistical software that was used is SPSS and SAS version 9.3.

CHAPTER FOUR: RESULTS

The study comprised of sixty-one participants who were booked for valvular replacement (mitral, aortic or both) in the Department of Cardiothoracic surgery at Inkosi albert Luthuli central hospital from May 2015 to January 2016. There was a dominance of females (54.1%), with 45.9% being males as shown in Table 4.1 below. The majority of subjects (36.1%) were seen in the 30-40 year old age group.

Table: 4.1 Demographic data

Age group	N (%)	Males	Females
18-20 years	1 (1.6%)		1(1.6%)
20-30 years	17 (27.9%)	9 (14.8%)	8 (13.1%)
30-40 years	22 (36.1%)	7 (11.5%)	15 (24.6%)
40-50 years	11 (18.1%)	7 (11.5%)	4 (6.6%)
50-60 years	10 (16.4%)	5 (8.2%)	5 (8.2%)
Total	61 (100%)	28 (46%)	33 (54.1%)

*N- frequency number

Participants were selected consecutively and were grouped based on the HIV status into the study group (HIV seropositive) and control group (HIV seronegative) in order to elicit differences in the systemic inflammatory response and myocardial injury whilst on, and post CPB. The clinical characteristics of the two groups are shown in Table 4.2 below.

The total study mortality from the sixty-one patients was two patients (3.3% mortality). Only one patient did not complete the study follow up period, as the patient died three hours after the operation (3.3% mortality in the HIV positive group). This patient could not be excluded from the data since the cause of death may be related to the stratified operative risks under study. All other sixty patients completed the follow period, with one other HIV negative patient dying later while still in hospital (3.2% mortality in the HIV negative group).

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Table 4.2 Clinical Characteristics of the study and control population

Variables	Study group (HIV positive)	Control (HIV negative)
Female	16 (53%)	17 (55%)
Male	14 (47%)	14 (45%)
Age (mean ±)	37.8 ± 10.6	37.1 ± 11.9
AVR	8 (27%)	4 (13%)
MVR	19 (63%)	10 (32%)
DVR	3 (10%)	17 (55%)
NYHA grading: I II III IV	 2 (7%) 21 (70%) 6 (20%) 1 (3%)	 2 (6%) 18 (58%) 8 (26%) 3 (10%)
Ejection fraction (mean):	48.6% ± 9.4	51.1% ± 11.2
Type of cardioplegia: ST Thomas II Blood 4:1	 18 (60%) 12 (40%)	 23 (74%) 8 (26%)
HAART: Yes No	 26 (86.7%) 4 (13.3%)	 ---- ----
Mortality:	1 (3.3%)	1 (3.2%)

The mean age for the HIV seropositive was 37.8years and 37.1years for the HIV seronegative group with the range being between 18 to 60years (Table 4.2). Types of operations comprised of aortic valve replacement (AVR) 19.7%, mitral valve replacement (MVR) 32.8% and double valve replacement (DVR) 47.5%, which is a combined operation for both AVR and MVR. Baseline New York heart association (NYHA) of all patients grading was statistically analysed to determine the frequency per each grade. Grade I frequency was four patients (6.6%), grade II frequency was thirty-nine patients (63.9%), grade III frequency was fourteen (23.0%) and grade IV frequency was four (6.6%). The baseline preoperative ventricular ejection fraction (EF) was analysed and compared between the two groups, with the mean EF of 48.6% in the study

group, and 51.1% in the control group. Two types of cardioprotective cardioplegia solution were used in the study; with the type of cardioplegia was to be employed being determined by the surgeon. Twenty (32.8%) patients used Buckberg blood 4:1 cardioplegia and forty-one (67.2%) used ST Thomas II crystalloid cardioplegia. Out of thirty patients in the study group, twenty-six (86.7%) were on HAART, and four (13.3%) were not on any antiretroviral treatment

Relevant biomarkers were used to determine whether or not HIV seropositive patients undergoing cardiac surgery generate excessive acute systemic inflammatory response (SIR) and myocardial damage when compared to HIV negative patients. The CRP and ESR were used as SIR biomarkers, and cTnI was used to determine myocardial damage. The preoperative CRP and ESR analysis between the study and control group showed no significant difference (p=0.388 and 0.817, respectively) as shown in Table 4.3 below.

Preoperative troponin I categorization was used to group the preoperative troponin I levels i.e. troponin I less than equal to 10 nanogram per liter (<10ng/l) and troponin I greater than equal to 10 nanogram per liter (>10ng/l). Sixty patients were analysed, thirty-one HIV negative patients and twenty-nine HIV positive patients. Out of sixty patients thirty-six patients had a preoperative troponin I of less than 10ng/l and twenty-four patients had a preoperative Troponin I greater than 10ng/l. There were no significant differences in the frequencies of categorized cTnI between the two groups (p = 0.489) as shown in table 4.3 below.

Table 4.3: Preoperative CRP, ESR and cTnI between study and control groups

Parameter	**Study group (HIV +)**	**Control group (HIV -)**	**P-value**
	Mean & Standard deviation	Mean & Standard deviation	
Preop CRP	13.48 ± 16.108	13.16 ± 28.471	0.388
Preop ESR	36.66 ± 23.731	37.58 ± 25.178	0.817
Preop cTnI (N) < =10 >10	 n=19 (31.1%) n=11 (18%)	 n=17 (27.9%) n=14 (23%).	
Preop cTnI < =10 >10	 10 ±1 69 ± 129	 10 ±1 30 ± 164	0.489

*CRP- C-reactive protein, *ESR- Erythrocyte sedimentation rate, *cTnI- Cardiac troponin I

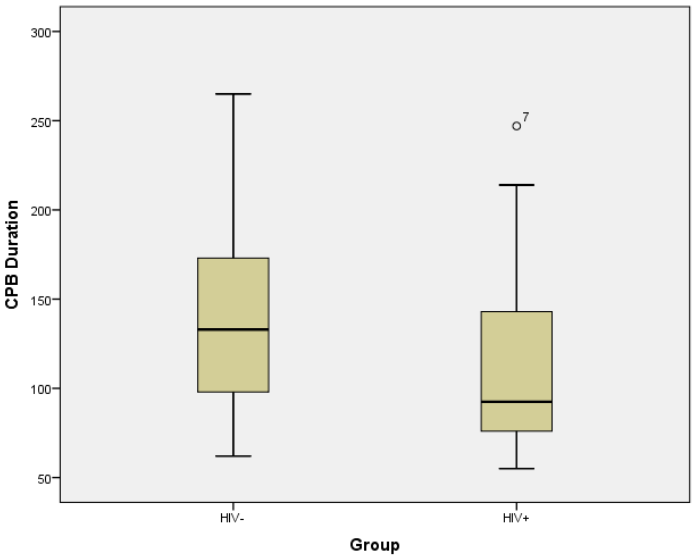
The CPB events and variables were analysed and compared between the study and control groups. The results are summarized in Table 4.4 and are illustrated as boxplots below. There were statistically significant differences for all parameters studied between the control and study groups.

Table 4.4: Summary of CPB variable between the two groups

Bypass parameters	HIV +		HIV -		p-value
	Mean	Std deviation	Mean	Std deviation	
CPB duration (minutes)	111.83	47.126	141.77	54.063	0.021**
CPB clamp duration (minutes)	82.97	34.573	107.74	43.346	0.026**
CPB P/cells transfusion (units)	0.87	.681	0.45	.675	0.013**
CPB urine output (ml)	1011.17	680.522	1531.45	1058.072	0.035*
CPB peak lactate	3.04	1.483	3.87	1.821	0.040*

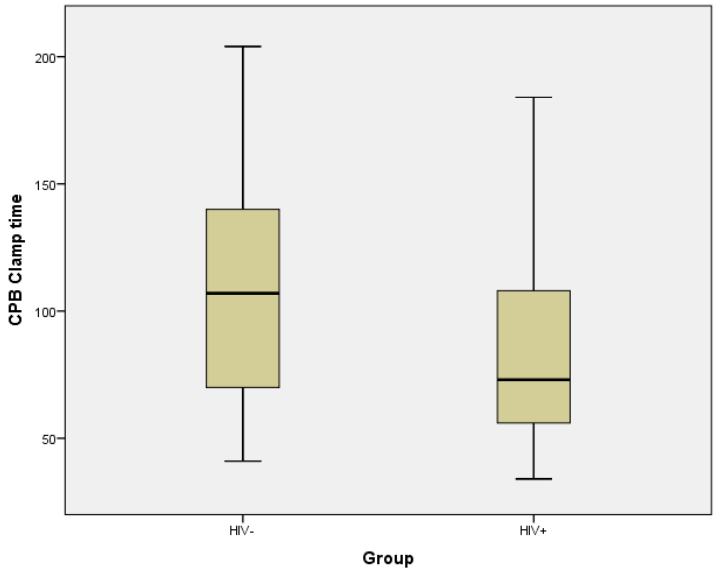
Cardiopulmonary bypass duration was significantly longer in the control group as compared to the study group (p=0.021) (Figure 4.1 below).

Figure 4.1: CPB duration between HIV negative vs. HIV positive group.



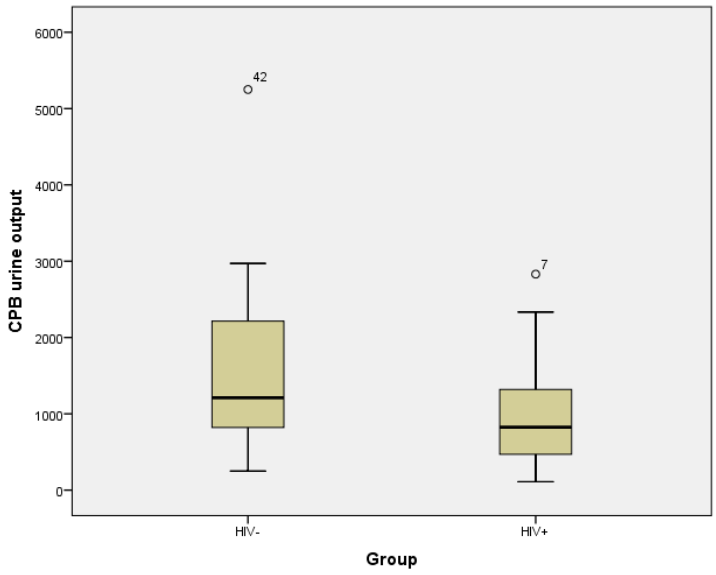
The CPB aortic cross clamp time was also significantly longer in the control group when compared to the study group (p=0.026) (Figure 4.2).

Figure 4.2: CPB aortic cross clamp between HIV negative vs. HIV positive group.



The overall CPB urine output per each group was statistically analysed and compared between HIV seropositive and HIV seronegetive patients. The boxplot in figure 4.3 below shows that HIV negative group had a significantly greater urine output compared with HIV seropositive group (p=0.035).

Figure 4.3: CPB urine output between HIV negative vs. HIV positive group.



The postoperative CRP mean was slightly higher in the study group (212.59 ± 23.731), as compared to the control group (190.68 ± 57.919), however statistical analysis showed that the difference in results was not significant (p=0.115). Using the ESR to investigate SIR between the two groups, postoperative ESR mean between the study group (43.07 ± 23.067) and control group (49.68 ± 19.139) showed no significant difference (p=0.214).The results are shown in Table 4.5 below. Both CRP and ESR results showed no significant differences between the two groups, both preoperatively and postoperatively.

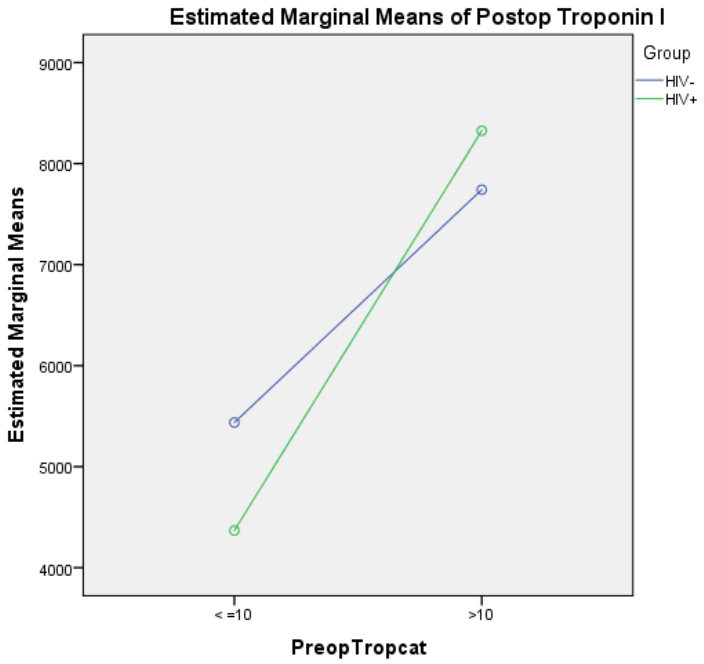
Table 4.5: Postoperative CRP, ESR and cTnI between study and control groups

Parameter	**Study group (HIV +)**	**Control group (HIV -)**	**P-value**
	Mean & Standard deviation	Mean & Standard deviation	
Postop CRP	212.59 ± 23.731	190.68 ± 57.919	0.115
Postop ESR	43.07 ± 23.067	49.68 ± 19.139	0.214
Postop cTnI			
< =10 preop	4367.37 ± 1575.69	5437.29 ± 4118.14	0.489
>10 preop	8325.20 ± 10902.07	7741.79 ± 7898.84	0.363

*CRP- C-reactive protein, *ESR- Erytrocyte sedimantaion rate, *cTnI- Cardiac troponin I

Postoperative cTnI means analysis results showed no significant statistical difference between the two groups (p=0.489, and 0.363, respectively) as shown in Table 4.5 above. The study however observed that in terms of the preoperative cTnI levels, in both the groups of categorized preoperative cTnI >10ng/l generate or suffer excessive myocardial injury when using lowest and highest marginal cTnI means as illustrated in figure 4.4 below.

Figure 4.4: Comparison between HIV- and HIV+ groups using Postop marginal means vs. Preoperative Troponin categories.



The preoperative and postoperative cTnI were analysed and correlated with the type of surgical operation i.e. aortic valve replacement, mitral valve replacement and double valve replacement, between the study and control groups. The frequency distributions per group as per the type of surgical operation are shown in Table 4.6 below.

Table 4.6: PreopTropcat vs. Surgery Cross tabulation

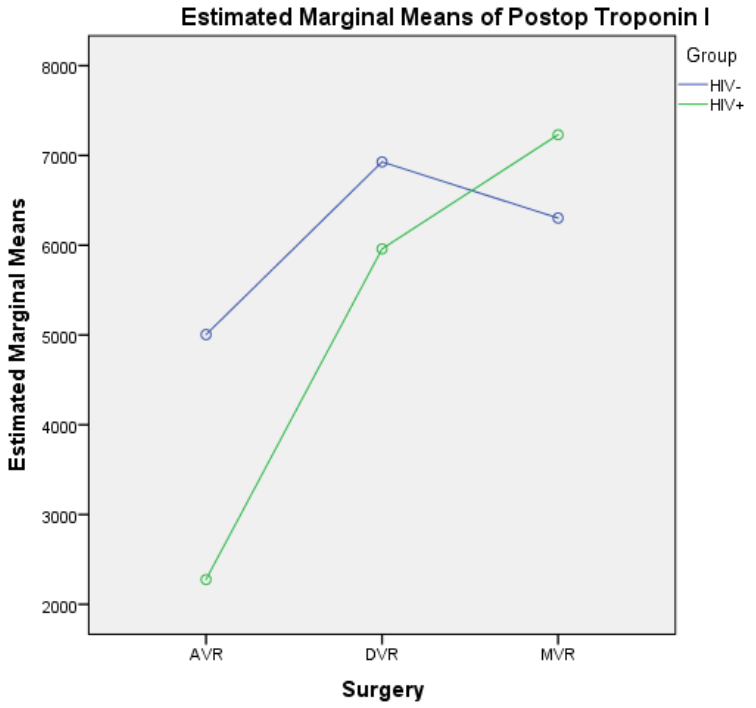
Group			Surgery			Total
			AVR	DVR	MVR	
HIV-	PreopTropcat	<10	1	8	8	17
		>= 10	3	9	2	14
	Total		4	17	10	31
HIV +	PreopTropcat	<10	4	2	13	19
		>= 10	4	1	6	11
	Total		8	3	19	30

*AVR- aortic valve replacement, *MVR-mitral valve replacement. *DVR-double valve replacement

The majority of patients with preoperative cTnI levels <10ng/L were admitted for both MVR and DVR in the HIV positive group, with those with preoperative cTnI levels >10ng/L being admitted largely for DVR. In the HIV negative group, the majority of patients with both preoperative cTnI levels <10ng/L and postoperative levels >10ng/L were admitted for MVR.

Figure 4.5 illustrates the postoperative cTnI marginal means comparison between the study and control groups as per the types of operation, with the highest cTnI observed in HIV seropositive group undergoing MVR operation. Of note, postoperative cTnI levels in those patients undergoing AVR were very low. This was in contrast to those patients in the seronegative group, who displayed lower postoperative cTnI levels, but undergoing DVR.

Figure 4.5: Postoperative troponin I marginal means vs. type of surgery.



To determine whether the acute systemic inflammatory response and myocardial injury (CRP and cTnI, respectively) correlate with perioperative determinants of morbidity and complications (outcomes), the experimental study and the control group were analysed separately. The difference between preoperative and postoperative CRP was correlated with age, preoperative NYHA grading, packed red blood cells transfused, mechanical ventilation duration and ICU stay. The results are shown as tabulated below in Table 4.7

There were strong inverse correlations between the difference in CRP and blood transfusion volume (r=-0.370; p=0.048) and ventilation duration (r=-548; p=0.02) in the study group.

The postoperative cTnI was correlated with the aortic cross clamp duration; postoperative inotropic support duration and ICU stay (Table 4.7). In addition, there was a strong positive correlation between post-op cTnI levels and inotropic support (r=0.384; p=0.040) in the study group, and this was not observed in the control (HIV negative) group

Table 4.7: CRP and cTnI correlation with morbidity/complications determinants

Variables	HIV +			HIV -		
	N	Pearson Correlation (r value)	p-value	N	Pearson Correlation (r value)	p-value
CRP diff vs. Age	29	.071	.716	31	-.039	.835
CRP diff vs. preop NYHA grading	29	-.259	.176	31	.256	.165
CRP diff vs. p/cells transfusion	29	-.370*	.048*	31	-.133	.475
Postop CRP vs. CPB Duration	29	-.432*	.019	31	.148	.426
CRP diff vs. Mechanical ventilation	29	-.548**	.002**	31	.025	.893
CRP diff vs. ICU stay	29	-.231	.229	31	.006	.975
Postop cTnI vs. clamp time	29	-.086	.656	31	.239	.195
Postop cTnI vs. Inotropic support	29	.384*	.040*	31	.092	.622
Postop cTnI vs. ICU stay	29	.164	.395	31	.208	.262
CPB urine output vs. CPB Duration	30	.700**	.000**	31	.467**	.008**
CPB urine output vs. Postop CRP	29	-.132	.495	31	-.106	.570
CPB peak lactate vs. Postop CRP	29	-.491**	.007**	31	.043	.818

*CRP diff- C-reactive protein difference*P/cells- packed red blood cells, *ICU- intensive care unit

To determine if there were predisposing factors (viral load, CD4 count and anti-retroviral medication) that could increase risks of cardiac surgery supported by CPB in HIV positive patients, patients infected with HIV were investigated to evaluate the changes in these parameters. The preoperative CD4 cells levels were compared with levels at three days postoperative. Paired sample statistical results showed preoperative CD4 cells mean of 598.76 ± 205.576 and the postoperative CD4 cells mean was 405.97 ± 119.089, as shown below in Table 4.8 below.

Table 4.8: Preoperative vs. Postoperative CD4 cells paired samples

		Mean	N	SD	Std. Error Mean	p-value
Pair 1	Preop CD4	598.76	29	205.576	38.174	<0.001
	Postop CD4	405.97	29	119.089	22.114	

As expected, there was a decrease in CD4 cells postoperatively, and this difference was strongly significant (p= <0.001) when compared to preoperative levels. The difference between preoperative and postoperative CD4 cells levels was further analysed and correlated with surgical outcome determinant variables such as CPB duration, age, NYHA grading and ICU stay to investigate whether or not CD4 cells level is a predictive factor for surgical outcome in HIV positive patients. There no significant correlation between change in CD4 cells and CPB duration, age, NYHA grading and ICU stay (p=0.177, 0.741, 0.775 and 0.195 respectively) as shown in Table 4.9 below.

Table 4.9: Correlation of predisposing factors and ICU stay

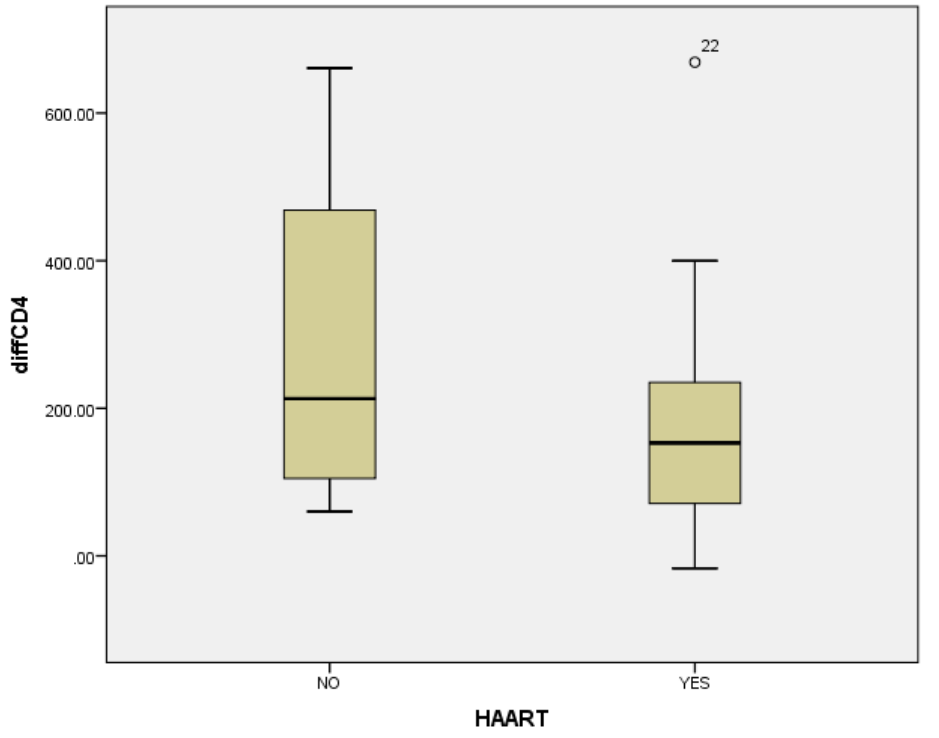
Correlations	**N**	**Pearson Correlation (r value)**	**P value**
CD4 cell diff vs. CPB duration	29	.258	.177
CD4 cell diff vs. Age	29	.064	.741
CD4 cell diff vs. NYHA grading	29	.056	.775
CD4 cell diff vs. ICU stay	29	.248	.195

In this study only highly active anti-retroviral treatment proved to be the predictive factor for CD4 cells level changes after cardiac surgery in these immune-compromised patients, as shown in figure 4.6. The group of patients on HAART had the CD4 cells difference mean of 177.7600 ± 151.36, as compared to the mean of 286.7500 ± 264.76 in patients not taking antiretroviral treatment, as shown in table 4.9 below.

Table 4.10 HAART and diff CD4: Group Statistics

HAART		N	Mean	Std. Deviation	Std. Error Mean
diffCD4	YES	25	177.7600	151.36278	30.27256
	NO	4	286.7500	264.76074	132.38037

Figure 4.6: Difference in CD4 cells between patients on HAART and those who are not.



Biochemical and CPB parameters were then compared between patients on HAART and those not on any antiviral treatment, the results are shown in table 4.11 below. Only the CPB duration emerges as statistically significant, where the duration was significantly higher in subjects who were not on HAART therapy (p=0.031). The cross-clamp time differences approached statistical significance (p=0.071), and was higher in subjects not on HAART therapy.

Table 4.11 Comparisons of CPB parameter between patients on and not on HAART

Variables	HAART				p-value
	NO		YES		
	Mean	Standard Deviation	Mean	Standard Deviation	
CPB clamp time	111	33	79	33	0.071
CPB duration	160	52	104	43	0.031*
CPB peak lactate	4	3	3	1	0.298
CPB urine output	1513	895	934	628	0.198
Postop CRP	171	58	219	50	0.142

* CRP- C-reactive protein, *CPB- Cardiopulmonary bypass

To document the morbidity and complications in HIV positive and HIV negative patients following cardiac surgery, study and control groups were analysed using postoperative determinants of morbidity and complications. The results are shown in Table 4.12 below. There was a strong significant difference (p=0.011) between the two groups, with the HIV seropositive group firstly weaned off inotropes faster compared to HIV seronegative patients. The results showed significant difference (0.047) between the two groups in terms of ICU stay, where HIV seronegative patients spent more time in ICU when compared to HIV seropositive. In terms of mechanical ventilation the study findings showed highly significant difference (p=0.012) between the two groups, with the study group spending less time on mechanical ventilation compared to the control group.

In this study during the follow up period, there were no patients reported to be septic, nor were there patients diagnosed with postoperative neurological complications or renal dysfunction that required heamodialysis.

Table 4.12: Morbidity and complications

Morbidity variable	Study group-HIV +		Control group-HIV –		P-value
	Mean	Std. deviation	Mean	Std. deviation	
Inotropic duration (days)	1.03	.345	1.51	.986	0.011**
ICU stay (days)	1.28	.591	1.87	1.258	0.047*
Mechanical ventilation (days)	1.14	.441	1.58	923	0.012**
Sepsis	NIL		NIL		
Renal dialysis	NIL		NIL		
Neurological complications	NIL		NIL		

CHAPTER FIVE: DISCUSSION

Cardiac surgery and cardiopulmonary bypass (CPB) initiates a systemic inflammatory response which is determined by blood contact with foreign surfaces and the activation of complement system (Day and Taylor, 2005), resulting in a whole-body inflammatory reaction. Although the extent of this inflammatory reaction will vary from patient to patient, the persistence of any degree of inflammation is considered potentially harmful to the cardiac patient (de Mendonça-Filho et al, 2006). This may further be exacerbated in patients infected with HIV since they have elevated cytokine levels, chronic vascular inflammation, and endothelial dysfunction (Ross et al 2009), and may be a cause for increased morbidity and mortality following cardiac surgery with CPB. As the gradual increase in the number of HIV positive patients requiring open heart surgery has been observed over the years and is expected to increase further as the incidence increases, it becomes imperative to understand the effect of cardiac surgery with CPB in HIV positive subjects.

In the era of the HIV pandemic, studies have earlier reported poor outcomes of cardiac surgery in HIV seropositive population (Trachiotis et al, 2003, Chong, et al 2003). As a result cardiac surgery in HIV seropositive patients was performed with caution and forbidden in patients with AIDS, due to fear of postoperative risks of infection (Alejandro et al, 1993, Mestres et al 2003). Perception of poor outcomes following cardiac surgery changed after medical advances led to the introduction of highly active antiretroviral treatment (HAART). Studies thereafter reported excellent surgical outcomes in HIV seropositive patients (Farzan et al, 2006). Life expectancy and the quality of life among this population have increased significantly to the extent that surgical survival rate parallel that of HIV seronegative patients. However, for the most part, sample sizes were very small with some study reviews identifying less than ten patients (Cipriano, et al 2000). Today, with the increased number of people living with the disease, it is possible to recruit an adequate sample size to conduct larger clinical prospective studies. In addition, there is a paucity of data related to the South African context, which our study has attempted to address.

In this clinical prospective study, thirty consecutively selected HIV positive patients undergoing elective valvular heart surgery were recruited over a period of nine months. This makes this study the first and largest prospective study to be ever conducted in HIV positive patients undergoing cardiac surgery supported by CPB in South Africa. An equal sample size of HIV negative patients was recruited to serve as control.

In this study of cardiac patients undergoing valvular replacement surgery under cardiopulmonary bypass, the primary objective was to investigate and determine the correlation of systemic inflammatory response and myocardial injury between HIV positive (study group) and negative patients (control group). The aim was to determine whether the post-surgical outcomes in HIV positive patients parallel that of HIV negative patients using laboratory biomarkers. Our study reports no postoperative complications, as well as a very low overall mortality, as out of sixty-one patients, only two patients (3.3%) died (one patient in each group).

One of the patients who died did not complete data collection since she demised three hours after the operation. However this patient was not excluded from the study sample size, in order to also investigate whether or not the cause of death was related to the variables under study. Although this decreased the number of patients in the study group postoperatively, it was certified by the biostatistician as having a non-significant effect on the power of the study since the study was not investigating paired individuals but rather group population correlations. In both demised patients preoperative and postoperative variables were within the same ranges as other patients, and there was no variable or biomarkers that were profoundly high when compared to the remaining patients to associate with a possible predictive cause of death. According to medical records this patient suffered persistent ventricular fibrillation (VF) and failed cardioversion. In the second patient who demised (control group) five days after the operation, the cause of death was cited as low cardiac output syndrome (LCOS) in the intensive care unit, while still on mechanical ventilation and high dose of positive inotropic support.

Our study also reports an absence of post-operative sepsis, acute renal failure requiring dialysis, neurological complications in both groups, including HIV seropositive patients who were not on HAART treatment. In HIV seropositive patients we noted a significant decrease increase in CD4 cells postoperatively, which we found to be excessive in patients who were not taking antiretroviral treatment. Other key findings were significant differences in the postoperative duration on inotropic support, ICU stay and mechanical ventilation between the seropositive and seronegative groups. We also found that differences in preoperative and postoperative CRP levels correlated strongly with duration of mechanical ventilation in the study group.

The C-reactive protein (CRP) is a reliable indicator for the acute systemic inflammatory response (limar et al, 2003), and has therefore become a necessity in the monitoring and management of cardiac patient during the preoperative and postoperative periods (Aouifi, et al 1999). Elevated preoperative CRP levels as minimal as 5mg/L have been found to be independent risk factors associated with increased risk of complications and postoperative infections (Gianguiseppe, et al 2006). Our study showed a mean CRP of 13.48mg/L in the HIV positive group, and 13.16mg/L in the HIV negative group (Table: 4.3), but in this study, our patients in either group did not present with complications or adverse outcomes postoperatively. The CRP levels in HIV seropositive patients have been associated with the disease progression independent of CD4 lymphocyte count and the viral load (Bryan, et al 2006). Bryan et al also found that regardless of progression to AIDS, HIV positive Individuals had significantly high levels of CRP. This was not observed in our study, as both the HIV positive and negative groups had relatively equal preoperative CRP means, with statistically non-significant differences (p=0.388). The preoperative CRP levels in both groups of our study are significantly higher than the CRP level. Gianguiseppe et al (2006) found CRP to be an independent risk predictor for postoperative mortality and infection. The high levels of CRP observed may very likely be explained by the fact that the etiology for the patients with valvular heart disease (VHD) in our sample, especially since South Africa is still considered to be a developing country, is due to rheumatic fever. Studies have shown that patients suffering from chronic rheumatic valvular heart disease have increased CRP levels (Zehra, et al, 2002).

Peter, et al (2014) recently conducted a study to investigate whether CRP levels observed before and after cardiac surgery relate to postoperative myocardial damage. They found that baseline CRP level higher than 10mg/L may be used as a predictive biomarker of myocardial damage following cardiac surgery with CPB. However they used creatine kinase BM (CK-MB) biomarker to measure the degree of myocardial damage, which is a relatively poor cardiac damage biomarker because of its low sensitivity (Rice and MacDonald, 1999). In our study myocardial injury was measured using the cardiac troponin I (cTnI) biomarker. Cardiac troponin I levels have been found to an essential and sensitive biomarker in the diagnosis of myocardial damage (Rice and MacDonald, 1999). In cardiac surgery, cTnI specifically has been found to increase in all types of cardiac surgery, but it is detected in greater amounts in surgery with CPB (Khan, et al 2004). Cardiac troponins have been found to be helpful in identifying risk conditions in different clinical settings and to determine the prognosis after cardiac events (Polanczyk, et al 1998). The European society of cardiology (ESC) and American College of Cardiology (ACC)

consensus document recommends that each laboratory should determine its cut-offs for each test at the 99th centile of normal with ≤10% coefficient of variation. The theory by ESC and ACC was further analysed by Sharma et al (2004), who suggested that mean serum cTnI values between 100ng/L to 2000ng/L were indicative of myocyte necrosis or myocardial damage. In our study, due to the laboratory tests results for preoperative cTnI being recorded as <10ng/L, a preoperative troponin I category grouping was used. Patients with the preoperative troponin I of less than ten (<10ng/L) were grouped together and greater than equal to ten (≥10ng/L) were also grouped together (Table 4.3). In this study the preoperative cTnI was lower than the cut-offs range set by Sharma et al (2004), in both groups. The study observed no significant difference (p=0.489) in preoperative cTnI between the two groups.

Both acute systemic inflammatory response and myocardial injury observed after cardiac surgery have been associated with CPB events (Laffey, et al 2002 and Khan, et al 2004). In our study CPB events such as CPB duration, aortic cross-clamp duration, CPB blood transfusion, CPB total urine output and CPB peak lactate were measured and analysed between the two groups (Table 4.4).

A shorter aortic cross clamp time (<150 minutes) and CPB duration (<240 minutes) have been associated with a low risk of immediate postoperative adverse events independent of the complexity of the surgery or the patients operative risk (Juha, et al, 2009). In our study the aortic cross clamp and CPB mean durations were below the predetermined durations reported by Juha, et al (2009) in both groups. However we observed that the CPB duration and aortic clamp duration were significantly longer in the control group compared to the study group (p=0.021 and 0.026, respectively). The CPB duration and aortic cross-clamp duration are dependent mostly on the type of operation and the experience of a surgeon to do a particular operation. Therefore in this study, CPB duration results do not necessarily show any clinical significance in HIV seropositive patients have an overall shorter CPB time compared to HIV seronegative patients.

A significant difference (p=0.013) was observed between the two groups in CPB blood transfusion with HIV positive patients being transfused larger amounts compared to negative patients. This finding is similar to that of Michael et al, (2014) who reported that HIV positive patients were more likely to receive a blood transfusion compared to non-infected patients undergoing similar type of cardiac surgery. The CPB total urine output (p=0.035) was compared between the two groups, with the HIV negative passing more urine during CPB compared to

positive patients and CPB peak lactate (p=0.040) levels higher observed in the HIV negative group. The observed CPB events were further correlated with postoperative CRP and cTnI levels in both groups.

Early after cardiac surgery, in patients without clinical or laboratory signs of acute infection, CRP levels are significantly elevated as a result of the acute systemic inflammatory response due to surgery-related stress (Mara, et al 2007). The postoperative inflammatory responses have been found to influence the development of multiple organ failure including myocardial dysfunction, respiratory failure and renal dysfunction (Paparella, et al 2002). In our study, CRP levels increased significantly postoperatively in both HIV positive and negative groups (212.59 ± 23.731 and 190.68 ± 57.919, respectively). Higher postoperative CRP levels in the HIV positive group was observed compared to the HIV negative group, but the difference was not significant (p=0.115). Although the postoperative acute systemic inflammatory response (CRP level) was similar in the two groups, significant differences were observed between the two groups when CRP levels were correlated with postoperative clinical outcomes.

We observed a strong negative correlation between the CRP levels and postoperative mechanical ventilation duration in the HIV positive group (r= -0.548 and p=0.002). This was in keeping with the results from Taher, et al (2014), who also reported a significant correlation between CRP levels and mechanical ventilation duration. This was however not observed in the HIV negative group, which had a positive, non-significant correlation (r= 0.025 and p= 0.893).

Khaled and Emad, (2014) reported that elevated CRP levels postoperatively are associated with a prolonged stay in the intensive care unit (ICU) and that postoperative CRP level of about 51mg/L correlate significantly with the ICU length stay (p=0.04) duration up to 7 days. In our study this was not observed even though postoperative CRP was much higher than 51mg/L in both groups. The results showed a positive non-significant correlation (p=0.975.) in the HIV negative group and a negative non-significant correlation (p=0.229) in the HIV positive group. In addition, none of our patients required re-admission to ICU or re-intubation for mechanical ventilation after ICU discharge. Our findings may be substantiated by those from Sophie, et al (2016) and Mara et al (2007), who found that postoperative CRP levels at the time of patients discharge from ICU do not necessarily indicate any clinical post-ICU adverse outcomes.

Negative correlations between the difference in preoperative and post-operative CRP levels and perioperative parameters were observed between the two groups (Table 4.7). Further analysis was performed in order to determine whether or not preoperative variables such as age and NYHA class had directly or indirectly contributed to the negative directional correlations observed between the two groups. Mark and Stephanie (2014) studied 382 consecutive patients to determine the correlation between CRP, age and gender, as erythrocyte sedimentation rate (ESR) is known to be dependent on both age and gender. The CRP results were found to be identical in both women and men, unlike ESR which was higher in 236 women than in 146 men ($p<0.0001$). They further found no correlation between CRP and the age of a patient, in contrast to ESR which showed significant correlation ($p=0.0012$). These findings are similar to the results observed in our study where both HIV positive and negative groups showed a non-significant correlation between CRP levels and age ($p=0.716$ and 0.835, respectively) (Table 4.7). The ESR is an additional inflammatory biomarker with CRP in rheumatic fever and rheumatic heart disease (Eastham, et al (1958). However, ESR is influenced by anaemia and polycythaemia, and is therefore found to be more frequently abnormal (Gitta, et al, 2011), and therefore less reliable.

To further determine other possible predisposing factors for observed increased postoperative CRP levels, the difference between preoperative and postoperative CPR levels in both groups were correlated to preoperative and CPB variables (Table 4.7). We observed a negative non-significant ($r= -0.259$, $p=0.176$) correlation between the CRP difference and baseline NYHA dyspnoea grading in the HIV positive group, while a positive non-significant correlation was observed in the HIV negative group ($r=0.256$, $p=0.165$). The findings in the HIV positive group are in contrast to current literature which supports a positive correlation between CRP and NYHA class (Arroyo-Espliguero et al, 2004).

The duration of acute systemic inflammatory response (SIR) and mechanisms that lead to the lengthening of acute SIR in patients that have been operated on under cardiopulmonary bypass have been explored by Shinji et.al (2003). They found that the duration of the systemic inflammatory response correlates significantly with the highest level of Interlukin-6 ($r=0.724$, $p=0.0038$) and the duration of CPB ($r=0.626$, $p=0.0201$). In our study we did not find a significant correlation ($r=0.148$, $p=0.426$) between the postoperative CRP and CPB duration in the HIV negative cohort. However, in the HIV positive group, a very significant correlation was

observed (r=-0.432, p=0.019). There are other factors which affect the levels of these inflammatory markers whilst the patient is on bypass, and these are discussed forthwith.

During bypass, blood transfusions induce a second insult to the systemic inflammatory response that already exists after cardiac surgery, leading to an exacerbation of the SIR (Bilgin and van de Watering 2013). In addition, this adverse effect of transfusion, which includes immune response reactions leading to activation of the inflammatory milieu, may be more pronounced in HIV-infected patients (Hillyer, et al 1999), and may explain the strong correlation between CRP levels and CPB time.

Our study further reports correlations between the postoperative CRP levels and red blood cells transfusion during CPB in both groups as negative and non-significant in both groups (p=0.605 and 0.141 respectively). Similar trends were observed with the CPB urine output and lactate levels (Table 4.7).

The urine output of 0.5ml/kg/hr. is predictive of renal failure post CPB, and has been found to be a lethal complication associated with multi-organ failure (Khinji and Khan, 2004). The acute postoperative renal failure observed is strongly associated with postoperative inflammatory reactions (Paparella, et al 2002). Our study indeed observed a negative correlation between postoperative CRP and total CBP urine output in both groups. However these were not statistically significant (r-0.132, p=0.495 and r-.0106, p=0.570, respectively).

Furthermore, in terms of lactate levels, hyperlactatemia is common after cardiac surgery and studies have found that a lactate threshold of about 3 mmol/L at ICU admission is able to identify a population at risk of morbidity and mortality after cardiac surgery, (Jean-Michel, et al 2003). In our study we observed mean lactate level of 3.04 mmol/L in the study group and 3.87mmol/L in the control group. The statistical comparison between the two groups was significant (p=0.040). Alexander, et al (2005) reported hyperlactemia in HIV positive patients, and found that it is strongly associated with antiretroviral medication; however in this study preoperative baseline lactate was not measured. In our study we conducted further analysis between peak CPB lactate levels and postoperative CRP. The results showed that a strong significant correlation was observed between postoperative CRP and the lactate level during CPB (p=0.007) in the study group (HIV+), but not observed in the control group (p=0.818). Our study notes the lack of published literature in this area of research and this merits additional

studies to be conducted in post CPB lactate levels in HIV positive patients to ascertain its value and implications.

Our study measured cTnI postoperatively to determine the degree of myocardial injury between the study and control groups. As earlier discussed, both groups had preoperative cTnI lower than the 100ng/L to 2000ng/L (Sharma et al 2004). However in our study, we report an exceedingly higher postoperative cTnI mean in the study group (6346.28 ng/L) and in the control group (6589.39ng/L), with no significant difference (p=0.363) between the two groups. Our findings are indeed indicative of postoperative myocardial injury due to CPB and surgery itself, since it was not observed preoperatively. This was substantiated by Khan et al (2004) and Asim et al (2009) who reported that postoperative myocardial injury is due to the acute systemic inflammatory reaction, inadequate myocardial protection and due to the heart being operated on.

In terms of postoperative clinical outcome, Imura, et al (2002), found a weak, but significant correlation between peak cTnI and clinical outcome. However, cTnI levels >1300ng/L measured two days postoperatively have been associated to be an independent predictor of in-hospital death after cardiac surgery (Sigismond, et al 2002 and Yvette, et al 2009). This was also reported by Nahum, et al (2008) who found that troponin levels exceeding 800ng/L are associated with increased major adverse cardiac events in patients without a history of preoperative myocardial infarction within 30 days of operation. In our study, further analysis were conducted between cTnI and perioperative events and our findings disputes findings by Khan et al (2004) and Nahum et al (2008), but strongly correlate to those by Imuna et al (2002). This relationship however, appears to be dependant on the type of surgery as reported by Kiyohiro et al (2010).

The relationships of other CPB perioperative parameters had various effects on biochemistry and clinical outcome. Kiyohiro et al (2010) reported a very significant correlation between aortic cross clamp time and cTnI (p=0.0038). This was not observed in our study, as we observed a non-significant correlation between postoperative cTnI and the duration of the aortic cross clamp (p= 0.656 and 0.195 respectively).

Siaplaouras et al (2001) reported significant correlation between postoperative cTnI and inotropic support after cardiac surgery. Similarly in our study we observed a significant positive

correlation between postoperative cTnI and postoperative inotropic support (p=0.040) in HIV positive group, however this was not observed in HIV negative group (p=0.622).

Kiyohiro et al (2010), who reported significant correlation between postoperative cTnI and ICU stay length. This was not observed in our study, as we a report non-significant correlation between postoperative cTnI and ICU stay duration in both groups, (p=0.262 HIV negative, and 0.395 in the HIV positive group).

Studies have proven that CD4 cells levels determine the progression of HIV in infected individuals, in other words, deterioration in the patients' immune response (Deneve et al, 2010). In our study the Wilcoxon-signed rank test for dependent samples was employed to determine the difference preoperative and postoperative CD4 cells count, and, as expected, was found to be significantly lower post-operatively (p=0.001), and mirror those reported by Alejandro, et al (1993). Further analysis on HIV positive patients taking HAART versus those who were not on therapy, was performed in order to quantitatively assess differences in response to CPB.

Of all variables tested, only the CPB duration was statistically longer in those subjects who were not on HAAART therapy (p= 0.031). A higher drop in CD4 cells in patients not taking HAART was observed suggesting that patients with suppressed HIV viral load using HAART experience less changes in CD4 cells levels compared to those with high preoperative HIV viral load (Table 4.11).

The mean CD4 cells difference was analysed and correlated to age, and a positive non-significant correlation (p=0.741) was observed (Table 4.9). Then the mean CD4 cells difference was correlated to baseline NYHA grading (p=0.775). The study results showed a positive weak correlation (p=0.177) between mean CD4 cells and CPB duration. These findings suggest that even though there is a significant change in CD4 cells level postoperatively, these changes however are not influenced by patient preoperative variables and CPB duration. The mean CD4 cells difference was correlated to intensive care unit stay duration, a weak positive correlation was observed. These findings are similar to those of Cacala, et al (2006) who reported that in HIV-positive surgical patients, CD4 counts seem to have no relation with in-hospital outcome. Unfortunately, we were not able to establish that HAART is associated with improved outcomes following cardiac surgery with CPB in HIV positive patients, due to a short postoperative follow up period.

CHAPTER SIX: CONCLUSION

6.1 Conclusion

In the early years of the HIV epidemic, the high mortality related to this disease was a major concern, with respect to any potential benefit that might be achieved after cardiac surgery. The introduction of modern drug regimens for the treatment of HIV infection and AIDS has led to a significant increase in the life expectancy of these patients and a steady increase in referrals for cardiac surgery. Our study has shown that cardiac surgery can be performed safely on patients who are infected with HIV with no post-operative complications. Furthermore, the response to CPB post-operatively does not seem to differ significantly in subjects with HIV, as compared to those who are not infected.

In addition, this study has shown that cardiac surgery may be safely performed even in subjects who are not on HAART therapy with no postoperative complications compared to those on HAART. However we found a significant drop in CD4 cells postoperatively in HIV positive patients, but this does not seem to affect the short-term surgical outcomes.

In conclusion, this investigation shows that the acute systemic inflammatory response in HIV positive patients is similar to that of HIV negative patients, with similar patterns of CRP levels, ESR levels, as well as myocardial injury measured using cTnI. To our knowledge this is the first study to be conducted prospectively in South Africa, we indeed bridged the gap between the clinical outcomes observed retrospectively by Blyth et al (2006). Thereby we confirm that laboratory biomarkers are significantly increased after cardiac surgery with CPB; however they do not seem to indicate any short-term complications or poor surgical outcomes.

6.2 Strengths and Limitations

The strengths of the study were its prospective design and appropriately powered sample size. In addition, both groups were similar similarly matched for age, NYHA grading, preoperative biochemical markers and preoperative ejection fraction and so can attribute significant differences between the two groups due to the cardiopulmonary bypass processes itself.

The limitation of our study centred mostly around lack of finance to employ other resources such cardiac function analysis using echocardiographically postoperatively, as well as inability to test our study biomarkers daily consecutively for three days after the operation. Lastly we could not measure CD4 cells in HIV negative patients for comparison with significant drop observed in HIV positive patients.

6.3 Recommendations

This study found various opposing correlations between HIV positive and negative patients, as discussed in our discussion, and we could not find any published literature to justify our findings. We there feel that although clinically these subject groups seem to be identical, there is still some fine details that have not been explored. We there recommend that larger prospective studies be conducted around this area of research, especially those that can go beyond our limitations.

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Appendix A: Biostatistician letter

UNIVERSITY OF
KWAZULU-NATAL

20 February 2013

TO WHOM IT MAY CONCERN

This is to confirm that Mr M Gojo has consulted with me on his research proposal for the M Tech (Clinical Technology). We have discussed the research proposal and the study is statistically sound and viable.

In order to test whether there is a difference in the measured markers for systemic inflammatory response for HIV positive patients compared to HIV negative patients, a two sample t-test for independent groups will be used.

To investigate whether the risk of myocardial infarction in the HIV positive group is larger than the risk for the HIV negative group, a z-test for two proportions will be used. (The z-test is based on the normal distribution and is a test for the equality of two proportions, in this case the risk of myocardial infarction or inflammatory response).

In order to test for the change in troponin levels before surgery (base line) and after surgery (3hours after surgery and the 24 hours after surgery) for the two groups, a longitudinal model with group, time and a group*time interaction will be fitted to determine whether there are group differences, time differences and whether there is an interaction effect.

The statistical software that will be used is SPSS and SAS version 9.3.

Yours faithfully,

[redacted]

Professor GB Matthews

School of Mathematics, Statistics and Computer Science,

Westville Campus
Postal address: Private Bag X54001, Durban, 4000, South Africa
Telephone: +27(0)31 2603011 Facsimile: +27(0)31 2601009

Appendix B (1): English consent

Department of Biomedical and Clinical Technology
Faculty of Health Sciences
P O Box 1334, DURBAN, 4000

Appendix B(1)

Letter of Information and Consent

Title of the Research Study:

Investigation of acute systemic inflammatory response and myocardial injury after cardiac surgery in patients infected with human immunodeficiency virus.

Principal Investigator:

Mr Mawande Gojo, student enrolled for the Master's Degree: Clinical technology (Cardiovascular Perfusion) at Durban University of Technology.

Brief Introduction and Purpose of the Study:

You are invited to be a volunteer for a research study. The information in this letter will help you understand what the research is about and how it will benefit your quality of surgery. If there is any questions, which are not clearly explained in this letter, do not hesitate to ask the promoter or investigator.

The purpose of this study is to determine variations in the generation of acute systemic inflammatory response and myocardial injury between HIV infected patients undergoing heart surgery and those who are HIV negative. If there are variations between the two groups then this trial will help the medical team to prepare related drugs as prophylaxis for that particular group of patients when undergoing heart surgery. Hence this study may help improve postoperative management of patients after heart surgery, with better understanding of HIV positive patients and heart surgery.

Outline of the Procedures:

Before surgery blood samples of approximately 1-2.5ml will be taken from one of your blood vessel in your arm by the cardiothoracic doctor during routine preoperative blood tests. These blood samples will be analyzed using laboratory equipment to obtain the levels of serum troponin I and C-reactive protein. Other blood samples will be taken after the surgery

from a catheter which is routinely inserted during surgery therefore you will not endure any pain. Only 3 samples of blood will be needed in a course of 3days i.e. one before surgery, another one on the day of surgery, and the last one next day after surgery. Blood samples will be discarded after being analyzed.

Risks or Discomforts to the Subject:

There are no additional risks or side effects involved because blood sampling will be done during routine blood samples before heart surgery. After blood samples will be taken from a catheter which is routinely inserted during surgery therefore you will not endure any discomfort or pain.

Benefits:

The new information gained from the study will help to identify patients who are at high risk and possibly establish better management so that they may have a better outcome associated with surgery.

Reason/s why the Subject May Be Withdrawn from the Study:

As a candidate in this research, you will undergo elective on pump cardiac surgery. Any changes or combined procedure(s) other than heart surgery will result in withdrawal from the study.

Remuneration:

There will be no remuneration for the participant.

Costs of the Study:

The patient will be liable for the normal costs for the routine medical procedures needed; no extra costs will be added.

Confidentiality:

All information obtained in this trial will be strictly confidential. Data that may be reported in the scientific journals or published will not include information that will identify you as a patient in this study.

Research-related Injury:

There will not be any additional research related injuries other than standard routine injuries when undergoing heart surgery. Your withdrawal at any time will not affect your medical treatment.

Persons to Contact in the Event of Any Problems or Queries:

Mr Mawande Gojo	Dr R Prakaschandra	Dr Yakeen Harilall
Principal Investigator	Supervisor	Co/supervisor
0733219435	031 373 5291	0832778586

Statement of Agreement to Participate in the Research Study: (I,……subject's full name(s), ID number……., have read this document in its entirety and understand its contents. Where I have had any questions or queries, these have been explained to me by ……to my satisfaction. Furthermore, I fully understand that I may withdraw from this study at any stage without any adverse consequences and my future health care will not be compromised. I, therefore, voluntarily agree to participate in this study.

Subject's name ……..…….. **Subject's signature**……..…….

Date:……..……

Researcher's name ……..…... **Researcher's signature**……..……

Date:……..……

Witness name ……..……. **Witness signature**……..…….

Date:……..……

Supervisor's name……..... **Supervisors signature**……

Date:……..……

Appendix B (1): Isizulu consent

Department of Biomedical and Clinical Technology

Faculty of Health Sciences

P O Box 1334, DURBAN, 4000

Appendix B (2)
Isivumelwano Sokungenela Ucwaningo

Iihloko socwaningo:

Ucwaningo ngokushisa kumithambo ehambisa igazi nokulimala kwentliziyo ngemuva kokuhlinzwa kwentliziyo kwizigulane ezinesifo sesandulela gculazi

Umcwaningi:

Mnumzane uMawande Gojo, umfundi owenza isidanga sakhe seMaster's kwiClinical Technology esikhugweni semfundo ephakeme saseDurban University of Technology.

Isingeniso nentloso yalolucwaningo:

Niyanxenxwa ukuba yingxenye yocwaningo. Okubhalwe kulencwadi kuzonisiza ukwazi kahle ukuthi ucwaningo lolu olwani nokuthi luzokwenza kanjani ubungcono ezingeni lokuhlinzwa kwakho. Uma kunemibuzo, engachazekile kahle kulencwadi, ungabuza umphathi wohlelo noma umcwaningi.

Inhloso yalolucwaningo ukuthola ukuthi ingabe izigulani ezihlinzwa zinesandulela ngculazi zisengcupheni ngaphezu kwalezi ezingelalo. Lokhu kuzojongwa ngendlela ezimbili, ekuwukujonga iTroponin I neC-reactive protein, nekuyizona ezichaza ngoku hlukumezeka kwamasosha omzimba kudaleke umshiso kanye nokulimala kwentliziyo ngesikhathi sokuhlinzwa.

Okudingeka kwisiguli:

Njengomunye wabantu abazobamba iqhaza kulolucwaningo, kuzodingeka ukuthi kudontswe igazi elincane kumthambo wegazi ngaphambi kokuba uye kohlinzwa. Udokotela ongumhlinzi wentliziyo nguyena ozodontsa leligazi njengentlala yenzeka kwiziguli ezisuke zizohlinzwa intliziyo. Lezigazi lizayohlolwa kwindawo yokuhlola igazi, bese kujongwa iTroponinI neC-reactive protein egazini. Amanye amagazi azothathwa kusetshenziswa ulayini wetube ozobe

ufakwe emthanjeni wegazi langa ngesikhathi sokuhlinzwa kwakho, ngokoke ngeke ubuzwe ubuhlungu uma kuthathwa lamagazi. Kulolucwaningo kuzodingeka amagazi amathathu, nokuzothi alahlwe uma eqeda kuhlolwa.

Ubungozi balolucwaningo:

Abukho ubungozi obengezwa yilolucwaningo, ngaphezu kwalolu olujwayelekile uma kwenziwa uhlinzo ntliziyo.

Okuzozuzeka kulolucwaningo:

Olwazi olusha olungatholakala ngalolucwaningo, lungasiza kakhulu ekunakekeleni izigulani ezihlinzwa sinesandulela ngculazi.

Ilungelo lokungela ucwaningo, nokungenza okhishwe:

Ukubamba kwakho iqhaza kulolucwaningo kungokokuzikhethela. Ukuyeka kwakho ukuba yingxenye yalolucwaningo ngeke kuphazamise ukulashwa kwakho. Akukho bungozi obukhona.

Umkomelo:

Awukho umkomelo ozotholakala ngokubamba iqhaza kulolicwaningo.

Kuyimfihlo:

Lonke ulwazi oluzotholakala kwimibuzo yalolucwaningo luzoba imfihlo. Ulwazi oluyoqokelelwa kwabanye abantu lufakwe emiqulwini yocwaningo, angeke luqukathe imininingwane engadalula wena njengesiguli.

Abantu ongabafonela uma unenkinga noma unemibuzo:

Mr Mawande Gojo	Dr R Prakaschandra	Dr Yakeen Harilall
Umcwaningi	obheke ucwaningo	umsizi wobheke ucwaningo
0733219435	031 373 5291	0832778586

Ingcwandi yesivumelwano sokungenela ucwaningo:

(mina……igama lovuma ukungenela ucwaningo,
Inombolo kamasizi……..ngikufundile okubhalwe kulelidokodo, ngikuzwile nganilisekile ngokubhalwe kulona. Lapho benginemibuzo nokungabaza, ngichazwelwe ngu…….nganeliseka. Ngephezulu ngiyazi ukuthi ngivumelekile nangesiphi na iskhathi uma ngifuna ukuhoxa kulolucwangingo, ngaphandle kokuthi ukunakekelwa kwempilo yam kubesengcupheni, ngako ke ngiyazikhethela mina ukubamba iqhaza kulolucwaningo..

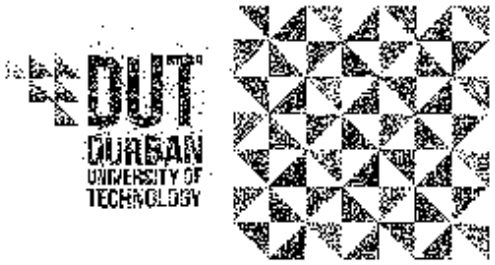
Igama longenela ucwaningo …….. ukusayina…..……...
Umhla……

Igama lomcwaningi ……..…..... ukusayina……..……
Umhla…….

Igama lofakazi……..……. ukusayina……...
Umhla……..……

Igama lobhekene nocwaningo…… ukusayina…….
Umhla……..……

Appendix C (1): IREC Full ethics approval



Institutional Research Ethics Committee
Faculty of Health Sciences
Room [illegible], Franklin Street Site
Steve Biko Campus
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www.dut.ac.za

12 February 2015

IREC Reference Number: **REC 96/14**

Mr M K E Gojo
P O Box 22
Maluti
4740

Dear Mr Gojo

An investigation of acute systemic inflammatory response and myocardial injury after cardiac surgery in patients infected with Human immunodeficiency virus using clinical and inflammatory markers

I am pleased to inform you that Full Approval has been granted to your proposal REC 96/14.

The Proposal has been allocated the following Ethical Clearance number **IREC 014/15**. Please use this number in all communication with this office.

Approval has been granted for a period of one year, before the expiry of which you are required to apply for safety monitoring and annual recertification. Please use the Safety Monitoring and Annual Recertification Report form which can be found in the Standard Operating Procedures [SOP's] of the IREC. This form must be submitted to the IREC at least 3 months before the ethics approval for the study expires.

Any adverse events [serious or minor] which occur in connection with this study and/or which may alter its ethical consideration must be reported to the IREC according to the IREC SOP's. In addition, you will be responsible to ensure gatekeeper permission.

Please note that any deviations from the approved proposal require the approval of the IREC as outlined in the IREC SOP's.

Yours Sincerely

[redacted]

Professor M N Gibbya
Deputy Chairperson: IREC

Appendix C (1): IREC permission letter

Institutional Research Ethics Committee
Faculty of Health Sciences
Room M6.49, Medilink School Block
Steve Biko Campus
Durban University of Technology

P O Box 1334, Durban, South Africa, 4001

Tel: 031 373 2900
Fax: 031 373 2407
Email: [redacted]
http://www.dut.ac.za/research/ethics/institutional_research_ethics

www.dut.ac.za

5 May 2015

IREC Reference Number: **REC 96/14**

Mr M K F Gojo
P O Box 22
Maluti
4740

Dear Mr Gojo

An investigation of acute systemic inflammatory response and myocardial injury after cardiac surgery in patients infected with Human immunodeficiency virus using clinical and inflammatory markers

The Institutional Research Ethics Committee acknowledges receipt of your gatekeeper permission letter.

Please note that you may now proceed with research on the proposed project.

Yours Sincerely,

[redacted]

Prof J K Adam
Chairperson: IREC

DUT DURBAN UNIVERSITY OF TECHNOLOGY
2015 -05- 05
INSTITUTIONAL RESEARCH ETHICS COMMITTEE
P O BOX 1334 DURBAN 4000 SOUTH AFRICA

Appendix D: IALCH clinical manager approval

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

Inkosi Albert Luthuli Central Hospital
Ethekwini Health District
Office of the Medical Manager
Private Bag X 03, Mayville, 4058
800 Bellair Road, Mayville, 4058
Tel.: 031 240 1059,
Fax.: 031 240 1050
Email.:ursulanun@ialch.co.za
www.kznhealth.gov.za

Reference: IREC 014/15
Enquiries: Medical Management

31 March 2015

Mr M K E Gojo
Department of Cardiothoracic Surgery
IALCH

Dear ~~Dr~~ MR Gojo

RE: PERMISSION TO CONDUCT RESEARCH AT IALCH

I have pleasure in informing you that permission has been granted to you by the Medical Manager to conduct research on: **An investigation of acute systemic inflammatory response and myocardial injury after cardiac surgery in patients infected with Human immunodeficiency virus using clinical and inflammatory markers.**

Kindly take note of the following information before you continue:

1. Please ensure that you adhere to all the policies, procedures, protocols and guidelines of the Department of Health with regards to this research.
2. This research will only commence once this office has received confirmation from the Provincial Health Research Committee in the KZN Department of Health.
3. Kindly ensure that this office is informed before you commence your research.
4. The hospital will not provide any resources for this research.
5. You will be expected to provide feedback once your research is complete to the Medical Manager.

Yours faithfully

[redacted]
.....
Dr M Letebele
Medical Manager

Appendix E: IALCH Cardiothoracic department approval

DEPARTMENT OF HEALTH

PROVINCE OF KWAZULU-NATAL

INKOSI ALBERT LUTHULI CENTRAL HOSPITAL

DEPARTMENT OF CARDIOTHORACIC SURGERY
800 Bellair Road, Mayville, 4091
Private Bag X03, Mayville, 4058
Tel.: 031 240 2114, Fax.: 031 240 2113
Email.: LeahGov@ialch.co.za

30 March 2015

Dear Dr Ramdass
Clinical Care Manager
Inkosi Albert Luthuli Central Hospital

RE : Research ; Inflammatory Markers in Bypass Patients

Dear Priscilla

This is to state that Mr Mawande Gojo, a Perfusionist at IALCH will be conducting research on patients undergoing bypass. I aware of the study and have given him permission. He will be making a formal application to you with the protocol for official permission.

Kind Regards,

R Madansein
Acting HOD Cardiothoracic Surgery

Appendix F: EThekwini Health District approval

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

Health Research & Knowledge Management sub-component
10 – 103 Natalia Building, 330 Langalibalele Street
Private Bag x9051
Pietermaritzburg
3200
Tel.: 033 – 3953189
Fax.: 033 – 394 3782
Email.: hrkm@kznhealth.gov.za
www.kznhealth.gov.za

Reference : HRKM60/15
NHRD Ref.: KZ_2015RP0_703
Enquiries : Ms G Khumalo
Telephone : 033 – 395 3189

Dear Mr M.K.E. Gojo

Subject: Approval of a Research Proposal

1. The research proposal titled '**An investigation of acute systemic inflammatory response and myocardial injury after cardiac surgery in patients infected with Human immunodeficiency virus using clinical and inflammatory markers**' was reviewed by the KwaZulu-Natal Department of Health (KZN-DoH).

The proposal is hereby **approved** for research to be undertaken at Inkosi Albert Luthuli Central Hospital.

2. You are requested to take note of the following:
   a. Make the necessary arrangement with the identified facility before commencing with your research project.
   b. Provide an interim progress report and final report (electronic and hard copies) when your research is complete.

3. Your final report must be posted to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za

For any additional information please contact Ms G Khumalo on 033-395 3189.

Yours Sincerely

[redacted]

Dr E Lutge
Chairperson, Health Research Committee
Date: 24/ 05 / 15

Appendix G: Data recording template

An investigation of acute systemic inflammatory response and myocardial injury after cardiac surgery in patients infected with Human immunodeficiency virus using clinical and inflammatory markers.

Appendix G

DATA SHEET

PARTICIPANT CODE		DATE		GENDER		AGE	

PREOPERATION

TYPE OF SURGERY	EXAMINATION	C-REACTIVE PROTEIN	TROPONIN I	LATEST CD4 CELLS COUNT	ESR	MEDICATION	OTHER DISEASES
	EF=						
	NYHA=						
	TYPE OF Dx=						

INTRAOPERATION

MYOCARDIAL PRESERVATION	BLOOD PRODUCTS TRANSFUSED	DRUGS ADMINISTERED	AORTIC CLAMP DURATION	CPB DURATION	PEAK CPB LACTATE
			TIME ON:	TIME ON:	
			TIME OFF:	TIME OFF:	
			DURATION:	DURATION:	

POSTOPERATION

DURATION ON INOTROPIC SUPPORT	DURATION OF MECHANICAL VENTILATION	C-REACTVE PROTEIN 24-48 HOURS	TROPONIN I 24-48 HOURS	ERYTHROCYTE SEDIMANTATION RATE	CD 4 CELLS COUNT	CLINICAL ASSESSMENT

1