An Evaluation and Comparison of Metabolic and Clinical Changes in Patients with Acute Coronary Syndromes Undergoing On-Pump and Off-Pump Coronary Artery Bypass Surgery

Dissertation submitted in fulfilment of the degree Magister Technologiae Clinical Technology

Altia Crous

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Dissertation submitted in fulfilment of the requirements of the degree:

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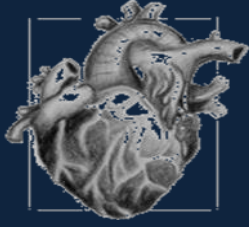Central University of Technology

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I, **ALTIA CROUS**, do hereby declare that this research project submitted to the Central University of Technology for the degree **MAGISTER TECHNOLOGIAE CLINICAL TECHNOLOGY** is my own independent work that has not been submitted to any institution by me or any other person in fulfilment of the requirements for the attainment of any qualification.

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Signature   **Date**

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Abbreviations / Acronyms / Symbols

%   percentage

≥   greater than or equal to

↑   increased

°C   degrees Celsius

<   less than

>   more than

ACS   acute coronary syndrome

ACTH   adrenocorticotrophic hormone

CABG   coronary artery bypass grafting

CAD   coronary artery disease

CHD   coronary heart disease

CHF   chronic heart failure

CPB   cardiopulmonary bypass

Cx   circumflex

ECG   electrocardiogram

FFR   fractional flow reserve

FMC   first medical contact

GI   gastro intestinal

H   hour

HL   Hyperlactatemia

IV   intra venous

kg   kilogram

LAD   left anterior descending

LDL   low density lipoprotein

LMWH   *low-molecular-weight heparin*

LV   *left ventricle*

mg   *milligram*

MI   *myocardial Infarction*

min   *minute*

NSTEMI   *non ST elevation myocardial infarction*

O₂   *oxygen*

OMT   *optimal medical therapy*

OPCAB   *off-pump coronary artery bypass*

PCI   *percutaneous coronary intervention*

RCT   *randomised controlled trial*

SIRS   *systemic inflammatory response syndrome*

STEMI   *ST segment elevation myocardial infarction*

SYNTAX   *synergy between percutaneous coronary intervention with TAXUS drug-eluting stent and cardiac surgery*

U   *units*

UA   *unstable angina*

ug   *microgram*

UH   *unfractionated heparin*

VD   *vessel disease.*

Important Definitions

Acute Coronary Syndrome	ACS is a series of conditions which include chest discomfort or any other symptoms caused by decreased oxygen supply to the myocardium. Coronary artery disease caused by erosion, fissuring, or rupture of a plaque (American Heart Association 2004).
Anti-Inflammatory	Reducing inflammation by acting on body responses, without directly antagonizing the causative agent (WebMD, 2006).
Atherogenesis	Patients with occlusive atherosclerotic vascular diseases regularly develop collateral blood vessels that bypass areas of arterial obstructions. The growth of these collateral arteries has been termed "arteriogenesis" (Cai and Schaper, 2008).
Atherosclerosis	Atherosclerosis is a condition of progressive thickening and hardening of the walls of medium-sized and large arteries in which cholesterol, fat, calcium, and other substances build up in the walls of arteries (Medicinenet.com, 2011).
Atherothrombosis	A condition in which a thrombus originates in an atheromatous blood vessel (http://medicaldictionary.thefreedictionary.com, 2007).
Coronary Artery Bypass Graft (CABG)	Coronary artery bypass graft (CABG) surgery is a surgical procedure performed to alleviate angina symptoms and reduce the risk of death as a result from coronary artery disease. Veins are grafted to the diseased coronary artery to restore coronary circulation of oxygen rich blood (Medicinenet.com, 2011).
CABG Off-Pump	Coronary artery bypass graft surgery done without the use of a heart-lung machine (Medicinenet.com, 2004).
CABG On-Pump	Coronary artery bypass graft surgery done with the use of a heart lung machine (Medicinenet.com, 2004).
Cardiopulmonary Bypass	A procedure to mechanically circulate and oxygenate the blood while surgery is performed on the heart, thus providing a motionless, bloodless operating field for the surgeon to operate. Draining oxygen poor blood from the heart through the heart-lung machine, and then returning oxygen rich blood back to the body (Medicinenet.com, 2011).
Clinical Outcomes	A reflection of the data obtained from the result of a treatment procedure (Whitcomb, 2005).

Complications	A secondary disease or problem that develops in the course of a primary disease or condition and arises either as a result of it or from independent causes (Merriam-Webster, 2011).
Coronary Heart Disease	Narrowing of the small blood vessels that supply blood and oxygen to the heart. Coronary heart disease is usually caused by a condition called atherosclerosis (MedlinePlus, 2010).
Coronary Plaque	A coronary plaque consists of fatty substances, cholesterol, waste products from the cells, calcium, and fibrin. The plaque formation process stimulates the cells of the coronary artery wall to produce substances that accumulate in the inner layer. Fat builds up within these cells and around them. The inner layer of the artery wall thickens, decreasing the artery's diameter and blood flow and oxygen delivery is decreased (http://medical-dictionary.thefreedictionary.com, 2007).
Endothelial Dysfunction	Physiological dysfunction of normal biochemical processes carried out by endothelial cell, the cells that line the inner surface of all blood vessels, arteries and veins. Compromise of normal function of endothelial cells is characteristic of endothelial dysfunction. Normal functions of endothelial cells include mediation of coagulation, platelet adhesion, immune function, control of volume and electrolyte content of the intravascular and extravascular spaces (www.websters-online-dictionary.org).
Hemodynamics	Hemodynamics is the study of all parameters influencing blood flow or circulation (Medilexico, 2006).
Hyperlactatemia	Increased levels of lactic acid in the blood (http://medical dictionary. thefreedictionary.com, 2007).
Hypoperfusion	Decreased blood flow through an organ, consequently there is a decrease in oxygen delivery. If hypoperfusion is prolonged it may cause cellular dysfunction and even death (http://medical-dictionary.thefreedictionary.com, 2007).
Inflammation	The body's response to either invading foreign substances (such as viruses or bacteria) or to direct injury of body tissue (http://medical-dictionary.thefreedictionary.com, 2008).
Morbidity	Loss of physical or psychological well-being, resulting from disease, illness, injury, or sickness, especially where the affected individual is aware of their own state (Merriam-Webster, 2011).
Mortality	The state or condition of being subjected to death, a fatal outcome (MedicineNet.com, 2011).
NONSTEMI	These patients may have symptoms indistinguishable from Unstable Angina

	(UA). There will always be a significant rise in serum markers to levels that are diagnostic of Myocardial Infarction (MI). This includes patients presenting with increased serum levels of creatine kinase, troponin I or troponin T, with no ST-segment elevation but with ST-segment depression or T-wave inversion (Banas, 2004).
Pathophysiology	The physiology of abnormal states; specifically: the functional changes that accompany a particular syndrome or disease (Merriam-Webster, 2011).
Pro-Inflammatory	Tending to cause inflammation (Medicinenet.com, 2003).
STEMI	It most often arises from the sudden, total occlusion of a coronary artery by a thrombus causing a trans mural Myocardial Infarction (MI) that may progress to infarction within 3 – 6 hours. The presence of ST-segment elevation on the ECG suggests complete occlusion of a coronary artery and Q waves usually develops. The management of STEMI differs dramatically from that of unstable angina and NONSTEMI. The primary medical treatment of STEMI is early reperfusion (Dalby, 2001).
ST Segment	Refers to a specific portion of an electrocardiogram (ECG), which is a graphic representation of heart beats. This segment on the ECG suggests that a heart attack is occurring when it is elevated away from the baseline (so called ST-elevation Myocardial Infarction (MI) or STEMI) (http://medical-dictionary.thefreedictionary.com, 2008).
Unstable Angina	Chest pain or discomfort that is unforeseen and usually occurs while at rest. The discomfort may be more severe and prolonged and it may be a person's first angina. Unstable angina is often accompanied by shortness of breath, indigestion and/or dizziness but is not associated with muscle damage but may progress rapidly to a heart attack (http://medical-dictionary.thefreedictionary.com, 2008).

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Summary

The best approach to surgical myocardial revascularization remains controversial. It is already known that an inflammatory response exists due to several factors related to the use of CPB. However, surgical trauma itself also contributes to the inflammatory response. Thus, a physiological stress response which leads to an increase in pro-inflammatory markers still remains during OPCAB surgery.

Cardiac surgery induces a wide range of endocrinological, metabolic, immunological, haematological and hemodynamic changes. Hemodynamic and metabolic optimization is of daily importance in the hospital environment.

Hypoperfusion resulting in increased lactate levels is associated with high post-operative morbidity and mortality. Lactate is also often used to predict clinical outcomes and complications but controversy remains about using this measure because of discrepancies in reference intervals and cut-off points.

The aim of the study was to evaluate how metabolic and clinical changes relate to the incidence of complications and clinical outcomes in ACS patients undergoing on-pump and off-pump CABG surgery.

Sixty patients diagnosed with ACS who received CABG surgery were recruited to participate in the study (30 patients on-pump and 30 patients off-pump). Patients not receiving isolated CABG surgery were excluded from the study. Comparisons between the two groups were made with reference to the intra-operative and post-operative metabolic data, intra-operative hemodynamic data and post-operative clinical outcomes/complications.

Irrespective of surgical technique, the 60 patients were divided into two groups, patients with lactate levels <5mmol/L or patients with lactate levels >5mmol/L. Comparisons between the two groups were made with reference to the intra-operative and post-operative metabolic data, intra-operative hemodynamic data and post-operative clinical outcomes /complications.

Intra-operative metabolic data indicated 11 (37.0%) on-pump patients and 6 (20.0%) off-pump patients had peak lactate levels of >5mmol/L during cardiac surgery. The difference between the proportions of on- and off-pump patients with peak lactate levels of >5mmol/L was statistically significant (p<0.05). However, since the study was not powered for this comparison, the difference cannot be considered clinically relevant.

Variables for the acid-base balance, HCO3- and BE (B), showed statistically significant differences (p<0.05) between the lactate < 5mmol/L group and the lactate > 5 mmol/L group. Intra-operative hemodynamic data showed statistically significant differences between the on-pump and off-pump groups for all hemodynamic variables (p<0.05) for most part of the surgery.

Post-operative metabolic data showed statistically significant differences (p<0.05) between the on-pump and off-pump groups for acid-base balance variables, pH, HCO3- and BE (B) from admission to ICU until 4 hours post-operatively.

The metabolites, glucose and lactate, showed statistically significant differences (p<0.05) between the on-pump and off-pump groups from admission to ICU until 12 hours post-operatively.

Despite the fact that elevated lactate levels have been described to be associated with adverse outcomes in paediatric- as well as general intensive care admission, no specific lactate level has been identified as a reliable indicator of adverse outcomes in adult coronary artery bypass surgery.

Lactate values for the on-pump group were significantly higher during the immediate post-operative period (p<0.05). Pulsatile flow is converted to laminar flow during on-pump CABG resulting in vasoconstriction and a redistribution of blood flow away from the peripheral tissue and the splanchnic circulation, creating an environment for increased lactate levels in the tissue.

We hypothesized that a lactate value of >5mmol/l may provide clinicians with an early indication of a patient's likelihood of experiencing various complications. Both groups recovered to lactate levels of <2mmol/L by the 24th hour post-operatively. According to literature if a patient does not recover to a lactate level of <2mmol/L within 24 hours post-operatively this is associated with an increased 60-day mortality.

The study did show a statistically significant difference between the on-pump and off-pump group with respect to lactate values. However, since the study was not powered for this comparison, the difference cannot be considered conclusive and we can only make suggestions as to the trends seen in the data. Elevated lactate levels show that they may be poorly

correlated with clinical outcomes and in order to see a more definite relationship between peak lactate levels and clinical outcomes, a larger study population will be required or perhaps a different lactate cut-off value should be considered. It may also be more useful to see if there is a positive correlation between the duration of time a patient is subjected to peak lactate levels of >5mmol/L and clinical outcomes.

We recommend larger study population and change lactate cut-off value to >10mmol/L.

Chapter 1

Introduction

The term "acute coronary syndrome (ACS)" is broadly used to describe a heterogeneous spectrum of clinical conditions. These conditions are referred to as "syndromes" for uncertainty remains whether ACS are a collection of clinical conditions sharing similar pathophysiology or are each of them associated with unique disease processes (Monaco *et al.,* 2005).

Coronary artery occlusion is commonly shared by these syndromes, decreasing or totally occluding blood flow to the myocardium causing acute myocardial ischemia resulting in chest pain due to insufficient blood supply to the heart muscle (Grech *et al.,* 2003).

Treatments for ACS includes medical treatment, percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG) with or without the use of cardiopulmonary bypass (CPB) (Warnica, 2008).

In an attempt to avoid some of the major adverse effects caused by CPB, off-pump coronary artery bypass grafting (OPCAB) has become an alternative technique for revascularisation (Pojar *et al.,* 2008). The purpose of OPCAB is to provide an alternative that is just as good, or even better, than conventional CABG with the use of CPB with respect to long-term clinical outcome. However, to date there is no clear evidence that off-pump CABG is preferable to on-pump CABG, both techniques have positive and negative attributes (Ascione *et al.,* 2003).

On- and off-pump CABG surgery are associated with hemodynamic changes very specific to each of the surgical techniques. The hemodynamic changes could result in changes in tissue metabolic activity and may in due course also influence post-operative clinical outcomes (Pojar *et al.,* 2008).

Currently, it remains very difficult to assess hemodynamic alterations and fluctuations, or to describe metabolic changes seen during CABG surgery. All of these alterations form a complex network of physiological changes and with better understanding might help clinicians to identify a sub-group of patients, at higher risk, requiring more intensive or more specific therapy to prevent other possible adverse clinical outcomes (Ngaage. 2003).

Glucose and lactate concentrations during the intra-operative and post-operative period may provide caregivers with a tool to establish whether or not metabolic demands are satisfied. It may also serve as an early warning sign of metabolic imbalances that may arise due to surgery or due to post-operative complications (Anderson *et al.,* 2011).

Therefore, the aim of the study was to evaluate and compare the metabolic and clinical changes in ACS patients undergoing on-pump and off-pump CABG surgery.

Chapter 2

Literature Review

2.1 Background

The prevalence of coronary artery disease (CAD) is increasing and is predicted to develop into a leading cause of mortality worldwide by 2020 (Ferrari *et al.,* 2009). Atherosclerosis, the beginning of CAD, is thought to underlie most acute coronary syndromes (ACS), including Unstable Angina (UA), Non-ST-Segment Elevation Myocardial Infarction (NONSTEMI) and ST-Segment Elevation Myocardial Infarction (STEMI), and is thus a major cause of overall morbidity and mortality (Grech *et al.,* 2009).

ACS can be treated either medically with pharmacological drugs or by myocardial revascularisation (CABG surgery or PCI). However, CABG surgery, with the use of CPB also known as on-pump CABG surgery, remains the golden standard as therapeutic method for myocardial revascularisation (Raja *et al.,* 2004).

Despite advances in perfusion, CPB still leads to profound physiological changes. Off-pump coronary artery bypass grafting (OPCAB) has become an alternative technique for revascularisation and avoids some of the major side effects of CPB. Both types of CABG surgery however are associated with changes in circulation. With conventional CPB, blood flow in the peripheral and splanchnic circulation is redistributed, which could lead to hypoperfusion, and in turn lead to further post-operative complications. Off-pump surgery requires stabilization of the heart and exposure of target sites, which may cause decreased blood pressure caused by handling of the heart. This change in the hemodynamic state of a patient ultimately also allows for changes in tissue metabolic activity and may also further influence the post-operative clinical outcomes (Pojar *et al.,* 2008).

Literature implicates inflammation as being central to atherogenesis and, ultimately, atherothrombosis (Anwaruddin *et al.,* 2007). As a matter of fact, the inflammatory process appears to be much more extensive than previously suspected (Libby *et al.,* 2009).

In order to develop an understanding of the metabolic and clinical sequelae encountered during on- and off-pump coronary artery bypass graft surgery (CABG), it is important to have an understanding of the underlying disease processes, as well as the existing treatment modalities for ACS. The study was designed to evaluate and compare the metabolic and clinical changes during off-pump CABG versus conventional on-pump CABG surgery.

2.2   Acute Coronary Syndrome (ACS)

2.2.1   Definition of ACS

The term "acute coronary syndrome" is broadly used to describe a heterogeneous spectrum of clinical conditions.   These clinical conditions include myocardial infarction (MI), non-ST-elevation myocardial infarction (NONSTEMI) and unstable angina (UA). These conditions are classed together under the assumption that they form a spectrum of conditions with the same underlying pathophysiology. These conditions are referred to as "syndromes" for uncertainty remains whether ACS are a collection of clinical conditions sharing similar pathophysiology or are each of them associated with unique disease processes (Monaco *et al.*, 2005).

Partial and/or total occlusion of the coronary artery is commonly shared by these syndromes, decreasing or totally occluding blood flow to the myocardium causing acute myocardial ischemia that result in chest pain due to insufficient blood supply to the heart muscle (Grech *et al.,* 2003).

2.2.2   Etiology of ACS

Fibrous plaque formation or thrombosis can cause occlusion of a coronary artery thus decreasing or totally occluding blood flow to the myocardium. A possible cause for the formation of these plaques or thrombi is atherosclerosis (Monaco *et al.*, 2005; Singh *et al.,* 2005).

2.2.2.1   Atherosclerosis

Atherosclerosis is a disease which can be asymptomatic for many decades but can lead to the initiation of acute manifestations like acute coronary syndromes, sudden death and stroke (Monaco *et al.*, 2005; Singh *et al.*, 2005). Atherosclerosis is characterized by the thickening, hardening and the loss of elasticity of the inner arterial walls due to the formation of atheromatous plaques.

2.2.2.2   Pathophysiology of Atherosclerosis and the Role of the Endothelium

Atherosclerosis begins with inflammation and immune cell activation at endothelial level, which leads to endothelial dysfunction and eventually to arterial damage and plaque-formation (Kharbanda *et al.,* 2005).

It usually presents either with a MI, unstable angina pectoris or sudden cardiac death. The cause of such acute episodes could be from a coronary thrombosis which usually originates from the rupture of an atheromatous plaque (Singh *et al.*, 2005). This process is fast tracked by risk factors such as high cholesterol levels, smoking, obesity, high blood pressure, and metabolic syndrome (Merck ©, 2008).

The process of plaque rupture is thought to underlie most acute coronary syndromes, including UA, NONSTEMI and STEMI myocardial infarctions, and is thus a major cause of overall morbidity and mortality (Gutstein *et al.,* 1999).

The atherosclerotic plaque is the origin of atherosclerosis, consisting of lipids (intracellular and extracellular cholesterol and phospholipids), inflammatory cells (macrophages and T cells), smooth muscle cells, connective tissue (collagen), thrombi and calcium deposits. All the stages of atherosclerosis, starting from the initiation through to plaque formation are considered an inflammatory response to injury (Figure 2.1).

Endothelial injury is considered to have a primary initiating or inciting role (Merck ©, 2008). Turbulent blood flow, within the coronary artery, leads to endothelial dysfunction and inhibits endothelial production of nitric oxide (potent vasodilator and anti-inflammatory molecule).

Turbulent blood flow also stimulates endothelial cells to produce adhesion molecules, which recruit and bind inflammatory cells.

The net effect is endothelial binding of monocytes and T cells, migration of these cells to the sub-endothelial space, and the initiation and maintenance of local vascular inflammatory responses. Monocytes in the sub-endothelium change into macrophages. Lipids in the blood, particularly low density lipoproteins (LDL), also bind to endothelial cells and are oxidized within the sub-endothelium. The uptake of these oxidized lipids and macrophage transformation into lipid-laden foam cells result in typical early atherosclerotic lesions known as fatty streaks (Merck ©, 2008).

The macrophages stimulate pro-inflammatory cytokines that employ smooth muscle cell migration from the media that further stimulates the attraction of macrophages. The result is a sub-endothelial fibrous plaque with a fibrous cap, which consists of intimal smooth muscle cells surrounded by connective tissue with intracellular and extracellular lipids (Faxon *et al.,* 2004).

There are several types of atheromatous plaques (Stary *et al.,* 1995).

- **type I-** early lesion, marked by foam cell infiltration. Early lesions develop within the first three decades of life in areas of turbulent blood flow. Early lesion development is stimulated by conditions such as hypertension, diabetes, high cholesterol and cigarette smoking.

- **type II-** mature into lesions with smooth muscle infiltration,

- **type III-** lipid and connective tissue deposition,

- **type IV-** early lesions grow into softer plaques with high extracellular lipid content,

- **type V-** develop a progressively thinner fibrous cap and become more susceptible to rupture.

- **type VI-** ruptured plaques with an overlying thrombus are known as complicated lesions.

When a significant amount of stenosis without sufficient collateralization is reached, these lesions result in ACS (Gutstein *et al.,* 1999).
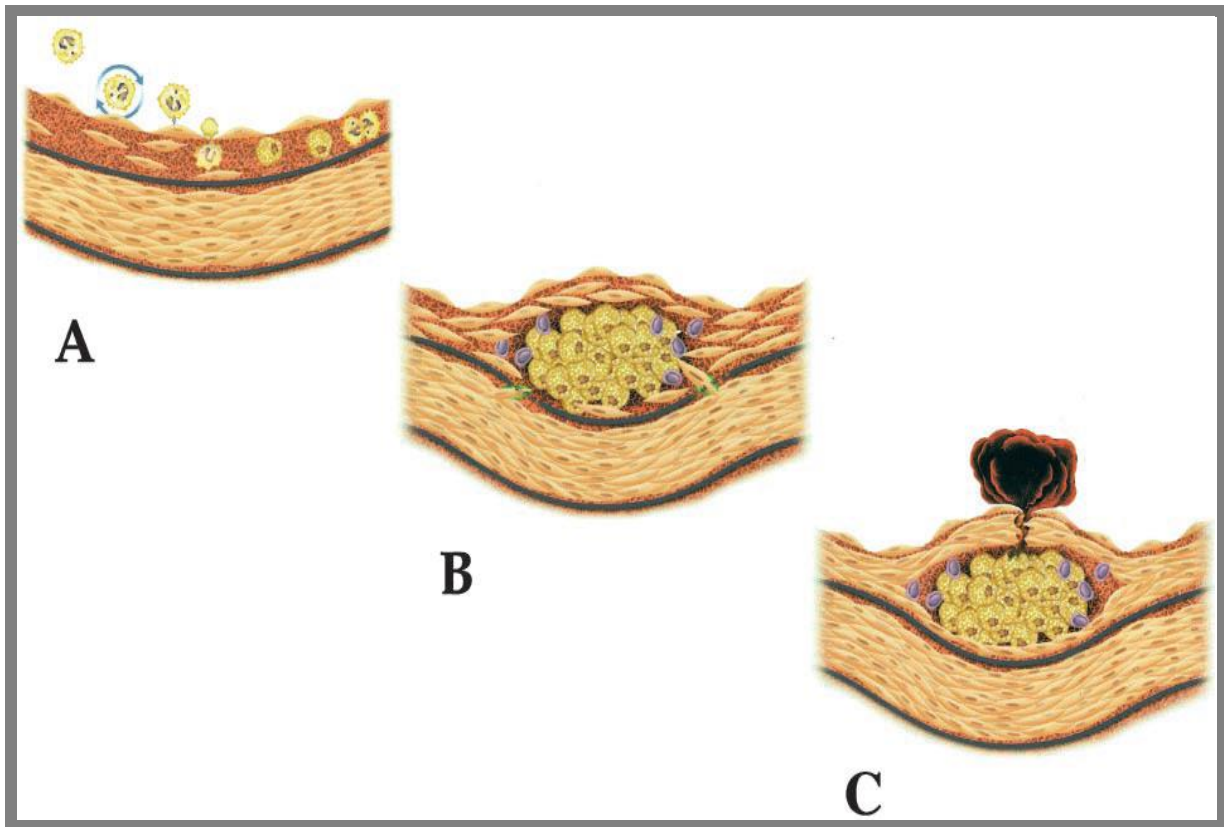
Figure 2.1   Pathophysiology of Atherosclerosis.

A, Leukocyte recruitment to the emerging atherosclerotic lesion. Blood leukocytes adhere poorly to the normal endothelium. When the endothelial monolayer becomes inflamed, it expresses adhesion molecules that bind cognate ligands on leukocytes. Selectins mediate a rolling, or saltatory, interaction with the inflamed luminal endothelium.   Integrins mediate firmer attachment. Proinflammatory cytokines expressed within atheroma provide a chemotactic stimulus to the adherent leukocytes, directing their migration into the intima. Inflammatory mediators such as M-CSF can augment expression of macrophage scavenger receptors leading to uptake of modified lipoprotein particles and formation of lipid-laden macrophages. M-CSF and other mediators produced in plaques can promote the replication of macrophages within the intima as well. **B**, T lymphocytes join macrophages in the intima during lesion evolution. These leukocytes, as well as resident vascular wall cells, secrete cytokines and growth factors that can promote the migration and proliferation of SMCs. Medial SMCs express specialized enzymes that can degrade the elastin and collagen in response to inflammatory stimulation. This degradation of the arterial extracellular matrix permits the penetration of the SMCs through the elastic laminae and collagenous matrix of the growing plaque. **C**, eventually, inflammatory mediators can inhibit collagen synthesis and evoke the expression of collagenases by foam cells within the intimal lesion. These alterations in extracellular matrix metabolism thin the fibrous cap, rendering it weak and susceptible to rupture. Cross-talk between T lymphocytes and macrophages heightens the expression of the potent procoagulant tissue factor. Thus, when the plaque ruptures, as shown here, the tissue factor induced by the inflammatory signalling triggers the thrombus that causes most acute complications of atherosclerosis (adapted from Libby *et al.,* 2009).

2.2.3   Classification and Clinical Manifestation of ACS

ACS includes clinical conditions that share a common end result referred to as acute myocardial ischemia which includes acute myocardial infarction (MI) with or without ST elevation (STEMI and NONSTEMI) and unstable angina (UA) (Monaco *et al.*, 2005). According to the American Heart Association (2004) patients that suffer from acute myocardial ischemia that received an electrocardiogram (ECG) may or may not have ST elevation (Antman *et al.,* 2004). Portions of an ECG are usually labelled P, Q, R, S and T. If an ST-segment elevation is present a rise in a particular portion of the ECG graph will occur. The majority of patients that present with an ST-segment elevation will ultimately develop a Q-wave (transmural) acute myocardial infarction. On the other hand patients who have ischemic discomfort without ST-segment elevation are either having an unstable angina (UA) or a non-ST-segment elevation (sub-endocardial) myocardial infarction that usually leads to a non-Q-wave myocardial infarction (Monaco *et al.*, 2005).

Therefore, ACS covers the spectrum of clinical conditions that range from UA to non-Q-wave myocardial infarction and Q-wave myocardial infarction.

2.2.3.1   Myocardial Infarction (MI)

MI is the death of myocardial cells that results from extended periods of myocardial oxygen deprivation. It is a culminating lethal response to unrelieved myocardial ischemia presenting as an abrupt onset of chest pain that is severe and crushing in nature and usually lasts for several hours. MI is defined according to the changes seen on the ECG which enables distinction between STEMI and NONSTEMI. For instance, if an absolute occlusion of the coronary artery is present myocardial ischemia will occur and will result in ST-segment elevation (Sheppard *et al,* 2004).

2.2.3.2 Non-ST-Segment Elevation Myocardial Infarction (NONSTEMI)

These patients may have symptoms indistinguishable from UA. There will always be a significant rise in serum markers to levels that are diagnostic of MI. This includes patients presenting with increased serum levels of creatine kinase, troponin I or troponin T, with no ST-segment elevation but with ST-segment depression or T-wave inversion (Banas, 2004). NONSTEMI is usually associated with white, platelet-rich, and only partially occlusive thrombus formation (Grech *et al.,* 2003).

2.2.3.3 ST-Segment Elevation Myocardial Infarction (STEMI)

STEMI, most often arises from the sudden, total occlusion of a coronary artery by a thrombus causing a transmural MI that may progress to infarction within 3 – 6 hours. The presence of ST-segment elevation on the ECG suggests complete occlusion of a coronary artery and Q-waves usually develops. The management of STEMI differs dramatically from that of unstable angina and NONSTEMI and primarily involves early reperfusion (Dalby, 2001).

2.2.3.4 Unstable Angina (UA)

UA is a combination of stable angina and Prinzmetal's angina and is seen in an individual with worsening CAD. UA is seen as a clinical state in which there is a change in the pattern of angina. This may be due to the onset of new symptoms, the recurrence or more severe angina and the development of chest pain at rest. It appears to result from coronary atherosclerosis, characterized by a growing, spasm-prone thrombus. As the thrombus continues to grow, episodes of UA increase in frequency and severity, therefore the individual is at increased risk of suffering irreversible damage. The pathological mechanisms of UA are similar to NONSTEMI (Sheppard *et al.,* 2004). Resting ECG may show ST-segment depression and/or T-wave inversion or transient ST-segment elevation, or may even appear normal. The serum markers usually remain within normal biological ranges or increase to diagnostic levels as in the case of MI (Dalby, 2001).

Therefore, the presentation of UA, STEMI and NONSTEMI results from a variation of the same pathological process (Sheppard *et al.,* 2004).

2.2.4   Treatment Methods for ACS

Several treatment modalities exist for the treatment of patients diagnosed with ACS. Primarily there are those treatment modalities that influence the pathogenesis of the disease (anti-platelet and anti-coagulant drugs) and there are those that provide symptomatic relief (anti-anginal agents, analgesics and sedatives). The majority of patients should receive aspirin, some should be treated in addition, with one of the heparin preparations and some of the patients should undergo revascularisation during treatment (Dalby, 2001).

Revascularisation is the restitution of blood supply to the ischemic myocardium in an attempt to limit ongoing damage, reduce ventricular irritability, and advance short-term and long-term outcomes. The treatment methodologies for revascularisation include thrombolysis with fibrinolytic drugs (pharmacological treatment), percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) with or without the use of CPB (Merck ©, 2008).

2.2.4.1   Pharmacological/Medical Treatment

The stability of ACS patients can easily deteriorate, thus the need for the rapid initiation of medical therapy. The pharmacological treatment of patients with ACS is primarily directed at the dissolution of the intracoronary thrombus with the use of anti-platelet (aspirin and clopidogrel) and anti-coagulant (heparin) therapies. Secondarily, the treatment modality is aimed at the relief of symptoms by administering anti-anginal and analgesic medications (Dalby, 2001).

A vast number of drugs are available and can be administered to treat ACS but the most commonly used drugs and their mode of action are summarized in Table 2.1 (Sheppard *et al.,* 2004; Dalby, 2001).

Table 2.1   Summary of Pharmacological Drugs Available for the Treatment of ACS (Dalby, 2001; Sheppard *et al.,* 2004)**.**

DRUGS	ACTION	DOSAGE	PRECAUTIONS
Oxygen	There is a role for O_2 in patients with ACS. O_2 therapy should be continued in patients with reduced O_2 saturation.	-	-
Aspirin	Inhibits thromboxane formation and partially inhibits platelet activation with no effect on platelet adhesion.	Initially 300mg Then 75-150mg indefinitely	GI bleeding Peptic ulcer Aspirin allergy ↑bleeding risk Antiplatelet therapy contra-indicated
Antithrombin therapies-Heparin	In combination with aspirin unfractioned heparin and low weight heparin's (LMWH) has shown to be beneficial. LMWH have a more predictable pharmokinetic profile, with a long-half life which does not require continuous infusion. The efficacy could be related to the anti-factor Xa; anti-factor IIa ratio.	Unfractioned heparin 60U/kg IV bolus to a maximum of 4000 units Then 12U/kg/h infusion to a maximum of 1000U/h Low molecular weight heparin's Fragman 120IU/kg subcut 12 hrly. Clexane 1mg/kg subcut 12 hrly	Any abnormal bleeding Thrombocytopenia-risk of bleeding
Glycoprotein IIb/IIIa inhibitors	Recommended in combination with heparin as well as aspirin as part of the initial treatment in high-risk NONSTEMI and UA patients.	180ug/kg IV over 1-2min then 2ug/kg/min infusion over 72hrs	Bleeding disorder Thrombocytopenia Puncture of a non-compressible vessel
Ticlopidine & Clopidogrel	Drug inhibits ADP-mediated platelet aggregation and therefore could possibly act in synergy with aspirin.	Initially 300mg then 75mg daily	Same as aspirin
Direct antithrombins	This inhibits thrombin activity.	Initial bolus should be 60 U/kg and the initial infusion, 12 U/kg/h	Increase in the risk of hemorrhage
Beta-adrenoceptor blockers, nitrates & calcium-channel blockers	Anti-ischemic therapy. Nitrates used to relieve pain as well as a coronary artery vasodilator. Beta-adrenoceptor blockers have multiple effects which reduce ischemia rates. In ACS they reduce myocardial work and O_2 demands, and also reduce the risk of ventricular arrhythmias.	Varies with the clinical characteristics of the patient	Bradycardia and AV block

ACS: Acute Coronary Syndrome, mg: Milligram, GI: Gastro-intestinal:↑ increase, LMWH: Low molecular weight heparins, U: units, kg: Kilogram, IV: Intra-venous, hrly: Hourly, h: Hour, NONSTEMI: Non-Stemi, UA: Unstable Angina, min: Minute.

2.2.4.2   Revascularisation

The indication for revascularisation in ACS patients depends on the identification of a culprit high-grade stenosis in a major vessel or when the coronary disease and left ventricular function has deteriorated dramatically. Revascularisation can be achieved by either PCI or by CABG surgery (Bertrand *et al.,* 2002).

Angiography is usually the start off point in order to make evidence based decisions about the revascularisation technique.   An informed decision about the optimal revascularisation technique can only be made after defining the anatomy and its associated risk features.

In cases when the anatomy is unfavourable for PCI or in case of PCI failure, CABG surgery has to be considered especially when an exceptionally large myocardial area is in jeopardy and when surgical revascularisation can be completed prior to necrosis of the affected area (William *et al.,* 2010).

2.2.4.3   Percutaneous Coronary Intervention (PCI)

PCI offers a non-surgical alternative to CABG surgery. The introduction of a stent helps to mechanically stabilize the disrupted plaque at the site of the atherosclerotic lesion and helps to re-establish blood flow to the ischemic area (Falk *et* al., 1995). Primary PCI is defined as percutaneous intervention in the setting of STEMI with no earlier or concomitant fibrinolytic treatment (William *et al.*, 2010).

However, in this study emphasis will be placed on CABG as the treatment modality of choice for patients diagnosed with ACS.

2.2.4.4   Coronary Artery Bypass Graft (CABG) Surgery

Cardiac surgery has been consistently performed by means of CPB ever since its clinical introduction during the 1950s. The first successful CPB procedure was done in 1953 and soon became the gold standard for all cardiac procedures (Westaby *et al.,* 1996).

The breakthrough in the development of CPB was not without controversy, soon issues like the disadvantages of laminar flow, cold myocardial ischemia, coagulation, complement activation,

activation of platelets and leukocytes during CPB became evident. However, research continued to seek for new and more sophisticated methods to improve patient outcomes. This led to the renaissance of cardiac surgery on the beating heart in the early 1980's (Larmann *et* al*.,* 2004).

Off-pump coronary artery bypass (OPCAB) surgery is performed on a beating heart using a cardiac stabilizer to stabilize the coronary artery and surrounding surgical field and occluding the coronary artery proximal and/or distal to the stenosis with temporary ligations. The heart and lungs continue to function throughout the surgery. Only the dependent myocardial tissue is exposed to brief ischaemia. Reardon and colleagues (1997) noted that in performing this procedure, the surgeon must consider the following:

- the accuracy and patency of the anastomosis,

- issues of incomplete revascularisation,

- hemodynamic stability, and

- long-term outcome (Stump *et al.,* 2001).

Today, CPB for the treatment of ACS patients can be performed in one of two ways either on-pump (on a non-beating heart with the aid of a heart-lung machine) or off-pump (on a beating heart without the use of a heart lung machine) (Larmann *et al.,* 2004).

A) Coronary Artery Bypass Graft (CABG) Surgery Using Cardiopulmonary Bypass (CPB)

CABG surgery is performed with the use of a heart-lung machine (on-pump CABG) when a proper medical evaluation warrants its use during cardiac surgery. This technique assures high quality anastomosis with satisfactory clinical outcomes (Dybdahl *et al.,* 2004). Nevertheless, a major complication of on-pump CABG surgery is the systemic inflammatory response which can contribute to the increase in morbidity and mortality rates.

The systemic inflammatory response is mainly triggered by the generation of shear forces from roller pumps driving blood through the bypass circuit, hypothermia as blood is expelled through the extracorporeal circuit, surgical trauma, ischemia and contact activation of plasma protein systems as circulating blood is exposed to artificial surfaces in the bypass circuit (Larmann *et al.,* 2004). CPB also initiates profound physiological alterations which include:

- Blood is brought into direct contact with large artificial surfaces,

- Pulsatile flow converted to laminar flow,

- Exposure of the heart to global ischemia with cardioplegic protection,

- The body temperature is lowered by several degrees (Larmann *et al.,* 2004).

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

B) Coronary Artery Bypass Graft (CABG) Surgery without Using Cardiopulmonary Bypass (CPB)

Since 1960 CABG surgery has been possible without the use of CPB (Stump *et al.,* 2001). This method is technically more demanding than using CPB and requires a surgeon with an innovative and more flexible attitude to create optimal operative conditions. Controversy still remains regarding the benefits of off-pump coronary artery bypass (OPCAB) surgery when compared to conventional on-pump CABG surgery (Wan *et al.,* 2004).

The rationale for the use of OPCAB/off-pump techniques is that it should be just as good as conventional surgery with regards to mortality and improvement in hospital morbidity with maintained long-term clinical outcomes. Therefore, OPCAB surgery has experienced a revival as routine heart surgery since the 1980s (Chassot *et al.,* 2004).

Developments in exposure techniques, together with pericardial traction sutures and slings, and a better perception of the hemodynamic impact of cardiac manipulation allowed broader application of OPCAB techniques. However, the manipulation of the heart for anastomosis of the circumflex (Cx) and the posterior descending artery poses a risk of inducing hypotension, impaired cardiac output, and generalized hemodynamic instability with risk of cerebral compromise and ischemia (Murkin, 2002). The corrective measures for this hemodynamic instability include an increase in volume load, use of inotropes, vasopressors, vasodilators and temporary suspension of cardiac manipulation. Occasionally severe and prolonged deterioration and failure to recover after corrective measures may occur. This can then result in the conversion to CPB (Ngaage, 2003).

Evidence exists that OPCAB reduces postoperative morbidity, including myocardial injury, renal dysfunction, neurocognitive deficit, and systemic inflammatory response syndrome (SIRS). OPCAB cardiac surgery still results in tissue trauma, cardiac manipulation, pericardial suction and the administration of exogenous drugs such as heparin, protamine and many anaesthetic agents. Thus, a physiological stress response which leads to an increase in pro-inflammatory markers still remains during OPCAB surgery (Day *et al.,* 2005).

With classic OPCAB for complete revascularisation, the surgical trauma experienced by the patient is similar to that of conventional CABG using CPB (Stump *et al.,* 2001). The magnitude of the inflammatory response, however, is significantly less than that observed when using CPB (Gasz *et al.,* 2004).

C)   On-Pump versus Off-Pump CABG Surgery

Today, cardiac surgery with- or without the use of CPB are among the most scrutinized surgical techniques, and continue to develop through research.

Alterations in organ function frequently accompany anaesthesia and cardiac surgery. Most individuals endure these physiological changes well and recover without incident, but some experience significant organ dysfunction and go on to develop postoperative complications (Haddy *et al.,* 1996).

Despite improvements in the method of CPB, the disadvantages of global myocardial ischemia, including the systemic inflammatory response, neurologic complications, renal failure, hemodynamic instability, lung dysfunction, and pulsatile flow converted to laminar flow, complement activation, coagulation, activation of platelets and leukocytes during CPB, are still a major cause of concern (Racz *et al.,* 2004).

All inflammation associated with cardiac surgery is linked to CPB, but it is also linked to surgical trauma and to frequently encountered co-morbidities such as:

- Diabetes - induces oxidative stress, paralyses of the immune system, activation and damaging of endothelial cells and platelets,

- Renal failure, either chronic or acute,

- hepatic failure,

- infectious diseases and,

- in the already preoperatively critically ill, pre-existing SIRS will probably have a similar impact on the inflammatory response to CPB (Racz *et al.*, 2004).

CPB may also increase the risk for tipping the balance between the exaggerated and necessary inflammatory response towards the development of other inflammation-related complications. However, it is incredibly difficult to pinpoint the sole role of CPB and its effects on inflammation with respect to clinically meaningful modifications of clinical outcomes (Larmann *et al.*, 2004).

Off-pump CABG surgery, on the other hand, requires different surgical as well as anaesthesiological skills. The major issue that remains about off-pump surgery is whether the need to contend with the beating heart and more blood in the operative field compromises the quality of distal coronary graft anastomosis and results in a less durable or less complete revascularisation (Cooley, 2000).

The advantages and disadvantages of conventional on-pump CABG surgery and off-pump CABG surgery has, thus far, been elaborated in small detail. Several meta-analyses have been performed comparing outcomes of revascularisation with- and without cardiopulmonary bypass (Table 2.2). The general feedback was that improved or at least equivalent outcomes were observed when comparing off-pump to on-pump surgery particularly with respect to postoperative mortality, stroke, myocardial injury, atrial fibrillation, need for transfusion and hospital stay. However, the majority of the studies performed were in highly selective and moderately low-risk patient groups, where mortality and morbidity rates were already low (Abu-Omar *et al.,* 2009).

Therefore, it seems that there is no clear evidence that on-pump CABG is preferable to off-pump CABG surgery or vice versa, both techniques have positive and negative attributes.

Table 2.2   **Meta-analyses Comparing On-Pump and Off-Pump CABG Surgery** (adapted from Abu-Omar *et al.,* 2009).

STUDY	NUMBER OF PATIENTS	META-ANALYSIS	MAIN OUTCOMES
Reston et al., 2003	39,647	RCTs & observational studies	Reduced hospital stay, operative morbidity and mortality for OPCAB.
Van der Heijden et al., 2004	1584	RCTs	OPCAB equivalent to conventional CABG.
Cheng et al., 2005	3369	RCTs	Reduction in the rate of atrial fibrillation, transfusion, inotropic requirements, respiratory infections, ventilation time, intensive care unit stay, hospital stay and cost for OPCAB.
Parolari et al., 2005	1105	RCTs	Reduced postoperative graft patency with OPCAB.
Wijeysundera et al., 2005	293,617	RCTs and observational studies	RCT: reduced AF and trends toward reduced 30-day mortality and MI Observational studies: reduced 30-day mortality, atrial fibrillation, stroke and myocardial infarction, but increased repeat revascularisation rate at 1–2 years for OPCAB.
Moller et al., 2008	5532	RCTs	Reduced AF but similar mortality, myocardial infarction, stroke, and renewed coronary revascularisation rates for OPCAB.

RCT: randomised controlled trial, OPCAB: Off-pump coronary artery bypass, CABG: coronary artery bypass graft, MI: myocardial infarction, AF: atrial fibrillation.

2.3   The Stress Response to Cardiac Surgery

The stress response to cardiac surgery encompasses a wide range of endocrinological, metabolic, immunological, haematological and hemodynamic changes induced by injury or trauma, and is also referred to as the systemic inflammatory response to surgery (Table 2.3).

Table 2.3   The Stress Responses to Surgery (adapted from Desborough, 2000).

CONSEQUENCE OF THE STRESS RESPONSE
Endocrine stress response • Pituitary hormone secretion • Insulin resistance
Immunological and Haematological changes • Cytokine production • Acute phase reaction • Neutrophil leukocytosis • Lymphocyte proliferation
Metabolic Response • Overall metabolic effect is one of catabolism of stored body fuels • Blood glucose concentrations ↑ • Peripheral use of glucose ↓ • Protein catabolism • Fat – increased mobilisation of triglycerides • Water and electrolyte – preservation of adequate body fluid volumes
Hemodynamic Response • Hypertension • Hypotension • Tachycardia • Bradycardia

Hypertension = Mean blood pressure>120% of baseline or >100 mmHg; Hypotension= Mean blood pressure <80% of baseline or <60 mmHg; Tachycardia = Heart rate >90 beats·min^{-1}, Bradycardia= Heart rate <80% of baseline or <45 beats·min^{-1}

Inflammation is the body's response to tissue injury and is a fast, amplified, controlled humoral and cellular response. It has already been determined that cardiac surgery provokes a significant systemic inflammatory response, which has important clinical implications (Levy *et al.,* 2003). A patient's risk of serious peri-operative complications are apparent as being somewhat preset (genotype, preoperative health status, surgical difficulty, *etc.*), but the degree to which these may be improved (*e.g.*, hemodynamic optimization using pharmacologic or mechanical support) is still under assessment (Laffey *et al.,* 2002).

The stress response to surgery is characterized by increased secretion of different stress hormones such as adrenaline and cortisol, due to increased activity of the pituitary and activation of the sympathetic nervous system. Changes in pituitary secretions have secondary effects on hormone secretions from other organs. The overall metabolic effect of these hormonal changes is increased catabolism which mobilizes substrates to provide energy, retain

salt and water to maintain fluid volume and cardiovascular homeostasis. Surgical patients have increased secretion of not just cortisol and catecholamines, but also glucagon, growth hormone (GH), as well as aldosterone. The mechanisms responsible for the increased synthesis are considered to be at least partly neuronally mediated. Afferent impulses from the site of injury stimulate the secretion of hypothalamic releasing factors, which then stimulate the pituitary to release GH and vasopressin. Adrenaline is secreted by the adrenal medulla due to the sympathetic nervous system activation. There is an interaction between the neuroendocrine stress response and the immunological response to surgical trauma (Toft *et al.,* 2008).

During the 1950s the speculation was that 'wound hormones' might be produced in injured tissues which activated the pituitary-adrenal axis. However, later the idea was formed that local substances might influence the changes associated with surgery and this notion was confirmed by the discovery of cytokines (Desborough, 2000).

The initiation of the stress response can be divided into an early/acute phase consisting of a number of changes that occur after tissue injury which is stimulated by cytokines and characterized as a hypodynamic state, a reduction in metabolic rate and depression of most of the physiological processes (Singh, 2003).

During the acute phase the liver starts producing acute phase proteins (Table 2.4). These proteins act as inflammatory mediators, anti-proteinases and scavengers during tissue repair.

Table 2.4   Features of the Acute Phase Response (adapted from Desborough, 2000).

Fever
Granulocytosis
Production of acute phase proteins in the liver   CRP   Fibrinogen   α2-macroglobulin
Changes in serum concentrations of divalent cations   Copper increases   Zinc and Iron decreases

C-reactive proteins (CRP); α- alpha

The late/flow phase is opposite to the early phase. The body develops a hypermetabolic state and may last anything from a few days to weeks depending on the severity of the surgical trauma or occurrence of a complication. This is also known as the period of compensation, with increased metabolic rate, enzyme modulation directed to glucose production and resultant compensation of blood volume and stimulation of the immune system (Singh, 2003).

2.3.1 The Immunological Response to Cardiac Surgery

2.3.1.1 Cytokine Production

Cytokines (include interleukins (IL) and interferons) are produced from activated leukocytes, fibroblasts and endothelial cells as an early response to tissue injury and have a major role in mediating immunity and inflammation. They act on surface receptors found on many different target cells and their effects are produced by influencing protein synthesis within these cells. After surgery the main cytokines released are IL-1, tumour necrosis factor -α (TNF- α), and IL-6. IL-6 is the main cytokine responsible for inducing the systemic changes known as the acute phase response (Desborough, 2000).

The release of cytokines influence hemodynamic regulation, contribute to myocardial stunning and negatively affect both renal and lung function. Therefore, cytokine release might also be involved in the development of systemic inflammatory response syndrome and multi-organ failure (Larmann *et al.,* 2004).

2.3.1.2 Leukocyte Production

A crucial step in tissue injury and its clinical consequences is the cytokine-mediated activation of leukocytes (monocytes and neutrophils). It is characterised by increased levels of neutrophil elastase, pro-inflammatory cytokines and the development of platelet-leukocyte conjugates. Leukocyte activation takes place due to increased levels of thrombin, kallikrein and C5a (Hunt *et al.,* 2007). C5a is a protein generated with the initiation of CPB that induces neutrophil chemotaxis, degranulation and super-oxide generation. Leukocytes are also activated by IL-1, IL-8, TNF-α, C5b-9, factor XIIa and heparin. When activated neutrophils degranulate and release cytotoxic enzymes, oxygen free radicals and, hydrogen peroxide, this stimulate

superoxides and directly activates endothelial cells. Monocyte activation plays a very specific role in thrombin generation via expression of tissue factor and the release of TNF- α, IL-1 and IL-6 (Day *et al.,* 2005).

Non-specific cell mediated immunity (neutrophils, monocytes, and natural killer cells) is suppressed after surgical trauma. After surgical stress leukocytosis is observed in peripheral blood while granulocytes accumulate in the injured area. However, to pass through the endothelium into the injured area, warrants an increased expression of adhesion molecules on the surface of neutrophils as well as on the surface of the endothelium.

2.3.2   The Endocrine Response to Cardiac Surgery

Activation of the endocrine response after surgery is caused by afferent neuronal impulses from the site of injury. These impulses travel along sensory nerve roots, up the spinal cord to the medulla to activate the hypothalamus. The hypothalamus then stimulates the release of pituitary hormones (Table 2.5) (Toft *et al.,* 2008; Desborough, 2000).

Table 2.5   Principal Hormonal Responses to Surgery (adapted from Desborough, 2000).

ENDOCRINE GLAND	HORMONES	CHANGE IN SECRETION
Anterior pituitary		
	ACTH	Increases
	Growth hormone	Increases
	TSH	May increase or decrease
	FSH and LH	May increase or decrease
Posterior pituitary		
	AVP	Increases
Adrenal cortex		
	Cortisol	Increases
	Aldosterone	Increases
Pancreas		
	Insulin	Often decreases
	Glucagon	Usually small increases
Thyroid		
	Thyroxine, tri-iodothyronine	Decrease

ACTH: adrenocorticotrophic hormone (corticotrophin), AVP: arginine vasopressin, FSH: follicle-stimulating hormone, LH: luteinizing hormone, TSH: thyroid-stimulating hormone (adapted from Desborough, 2000).

2.3.2.1   Hypothalamic-Pituitary-Adrenal Axis

A)   Anterior Pituitary

The anterior pituitary hormone secretion is stimulated by hypothalamic releasing factors. The changes of pituitary secretion allows for the synthesis of corticotrophin or adrenocorticotrophic hormones (ACTH) as part of a larger forbearing molecule, pro-opiomelanocortin. This molecule is metabolized in the pituitary into ACTH, Beta-endorphin and an N-terminal precursor (Burton *et al.,* 2004). The surgical stimulus also results in the increased secretion of GH and procalcitonin.

The stress response leads to secretion of several anabolic and catabolic hormones causing hypermetabolism, and acceleration of biochemical reactions. This compensatory mechanism ensures maximum chance of survival during increased cardiac functions, fluid preservation and supply of increased demands for energy generating substrates (Desborough, 2000).

B)   Posterior Pituitary

The posterior pituitary produces arginine vasopressin which has an important role as an antidiuretic hormone. Arginine also has an endocrine function, acting with corticotrophin-releasing factor (Burton *et al.,* 2004).

C)   Corticotrophin

Produced in the pituitary from a larger molecule called pro-opiomelanocortin, Corticotrophin-releasing hormone (CRH) also known as Adrenocorticotropic Hormone (ACTH), stimulates the adrenal cortical secretion of glucocorticoids so that circulating concentrations of cortisol increase. Surgery is one of the most potent activators of ACTH and cortisol secretion (Desborough, 2000).

D)   Growth Hormone (GH)

GH is a protein secreted from the anterior pituitary and its release is stimulated by growth hormone releasing factor from the hypothalamus. GH secretion increases in response to surgery and trauma according to the severity of the injury (Desborough, 2000). GH has many effects on the metabolism as well as the regulation of growth. It stimulates protein synthesis and inhibits protein breakdown, promotes lipolysis and has an anti-insulin effect. Therefore, GH inhibits glucose uptake and usage by cells. GH may also stimulate glycogenolysis in the liver (Singh *et al*, 2005).

E)   β-Endorphin and Prolactin

The increased, β-Endorphin (opioid peptide) concentrations in the circulation after surgery reflects increased pituitary hormone secretion. It has no key role in metabolic activity. Prolactin secretion is increased as part of the stress response to surgery but has little to no metabolic effect (Desborough, 2000).

F) Cortisol

The increased secretion of ACTH initiates a sudden increase in cortisol levels and its main metabolic effect is to overcome the stressful state. There is a direct feedback mechanism for cortisol, to both the hypothalamus and the pituitary gland, to decrease the concentration of cortisol in plasma. Cortisol has a vast number of effects on the metabolism and utilization of glucose. Cortisol causes rapid recruitment of amino acids and fat from cellular stores, making them immediately available both for energy and synthesis of other compounds (Singh *et al*, 2005).

G) Insulin and Glucagon

Insulin is a very important anabolic hormone (Burton *et al.*, 2004). Insulin is synthesized and secreted by the Beta cells within the pancreas. Insulin is released when blood glucose and amino acid concentrations increase. Insulin ensures the uptake of glucose into muscle and adipose tissue as well as the conversion of glucose into glycogen and triglycerides. Usually insulin concentrations decrease after the administration of anaesthesia, whilst during surgery there is a marked decrease of insulin secretion to match the catabolic, hyperglycemic response. In addition, insulin resistance becomes evident during the peri-operative period (Desborough, 2000).

2.3.3   Metabolic Response to Cardiac Surgery

The metabolic response also forms part of the overall stress response. The catabolic changes that occur result in substrate mobilization, muscle protein loss and sodium and water retention, with suppression of anabolic hormones (Burton *et al.*, 2004). It has been demonstrated that the magnitude of the metabolic response is proportional to the severity of the surgical trauma.

Initiation of the response is with activation of the hypothalamic-pituitary axis and the sympathetic nervous system. The result is failure of the normal feedback mechanism to control hormone secretion. Therefore, the result is an expression of catabolic hormones such as catecholamines and pituitary hormones but a suppression of anabolic hormones such as insulin.

Insulin is typically secreted in response to hyperglycaemia promoting glucose utilization and glycogen synthesis. Hyperglycaemia is a major attribute of the metabolic response to surgery (Burton *et al.,* 2004).

2.3.3.1 Glucose Metabolism during the Stress Response to Cardiac Surgery

Glucose metabolism involves complex metabolic reactions to maintain normal glucose levels. Exogenous glucose is supplied through dietary intake, whilst endogenous glucose is supplied through glycogen stores that release glucose through liver glycogenolysis as well as from non carbohydrate precursors (lactate and alanine). Endogenous glucose is converted to glucose through gluconeogenesis mainly in the liver and to a certain degree in the kidneys. During normal conditions 50-80% of ingested glucose will be used by glucose dependant tissues. Excess glucose is converted to produce energy through glycolysis and is stored as glycogen in the liver and skeletal muscles, or converted to fat (Butler *et al.,* 2005).

Blood glucose levels are regulated by hormonal, neural, as well as hepatic autoregulatory mechanisms (McCowen *et al.,* 2001). The hormonal mechanism involves insulin through its anabolic function to increase glucose uptake and storage. The effect of insulin is also mediated by its anti-inflammatory suppression of proinflammatory cytokine production and signalling for the reduction in blood glucose levels. It is accomplished by stimulating glucose uptake and glycogen synthesis, and inhibiting glyconeogenesis. The anabolic effects of insulin are stopped by the counter-regulatory hormones such as glucagon, catecholamines, cortisol and growth hormone. These hormones stimulate glycogenolysis and gluconeogenesis and inhibit insulin mediated glucose uptake (McCowen *et al.*, 2001).

The neural mechanisms involve central and peripheral glucosensors that respond to changes in blood glucose levels by releasing or inhibiting insulin secretion (McCowen *et al.*, 2001).

The hepatic mechanism involves a direct response to increased blood glucose levels by decreasing its glucose production (McCowen *et al.*, 2001).

Significant alterations to glucose metabolism occur during conditions of stress such as trauma, major surgery, and sepsis (Burton *et al.*, 2004). Today it is a well known fact that any type of prolonged stress or injury leads to insulin resistance, glucose intolerance, and hyperglycaemia. These changes follow closely after the increase in catecholamines. Independent of diabetic

status, the body experiences cardiac surgery as a dramatic and stressful event and the degree of hyperglycaemia depends on the severity, extent and duration of surgery. The surgical stress activates neuro-endocrine pathways, stimulating the adrenergic system and the hypothalamic-pituitary-adrenal axis (Desborough, 2000).

There are numerous mechanisms causing a considerable rise in glucose levels. Firstly, an increase in hepatic gluconeogenesis and glycogenolysis due to counter-regulatory hormones and the release of epinephrine and norepinephrine, secondly because of decreased glucose uptake and clearance due to insulin resistance during surgery. Mechanisms to maintain glucose homeostasis become ineffective during surgery. The hyperglycaemia persists due to catabolic hormones promoting glucose production (Desborough, 2000).

Insulin resistance occurs mostly in the skeletal muscle but other tissue such as adipose and liver may also contribute to this phenomenon. There is also an increased release of proinflammatory cytokines and acute phase reactive proteins such as TNF-α, IL-1, IL-6 and C-Reactive Protein (CRP) causing further peripheral insulin resistance. The negative feedback mechanism of glucose on gluconeogenesis also fails to continue as normal. Due to the high levels of catecholamines, the feedback to stimulate insulin secretion and glucagon inhibition decreases significantly. Lastly, surges in glucose levels may also occur from hyperglycaemia itself, which is proinflammatory and perpetuates the glycemic response. At cellular level, hyperglycaemia increases proinflammatory transcription factors, which, induces transcription of proinflammatory cytokines (TNF-α, IL-I, IL-6, IL-8 and IL-18) which contributes to more severe hyperglycaemia. It is important to remember, hyperglycaemia leads to inflammation and will, if left untreated elevate glucose levels even further, leading to greater oxidative stress and increased cytokine production (Shilling *et al.,* 2008).

2.3.3.2 Glucose Levels during Coronary Artery Bypass Graft Surgery

The development of hyperglycaemia during CABG intervention is not unusual irrespective of the anaesthetic technique (Doenst *et al*, 2008). This is due to a delay in the release of plasma insulin relative to the glucose concentration during normo-thermic CABG. Hyperglycaemia usually peaks within the first few minutes of bypass, while the rise in the plasma insulin level is delayed, increasing continuously during the CABG procedure. The relatively slow response to insulin with continued hyperglycemic stimulation indicates that the secretory response is inhibited

during CABG. Since the hyperglycaemia is not accompanied by a rise in plasma insulin concentration, the failure of an adequate insulin secretory response to noticeable hyperglycaemia indicates a secondary complication, the direct inhibition of insulin secretion. Evidence is lacking whether either a direct inhibitory effect of hypothermia on intrinsic pancreatic beta cell function *in vitro* or an effect on the ability of the pancreas to secrete insulin *in vivo* during CABG is responsible for this outcome (Desborough, 2000).

During the re-warming phase of CABG, plasma insulin begins to increase. At the end of the CABG procedure a slow but steady decrease in plasma glucose levels are seen, reaching pre-anaesthesia levels several hours to several days post-operatively (Gravlee *et al.,* 1993).

The net effect of the endocrinal response to surgery is an increased secretion of the catabolic hormones. Blood glucose concentrations increase with the onset of surgery. Cortisol and catecholamines facilitate the production of glucose due to increased hepatic glycogenolysis and gluconeogenesis. Mechanisms that maintain glucose homeostasis are ineffective in the peri-operative period. The risks of prolonged hyperglycaemia are less well established (Desborough 2000) but it does help to decrease the risk of hyperglycaemia because as this may lead to further complications (Marik *et al.,* 2004).

2.3.3.3   Hyperglycaemia, On-Pump vs. Off-Pump CABG Surgery

During cardiac surgery alterations to cardiac output (CO) may occur causing peripheral tissue vasoconstriction and as a result decreased peripheral tissue energy production. It is already known that a hypermetabolic response can be seen after cardiac surgery. It has been documented that a hypermetabolic state is present in both on- and off-pump coronary surgery as reflected by increased O_2 consumption. However, whole body O_2 consumption represents the general metabolic behaviour and does not provide any information about peripheral tissue metabolism. A progressive increase in glucose concentration in both the on- and off-pump groups can be seen (Cossu *et al.,* 2012).

2.3.3.4   Adverse Effects of Hyperglycaemia

The adverse effects of hyperglycaemia include the promotion of oxidative stress, impairment of endothelial function, promotion of coagulation, non-enzymatic glycation of platelet glycoproteins with abrupt changes in aggregability, amplification of inflammation, suppression of immunity and direct toxicity to myocytes and the promotion of apoptosis. Hyperglycaemia may also promote microvascular dysfunction which will lead to poorer clinical outcomes (Anantharaman *et al.,* 2009).

Hyperglycaemia causes a number of damaging effects on the immune defence mechanisms-both cellular and humoral. Alterations include changes in leukocyte function, altered microvascular response, and changes in the complement cascade and cytokine network. Hyperglycaemia affects leukocyte function in several ways; (1) decreased chemotaxis; (2) decreased phagocytosis; (3) decreased adherence; and (4) decreased bacteriocidal activity. Hyperglycaemia may also affect leukocyte function through antigen presentation by monocytes. Hyperglycaemia causes decreased antigen presentation and clearance which contributes to a decrease in infection prevention capabilities (Shilling *et al.,* 2008).

A)   Oxidative Stress

Oxidative stress is a well-recognised pathogenic process in the development of atherosclerosis, hyperglycaemia, endothelial dysfunction, activation of coagulation (impaired platelet function and increased platelet adhesion), and inflammation, suggesting that the action of hyperglycaemia is mediated by the production of free radicals (Ceriello, 2004).

Microvascular and macro-vascular complications are mainly or partly dependant on hyperglycaemia. Hyperglycaemia induced vascular damage may lead to (1) enhanced polyol activity, causing fructose accumulation; (2) increased formation of glycation end products (free fatty acids); (3) activation of protein kinase C; and (4) increased hexosamine pathway flux. Hyperglycemic states trigger all of these damaging metabolic events through the overproduction of superoxide radicals through the mitochondrial electron-transport chain leading to endothelial dysfunction (Monnier *et al.,* 2006).

Superoxide over production is accompanied by increased Nitric Oxide (NO) levels, due to endothelial NO synthase, favouring the formation of peroxynitrite, which in turn damages DNA.

The damaged DNA stimulates the activation of the nuclear enzyme poly (ADP-ribose) polymerase. Poly (ADP-ribose) polymerase diminishes the intracellular levels of its substrate NAD^+, decreasing the rate of glycolysis, electron transport, and ATP formation. These processes lead to endothelial dysfunction (Ceriello, 2005).

B)   Endothelial Dysfunction

It has already been discussed that endothelial cells are extremely sensitive to injurious stimuli. Endothelial dysfunction is seen in the earliest stages of arthrosclerosis, even before the appearance of plaque (Akbari *et al.,* 1998). Endothelial cell activation is stimulated by hypoxia, exposure to cytokines, endotoxin, and cholesterol, physical injury in the form of surgical manipulation or hemodynamic shear stress. In response to stimuli the endothelial cells undergo changes that allow them to actively participate in the inflammatory response. This response allows for endothelial-derived factors to disrupt barrier function and enhance vasoconstriction, coagulation, leukocyte adhesion, and smooth muscle cell proliferation. Although these changes exist as a protective mechanism this reaction may have serious consequences if the insult is severe or continue to spiral out of control (Verrier *et al.,* 1996).

The end result of the humoral response, leads up to endothelial cell activation, and results in the diffuse expression of leukocyte adhesion molecules on surfaces of vascular endothelial cells. Once adhering to the endothelium, neutrophils release cytotoxic proteases and oxygen derived free radicals that are responsible for organ damage (Boyle *et al.,* 1997).

C)   Ischemic Reperfusion Injury (IRI)

IRI is mainly mediated through neutrophil-endothelial interactions. The ischemic period causes high levels of endothelial injury, leading to neutrophil activation and sequestration once reperfusion is achieved. IRI is a manifestation of an acute inflammatory response initiated by overlapping cascades of the inflammatory mediators expressed at a local and systemic level. Oxygen is vital to cellular aerobic metabolism and the maintenance of high energy stores for normal function. Reintroduction of oxygen to previously hypoxic cells can result in irreversible tissue injury and is known as IRI (Boyle *et al*., 1997).

Reperfusion injury results from a number of interdependent mechanisms that are involved in the production of reactive oxygen species (ROS). The ROS, formed during oxidative stress, result in the oxidation of proteins, lipid peroxidation, inactivation of nitric oxide (NO), and most importantly, also causes endothelial injury and microvasculardysfunction (Chandrasena *et al.,* 2009).

During cardiac surgery, ischemic/reperfusion injury is initiated during aortic cross-clamping where blood supply to the heart and the majority of the lungs is removed. The heart and lungs become ischemic and on release of the clamp they are fully re-perfused. However, myocardial protection extends ischemic tolerance of the myocardium by the reduction of metabolic activity but IRI is still exacerbated by increased cross-clamp times (Rao *et al.,* 2001).

2.3.3.5   Hypoglycaemia during Cardiac Surgery

The regular monitoring of glucose levels is important because during the intra-operative period insulin resistance increases followed by a rapid decrease post-operatively which could lead to severe hypoglycaemia

Acute hypoglycemia causes distinct physiological responses as a result of autonomic activation, principally of the sympatho-adrenal system, and results in end-organ stimulation and a teeming release of adrenaline. This profound autonomic stimulus provokes hemodynamic changes, and consequently influences the body's ability to maintain the supply of glucose to the brain and promote the hepatic production of glucose (Cryer, 2004).

As a consequence of hypoglycaemia the following hemodynamic changes might occur:

- increased heart rate and peripheral systolic blood pressure,

- increased blood flow to the myocardium, the splanchnic circulation, and the brain,

- decreased central blood pressure,

- decreased peripheral arterial resistance and

- increased myocardial contractility (Frier *et al.,* 2011).

The workload of the heart is therefore temporarily, but markedly, increased and may have dangerous consequences in older people with coronary heart disease.

Hypoglycemia is also known to affect the electrocardiogram (ECG), causing ST wave changes with lengthening of the QT interval and cardiac repolarisation. Both induced and spontaneous clinical hypoglycaemic episodes prolong cardiac repolarisation. Changes are reflected by changes in the T-wave of the electrocardiogram and may increase the risk of cardiac arrhythmia, including ventricular tachycardia and atrial fibrillation (Frier *et al.*, 2011).

2.3.4 The Hemodynamic Response to Cardiac Surgery

Hemodynamic optimization is a daily occurrence in the hospital environment. Optimizing tissue perfusion is not just the improvement of arterial pressure and CO, but rather the delivery of O_2 from the lungs to the mitochondria in amounts sufficient to sustain required metabolism (Mongardon *et al.,* 2009).

Circulatory abnormalities seen during critical illness lead to an imbalance between systemic oxygen delivery and oxygen demand, resulting in global tissue hypoxia or shock.

At organ level, tissue blood flow and perfusion pressure are controlled by the following extrinsic factors:

- neurological (sympathetic innervations),

- biochemical (pH, PCO_2, and PO_2),

- hormonal (rennin-angiotensin system),

- vasoactive mediators (NO and prostaglandins) (Mongardon *et al.*, 2009).

Autoregulation represents intrinsic control and afferent arteriolar tone changes due to modifications in perfusion pressure (Mongardon *et al.*, 2009).

The hemodynamic profile and clinical management of patients are typically characterized in terms of global hemodynamic (macro-vascular) parameters, but it remains the responsibility of the micro-circulation for delivering blood flow from the cardiovascular system to the tissues. With restoration of an acceptable arterial blood pressure, caregivers may be falsely reassured that the patient is 'stable'. In this case the pathophysiology of events may be described as 'what lies beneath' in the micro-circulation which may include: global tissue hypoxia, endothelial cell injury and the activation of the coagulation cascade and lastly micro-circulatory and mitochondrial distress syndrome (MMDS) (Trzeciak *et al.,* 2005; Demers *et al.,* (2000).

Profound peripheral vasoconstriction occurs during the initial shock phase of injury where blood loss or other causes of hypovolaemia occur. This leads to renal conservation of water and sodium, and the redistribution of circulating blood volume to vital organs. Early goal directed therapy for hypovolaemia is the administration of fluids and vasoactive drugs (Table 2.6). After fluid resuscitation the initial shock phase is followed by a hypermetabolic phase with increased O_2 consumption and CO_2 production. Due to the increased O_2 consumption the body responds with actions of vasodilation, increased cardiac output, increased heart rate and increased respiratory rate. The micro-circulation is now compromised in injured tissue due to trauma. The body's effort to provide nutrients to the damaged tissue initiates local vasodilation and capillary leakage which leads to local oedema. Tissue repair occurs within 3-7 days in uncomplicated scenarios. In cases where tissue repair takes longer, postoperative complications are most likely to follow (Toft *et al.,* 2008).

Table 2.6   Pharmacological Treatment of Acute Circulatory Failure (adapted from Priebe, 2004).

DRUG	MEDIATING RECEPTOR(S)	DOSE ($\mu G \bullet KG^{-1} \bullet MIN^{-1}$)	INOTROPIC EFFECT	HR-EFFECT	SVR-EFFECT	BP-EFFECT
Dobutamine	$\beta_1>\beta_2>\alpha$	2–15	↑↑	↑	↓ HD:↑	↑
Dopamine	DA>β>α	↑Inotropy: 5–10 "renal": 2–5 ↑SVR: 10–20	↑↑	0, ↑	↓↓ 0 HD: ↑↑	0 0 HD: ↑
Norepinephrine	$\beta_1>\alpha>\beta_2$	0.01–0.03 maximal: 0.1	↑	↑	↑↑	↑
Epinephrine	$\beta_1=\beta_2>\alpha$	0.01–0.03 maximal: 0.1–0.3	↑↑	↑↑	↓ HD: ↑↑	0, ↑
Isoproterenol	$\beta_1>\beta_2$	0.01-0.1	↑↑↑	↑↑↑	↓	↑
Phenylephrine	A	0.2-0.3	0	0	↑↑↑	↑↑↑
Amrinone	PDE Inhibitor	bolus: 750 (3 min) infusion: 2–10	↑	0	↓↓	↓

↓=decrease; ↑= increase; 0 = no change; HR = heart rate; SVR = systemic vascular resistance; BP = blood pressure; HD = high dose; DA = dopaminergic; PDE = phosphodiesterase (adapted from Priebe, 2004).

2.3.4.1   Microvascular and Macrovascular Perfusion

The endothelium regulates the micro-vasculature, reacting to the metabolic needs of tissue. Endothelium is important in organ auto regulation and facilitates the response of the microvasculature to change local blood flow. Therefore, it is safe to say that the endothelium actively participates in maintaining normal cardiovascular homeostasis (Verrier *et al.,* 1996). The micro-circulatory unit consists of the arteriole, the capillary bed, and the post-capillary venule, of which the arterioles specifically were of interest where vasoactive mediators exert their vasodilatory effects. Clinically this results in the alteration of the systemic vascular resistance (SVR). During an intense inflammatory response it is in this capillary network where endothelial injury and ongoing capillary leakage occur (Trzeciak *et al.,* 2005). When tissue perfusion is continually impaired, cellular dysfunction may become irreversible.

The causes of impaired tissue perfusion:

- Low cardiac output,

- Mal-distribution of blood flow secondary to micro-circulatory dysfunction,

- Impaired use of substrate due to defects in cellular oxygen utilization (Trzeciak *et al.,* 2005).

The clinical signs of hypoperfusion include hypotension, tachycardia, oliguria, cool extremities, and metabolic (lactate) acidosis (Trzeciak *et al.,* 2005). Arterial hypotension itself is not a very accurate marker of tissue hypoperfusion because it has been noted from previous studies (Rivers *et al.,* 2001; Demers *et al.,* 2000) that tissue hypoperfusion abnormalities, with or without impaired cardiac output, can occur long before the appearance of hypotension. Therefore, BP parameters are insufficient to identify the need for resuscitation. Without evident hypotension, there appears to be a complex relationship between macro-circulatory hemodynamic parameters and micro-circulatory blood flow. De Backer and co-workers (2002) and Sakr *et al.* (2004) reported that micro-circulatory perfused vessel density was independent of arterial blood pressure. They suggested that micro-circulatory blood flow during severe illness is not simply a function of local perfusion pressures but there seems to be a degree of disconnection between the macro-circulation and the micro-circulation (Sakr *et al.,* 2004; De Backer *et al.,* 2002).

During CABG surgery impaired micro-circulation can act as one possible mechanism for the development of hyperlactatemia and the other is related to metabolic derangements that reduce the prognosis of a patient significantly (Trzeciak *et al.,* 2005). No matter what the cause, unrelenting increased levels of more than 5% of baseline values of lactate can reduce the prognosis of a patient significantly (Demers *et al.,* 2000).

A)   Oxygen Transport and the Role of the Micro-circulation

The intact micro-circulatory network is a critical intermediate link between the cardiovascular system and effective tissue oxygenation, serving as the bridge between the upstream as well as the downstream parameters (Figure 2.3). The Krogh model of micro-circulatory oxygen diffusion is a conceptual framework that highlights the significance of the micro-circulation in oxygen transport. When the diffusion distance for oxygen becomes too deep, the anaerobic metabolism will most likely take over (Trzeciak *et al.,* 2005; Ranucci *et al.,* 2006).

Vital information can be retrieved by measuring the mixed venous oxygen saturation (SvO_2). SvO_2 is a global parameter that indicates the oxygen saturation of pooled blood from post-capillary venules and a low value may indicate anaerobic metabolism; in other words global tissue hypoxia (Trzeciak *et al.,* 2005; Ranucci *et al.,* 2006). Tissue hypoxia has been associated with endothelial cell activation, stimulation of systemic inflammation, activation of the coagulation cascade as well as multi-organ dysfunction. Therefore, avoidance of tissue hypoxia is an important goal of cardiovascular support (Trzeciak *et al.,* 2005; Ranucci *et al.,* 2006).

Finding normal or high SvO_2 values does not rule out the occurrence of tissue dysoxia. Derangements of cellular oxygen utilization may also be playing a significant role. Cytopathic hypoxia is a well recognized mechanism that can cause venous hyperoxia. An alternative explanation may be that micro-circulatory shunting may be the contributing factor. Blood is shunted to open areas of the micro-circulation when weak micro-circulatory units are effectively shut down from severe flow impairment. Shunting results in decreased systemic oxygen utilization, venous hyperoxia and also elevated lactate concentrations (Trzeciak *et al.,* 2005; Ranucci *et al.,* 2006).

O_2 Supply & Demand

Upstream Parameter

•**Hemodynamic Parameters**

•After-Load (MAP, SVR)
•Pre-Load (CVP)
•Contractility (SV)
•HR (BPM)
•Coronary perfusion pressure

•**DO_2**

•PaO_2
•Hemoglobin
•Cardiac Output

Micro-circulation

Downstream Markers

•**Cell**

•SvO_2
•Lactate
•(a-v) CO_2
•Base deficit
•pH
•Psi CO_2
•Mediators
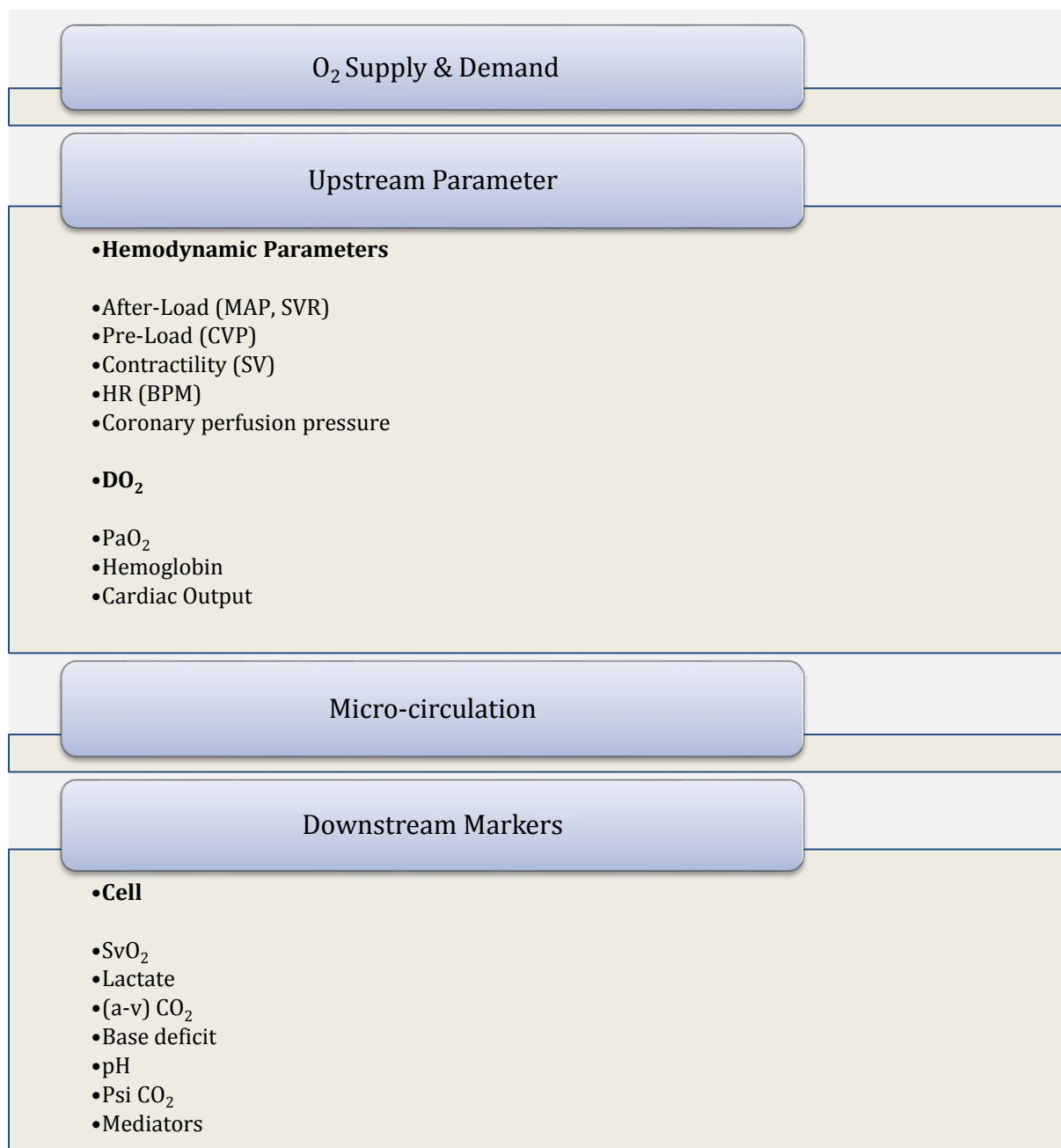
Figure 2.2   The role of the micro-circulation in goal-directed circulatory support.

The upstream endpoints of resuscitation are hemodynamic and oxygen-derived variables that can be modulated by circulatory support interventions. The downstream variables are markers of tissue perfusion and effectiveness of resuscitation. The micro-circulation is the critical intermediary that delivers blood flow from the cardiovascular system to the tissues. [beats per minute (BPM);central venous pressure (CVP); oxygen delivery (DO_2); heart rate (HR); mean arterial pressure (MAP); pulmonary capillary wedge pressure (PCWP);gastric intra-mucosal (pH); sublingual pCO_2($PsiCO_2$); systolic blood pressure (SBP);stroke volume (SV); mixed venous oxygen saturation (SvO_2); systemic vascular resistance (SVR)] (adapted from Trzeciak *et al.*, 2005).

2.3.4.2   Hypoperfusion during Cardiac Surgery

When tissues are injured the micro-circulation of the effected tissues are compromised. Alterations in microvascular perfusion during cardiac surgery results in various pathophysiological changes including the production of vasoactive mediators, activation of complement, kinin, cytokine and inflammatory cascades, changes in the endothelial permeability, and neutrophil activation. The redistribution of blood flow to maintain perfusion of vital organs results in a decreased perfusion to the skeletal muscles, which is an important lactate oxidiser, but due to decreased perfusion now becomes a lactate producer (Chiolero, *et al.,* 2000).

The splanchnic circulation may be specifically at risk during the operative period. Hypoperfusion of the intestinal mucosa is frequent during major surgery. This results in increased permeability to endotoxin, leading to endotoxemia. Severe stimulation of the inflammatory cascade leads to systemic vasodilation with consequent divergence of oxygen away from the splanchnic vascular bed. The endotoxins inactivate pyruvate dehydrogenase causing an increase in lactate not related to tissue oxygenation. Adrenalin improves cardiac output and systemic oxygen delivery, but might also induce anaerobic metabolism, worsen tissue hypoxia, leading to lactic acidosis, and decreased splanchnic consumption. Furthermore, glycogenolysis is enhanced resulting in increased pyruvate production. Vasopressin is another vasoconstrictor used and is characterized by its potent vasoconstrictive action, especially in hemodynamic unstable patients. However, vasopressin compromises splanchnic circulation and can lead to excessive lactate production. The hepatic blood flow also decreases, which results in a decreased capacity of the liver to use lactate. During severe splanchnic hypoperfusion, the liver now becomes the producer of lactate (Chiolero *et al.,* 2000).

2.3.4.3   Hyperlactatemia during Cardiac Surgery

Hypoperfusion causing increased lactate levels is associated with high postoperative morbidity (Ranucci *et al.,* 2006). Hyperlactatemia may also be due to hemodilution or problematic oxygen delivery to various tissues. Therefore, hyperlactatemia serves as an indicator for circulatory failure or insufficiency.

Circulatory support therefore involves manipulation of the three determinants of stroke volume (preload, taken over by venous return to the pump), myocardial contractility and afterload, (taken over by the arterial pump) as well as heart rate (Allsager *et al.,* 2003).

During CPB systemic microvascular control may deteriorate, inducing peripheral arteriovenous shunting that is associated with a rise in lactate levels (Trzeciak *et al.,* 2005; Ranucci *et al.* 2006).

It is important to fulfil the metabolic O_2 needs of the patient to avoid hyperlactatemia (acidosis Type-A) and to keep maximum flow rates to prevent negative post-operative outcomes (Demers *et al.*, 2000).

The thought of critical O_2 delivery is based on the hypothesis that when a patient is perfused below maximal flow rates (according to temperature) the oxygen expenditure (V_{O_2}) becomes dependent on the oxygen delivery. Energy production is then to a certain extent supplied by anaerobic glycolysis. Thus when a decrease in peripheral oxygen supply occurs during CABG, an increase in lactate production will follow (Ranucci *et al.*, 2006).

There are three mechanisms that may lead to hyperlactatemia during CABG surgery:

a) **Type A lactic acidosis** (Cohen-Woods classification) is caused by poor tissue perfusion, shock (hypovolaemic, cardiogenic, haemorrhagic, or septic), acute hypoxaemia or CO_2 poisoning.

b) Increased lactate production may be stimulated irrespective of tissue dysoxia, as a response to inflammatory mediators or through other mechanisms referring to **Type-B lactic acidosis** (Chiolero *et al.,* 2000).

c) Decreased utilisation of lactate by underperfused liver or muscle cells or glucose failing to enter the oxidative pathway and being broken down to lactate by the glycolytic pathway (Ranucci *et al.*, 2006). Tissue dysoxia and inflammatory mediators are a strong stimulus for lactate production. However, hyperglycaemia and increased nonoxidative glucose disposal, indicates glucose induced stimulation of tissue glucose uptake and glycolysis. This suggests that hyperglycaemia itself is a large contributor to the development of hyperlactatemia (Chiolero *et al.,* 2000).

Lactate is often used for prediction of clinical outcomes but the question remains if it is correctly interpreted in clinical decision-making. The use of lactate is still controversial because of discrepancies regarding reference intervals, cut-off points (Meyer *et al.,* 2013).

Changes in lactate level >6mmol/L during cardiopulmonary bypass is an indication that the patient is experiencing difficulty and has a significant sensitivity (78%) and specificity (83%) for mortality within 3 days (Haterill *et al.,* 1997).

A)   Hyperlactatemia: On-pump versus Off-pump

Tissue hypoperfusion is one major risk associated with cardiac surgery. It is known that CPB induces a profound systemic inflammatory response that can alter tissue oxygenation and extraction and cause both a decrease in lactate clearance and an increase in lactate production (Larmann *et al.,* 2004).

Hypothermia, re-warming, IRI, and gut-derived endotoxemia are all latent contributors to tissue hypoperfusion. The use of vasoconstrictors may also contribute to tissue hypoperfusion. Elevated lactate levels during cardiac surgery may become a unique diagnostic dilemma in the sense that increased lactate levels may be secondary to factors inherent to cardiac surgery (CPB inflammatory response, and use of vasoconstrictor drugs) or pathological processes (global hypoxia, shock, and hypovolemia). Determining the cause of increased lactate levels may be of clinical importance because efforts can then be made to diagnose and treat these pathological processes.

CPB is also a major cause of impaired splanchnic perfusion. The laminar flow created by CPB may cause the release of large amounts of angiotensin II, which is a selective splanchnic vasoconstrictor. Splanchnic ischemia also can increase gut permeability to endotoxin, leading to endotoxemia with consequent mismatch of O_2 supply and demand and ineffective O_2 extraction.

All of these derangements contribute to the increased risk of increased lactate levels even in the presence of normal oxygenation and circulation (Jones *et al.,* 2009; Weissman, 2009).

Off-pump surgery requires stabilization of the heart and good exposure of the target place of the anastomosis. Altered coronary perfusion by manipulation of the beating heart can lead to metabolic changes and electrophysiologic disturbances followed by a reduction in contractility which results in an interruption of myocardial oxygen supply (Pojar *et al*., 2008). An acute deterioration of coronary blood supply can result in a release of ischemic metabolites. With off-pump CABG surgery surgical stress is also induced which activates the inflammatory response and leads to metabolic changes, and last but not least due to the increased hemodynamic instability off-pump patients may need more vasoactive drugs to maintain CO (Stump *et al.,*

2001). This will lead to the same reaction of metabolic changes seen during CPB which in turn may lead to increased lactate production.

Persistent lactate production after reperfusion reflects delayed recovery of aerobic metabolism. Hence monitoring of postoperative lactate levels may be useful for assessing the status of aerobic metabolism (Chandrasena *et al.*, 2009).

2.4 Metabolic and Hemodynamic Monitoring During CABG Surgery

An arterial blood gas (ABG) analysis is performed on arterial blood, drawn from the arterial catheter inserted into the radial artery measuring blood pressure. Table 2.7 represents the normal reference ranges for the different ABG variables. It is important to monitor the physiological responses seen during CABG surgery. This not only allows the assessment of the physiological reserve of the patient but will also give a baseline against which the effectiveness of any applied treatment can be judged. Monitoring helps in the early diagnosis of change in physiological parameters and provides guidelines towards institution of appropriate therapy. There are many physiological variables which can be assessed and these range in complexity as well as degrees of invasiveness (Webster, 1999).

Routine invasive monitoring for all cardiac patients includes arterial cannulation for systolic pressure, diastolic pressure and mean arterial pressures (MAP) and routinely central venous access to monitor central venous pulmonary artery catheters (PAP) are not used routinely in all cardiac patients. For the purpose of this study pulmonary artery catheter readings were not recorded and will not be discussed. Hemodynamic assessment is important not only to establish the patient's initial profile and risk but also to monitor the efficacy of therapies. Routine monitoring provides important clues to possible decompensation, but most resolve rapidly during initial therapy (Borst *et al.,* 1999). Other parameters are also routinely measured, but are less invasive in nature, such as temperature, electrocardiogram (ECG) and pulse oximetry.

2.4.1   Arterial Blood Gas (ABG)

ABG's are done to determine pH, lactate, partial pressures of oxygen (PaO_2) and carbon dioxide ($PaCO_2$) as well as the bicarbonate levels (HCO_3- std mmol/L) and base excess (BE (B) mmol/L), glucose (mmol/L) and lactate (mmol/L). Other readings include hemoglobin levels and several electrolyte balances (Na_+ (mmol/L), K_+ (mmol/L), Ca_{++} (mmol/L) and Cl_-(mmol/L). pH designates the acid-base balance of arterial blood (Table 2.7). pH is the units in which the relative concentration of hydrogen ions are measured. The more hydrogen ions in a solution, the more acidic the solution is (Kallet *et al.,* 2003). Normal pH is calculated at 7.45, as long as the arterial pH is greater than 7.20, the cardiovascular effects of acidosis are mild because of the activity of the compensatory sympathetic nervous system. The direct depressive effects of acidosis on cardiovascular function become more prevalent as the pH falls below 7.20 (Kallet *et al.,* 2003).

Extreme acidosis could potentially lead to increased metabolism, insulin resistance, inhibition of anaerobic glycolysis, decreased ATP synthesis, increased protein degradation and hyperkaleamia. It can also cause decreased cardiac contractility, arteriolar dilation, veno-constriction and centralization of circulating blood volume, as well as increased pulmonary vascular resistance. This may in turn ultimately result in decreased cardiac output and decreased arterial blood pressure with reduced renal and hepatic perfusion (Kallet *et al.*, 2003).

When tissue perfusion is inadequate, serum lactate levels rise due to increased anaerobic metabolism. Inadequate tissue perfusion and oxygenation is manifested by increased lactate production and a decrease in pH (Souza *et al.,* 2000).

Normal arterial pCO_2 is maintained between 35 mm Hg and 45 mm Hg. Arterial pCO_2 reflects the balance between the production of CO_2 and its removal is an independent determinant of pH and is produced by cellular metabolism or by the titration of HCO_3- by metabolic acids (Davies *et al.,* 1997). According to the Henderson-Hasselbalch (HH) equation an increase in pCO_2 will result in a decrease in pH and an increase in HCO_3- concentration (Kellum, 2005). The balancing component of the respiratory system is the dissolved CO_2 that is produced by cellular processes and removed by the lungs. The balancing component of the renal system is the dissolved HCO_3 produced by the kidneys. The kidneys also help control pH by eliminating hydrogen (H_+) ions (Kellum, 2005).

BE (B) (mmol/L), is the measure of metabolic acidosis or alkalosis that is defined as the amount of acid or base that must be added to whole blood to restore the pH of the sample to 7.40 while the pCO_2 is held at 40 mm Hg (Kellum, 2005).

Potassium (K^+) is a critical ion that may present acute changes during cardiac surgery, followed by calcium (Ca^{++}). Other ions such as Cl^- and Na^+ mmol/L rarely show major changes therefore their correction is less demanding. Hyperkalemia has a prominent effect on cardiac conduction, such as a temporary AV block. With normal renal function, mild hyperkalemia represented by a serum level of 6mEq/L will not require special treatment and will resolve spontaneously. Hypokalemia on the other hand should be treated to avoid the risks of atrial and ventricular arrhythmias (Souza *et al.*, 2000).

Ca^{++} levels usually decrease during CPB but appear to recover quickly during the post-operative period. Elevated serum Ca^{++} levels have been associated with increased peripheral vascular resistance and improved coronary, renal and cerebral micro-circulation because of its positive inotropic effect. There is, however, some concern as to the potential role of elevated serum Ca^{++} levels in the aggravation of reperfusion injury (Souza *et al.*, 2000).

Two sets of information can be obtained from an ABG. The first is the blood acid-base balance, and the second is blood oxygenation. The measures of blood oxygenation are the oxygen (pO_2) and the oxygen saturation (O_2 sat). The dissolved oxygen in the blood is called the pO_2 and is measured in mmHg. The second measure is the oxygen saturation, which represents the amount of hemoglobin sites with attached oxygen. Oxygen saturation is expressed as a percentage of the total sites that have hemoglobin. The O_2 Sat can be continually monitored non-invasively with pulse oximetry (Woodruff, 2003).

Table 2.7   **Reference ranges for Arterial Blood Gas Variables** (adapted from Verma *et al.,* 2010).

VARIABLE	NORMAL VALUES	UNITS OF MEASURE
Acid-base Balance		
pH	7.35-7.45	
PaO_2	80-100	mmHg
$PaCO_2$	35-45	mmHg
HCO_3-	22-26	mmol/L
BE(B)	-2-+2	mmol/L
Saturation		
Hemoglobin (Hb)	12-14	g/dL
Saturation	>94	%
Electrolyte Balance		
K+	3.5-5.0	mmol/L
Na+	135-145	mmol/L
Ca++	0.9-1.1	mmol/L
Cl-		
Metabolites		
Glucose	5-7	mmol/L
Lactate	<2	mmol/L

mmHg= units of measure for pressure;g/dL= gram/decilitre; %= percentage; mmol/L= units of measure for all other values.

2.4.2   Temperature

Peripheral temperature (°C) reflects tissue perfusion and is affected by vasoconstriction and low cardiac output. There is an increased gradient between core and peripheral temperature in shock states (Webster, 1999*).*

2.4.3   Electrocardiogram (ECG) / Heart Rate (HR)

ECG is a familiar method to monitor cardiac activity, such as ischemic episodes, and may be used in the form of continuous bedside monitoring. ECG is an indispensable part of cardiovascular assessment in the significantly ill. Confirmation of myocardial ischemia, electrolyte imbalance and other metabolic disturbances may also be detected. Patient monitoring such as ECG and

hemodynamic monitoring are used but remain restricted in establishing the cause of hemodynamic instability (Borst *et al.*, 1999).

2.4.4   Pulse Oximetry

Measurement of the arterial oxygen saturation (SaO_2) is essential in the critically ill. By measuring absorption of light at two wavelengths, oxygenated as well as deoxygenated haemoglobin can be differentiated, so allowing estimates of arterial saturation (SaO_2) to be made. Arterial flow is pulsatile, allowing measurement of the relative percentage of oxygenated haemoglobin within arterial blood. Properly functioning pulse oximetry does reliably reflect arterial blood oxihemoglobin saturation. Pulse rate is also displayed by a pulse oximeter. Pulse oximetry is indicated in any clinical setting where hypoxia may occur (Pearse *et al.,* 2004).

2.4.5   Arterial Blood Pressure

Sudden changes in blood pressure are often associated with cardiac surgery therefore blood pressure is continuously monitored. For this purpose, a cannula is usually inserted percutaneously into the radial artery of the left hand. It is inserted under local anaesthetic prior to induction of anaesthesia (Schroeder *et al.,* 2007). The arterial cannula also allows for repeated sampling of blood for ABG and acid base analysis. This is crucial when sudden hemodynamic changes are anticipated—for instance, when administering inotropic or vasoactive drugs (Hinds *et al.,* 1999).

Arterial blood pressure is proportional to cardiac output when peripheral resistance is constant. Arterial pressure is affected by changes in the volume status of the patient, vasomotor tone and cardiac output. Blood pressure is maintained by physiological compensation in the face of changes in blood volume and cardiac output. Indeed, blood pressure may be normal despite grossly impaired cardiac function and, therefore, is only a crude indicator of the state of the circulation. However, if blood pressure is inadequate then tissue perfusion will be inadequate. Flow to tissues is dependent on mean arterial pressure (MAP). MAP is not simply an average of the systolic and diastolic pressures but is weighted more towards the diastolic pressure - one-third of the systolic plus twice the diastolic pressure. Knowledge of the MAP is also required for

the calculation of systemic vascular resistance and is often calculated automatically by electrical monitors of blood pressure and cardiac output (Webster, 1999*).*

The target level of MAP is not necessarily similar in patients. Even though MAP is usually 60mmHg, Anderson *et al.,* (2011) suggested that this is not true for all patients. A MAP of less than 60 mmHg could compromise autoregulation in the coronary and renal blood flow in the vascular bed of the central nervous system, and blood flow to renal systems. A number of patients, however, do require blood pressures higher than 60 mmHg to maintain adequate perfusion (Hinds *et al.,* 1996).

2.4.6   Central Venous Pressure (CVP)

Central venous access is established after induction of anesthesia. Central venous access is primarily required to determine the filling pressure of the right heart (estimation of preload), and it also provides, a relatively easy way to determine or monitor intravascular volume status (Pearse *et al.,* 2004).

Normally CVP ranges between 6-12 mmHg. However, the absolute value is often unaccommodating, except in severe cases of hypovolaemia, fluid overload, or heart failure. Accurate interpretation requires assessment of the change in central venous pressure in response to a fluid challenge in combination with alterations in other monitored variables (such as heart rate, blood pressure and urine flow). CVP monitoring aids in primary resuscitation; however, because of the inability to directly assess left ventricular filling pressures and volumes, its use is limited by cardiac performance (Hinds *et al.,* 1999).

2.5 Post-Operative Clinical Outcomes Associated with CABG

2.5.1 Clinical Outcomes

Morbidity refers to the diseased state of the patient and may often lead to mortality, which is the fatal outcome of morbidity. The long-term outcomes of CABG surgery depend on the intricate interaction of patient related and procedure related factors (Laffey *et al*., 2002).

Whether OPCAB surgery results in better clinical outcomes when compared to conventional CPB with the use of cardioplegic solution (CPS) and an arrested heart remains one of the most controversial debated issues in cardiothoracic surgery (Sellke *et al.,* 2005).

Conventional CABG with the use of CPB still remains the golden standard for revascularisation but off-pump coronary artery bypass grafting is used as an alternative technique for revascularisation and is said to avoid some of the major side effects of CPB (Pojar *et al*., 2008).

Conventional CABG with the use of CPB and CPS assures high quality anastomosis with acceptable clinical outcomes (Dybdahl *et al*., 2004). Nevertheless, a major complication of on-pump CABG surgery is the systemic inflammatory response that it provokes which can contribute to increased morbidity and mortality rates.

Evidence exists that OPCAB surgery reduces postoperative morbidity, including myocardial injury, renal dysfunction, neurocognitive deficit, and systemic inflammatory response syndrome (SIRS). Despite this the surgical trauma experienced by the patient is similar to that of conventional CABG using CPB and OPCAB cardiac surgery (Stump *et al.*, 2001).

The complications and outcomes often associated with post-operative CABG surgery are depicted in Table 2.8. The STS Adult Cardiac Database: Post-Operative Complications Version 2.41 was used as a guideline to indicate which complications and clinical outcomes should be monitored.

Length of hospital stay	Reoperation	GIT complications	Atrial fibrillation	Sternal wound infection
Heart block	Renal complications	Re-intubation	Tamponade	Acute limb ischemia
Neurological complications	Ventilator time	SIRS	Anticoagulant complication	Postop dissection of major artery
Postop dissection of major artery	Pulmonary complications	Return to ICU	Septicemia	Cardiac arrest
Multi system failure	Periop MI	ICU length of stay	Other infection	

Figure 2.3   STS Adult Cardiac Database: Post-operative Complications (adapted from STS Society of thoracic Surgeons, 2008).

STS Adult Cardiac Database: Post-Operative Complications [Online]. Version 2.41. Available from: http://www.ctsnet.org/file/241DataSpecs.pdf [Accessed 22/03/2012]).ICU: intensive care unit, [MI: Myocardial Infarction, GIT: Gastro-intestinal tract, SIRS: Systemic Inflammatory Response Syndrome].

2.6   Relevance of the Study

Intra-operative hyperlactatemia and hyperglycaemia are associated with early postoperative adverse outcomes in patients undergoing cardiac surgery with CPB. Hypoperfusion during the intra-operative period is suggested to be the major cause of increased lactate concentrations due to a decreased oxygen supply to tissue resulting in anaerobic metabolism increasing lactate production.
Hence monitoring of postoperative lactate and glucose levels may be useful for assessing the status of aerobic metabolism (Chandrasena *et al.*, 2009).

Hemodynamic instability, resulting in impaired micro-circulation, is one possible mechanism for hyperlactatemia and the other is related to metabolic derangements that reduce the prognosis

of a patient significantly. No matter what the cause, uncontrolled levels of lactate >5mmol/L can reduce the prognosis of a patient significantly (Trzeciak *et al.,* 2005).

Literature provides evidence that the degree of hyperglycaemia depends on the severity, extent and duration of surgery and mechanisms to maintain glucose homeostasis are ineffective during surgery (Desborough, 2000). The risks of this prolonged hyperglycaemia are less well established (Desborough, 2000) but decreasing the risk of hyperglycaemia helps as it has been linked to complications associated with SIRS (Marik *et al.,* 2004).

Due to the fact that metabolic changes are found in both on-pump and off-pump CABG patients efforts are made to improve monitoring of both metabolic and clinical changes during CABG surgery.

In this study the value of intra-operative metabolic and clinical monitoring will be assessed by evaluating metabolic data and hemodynamic changes, in patients presenting with acute coronary syndrome, as a predictor of post-operative clinical outcomes/complications in patients that had coronary bypass graft surgery (CABG).

2.6.1 Aim

The aim of the study is to evaluate how metabolic and clinical changes relate to the incidence of complications and clinical outcomes in ACS patients undergoing on-pump and off-pump CABG surgery

2.6.2 Objectives

- The evaluation and comparison of on-pump vs. off-pump with respect to:
  → Intra-operative metabolic data.
  → Intra-operative hemodynamic data.
  → Post-operative metabolic data.
  → Clinical outcomes and complications.

- The evaluation and comparison of lactate <5 mmol/L vs. lactate >5 mmol/L with respect to:

  → Intra-operative metabolic data.

  → Intra-operative hemodynamic data.

  → Post-operative metabolic data.

  → Clinical outcomes and complications.

Chapter 3

Methodology

3.1   Study Location

The research study was conducted at Universitas Academic Hospital in the department Cardiothoracic Surgery. Universitas is a state/private hospital located in Bloemfontein, the capital city of the Free State, South Africa.

3.2   Study Population

3.2.1   The Number of Subjects

Sixty patients diagnosed with ACS who received CABG surgery were recruited to participate in the research study. The 60 CABG patients were divided into two groups (30 patients who received on-pump CABG surgery and 30 patients who received off-pump CABG surgery).

3.2.2   Subject Identification

The patients were selected by either a Cardiologist or a Cardiothoracic Surgeon at the respective department situated in UAH.

The patients were identified by their hospital number (UM number) therefore preventing disclosure of the patient's personal details and ensuring patient confidentiality.

3.3 Inclusion and Exclusion Criteria

3.3.1 Inclusion Criteria

- Patients diagnosed with ACS displaying one of the following clinical conditions:

  - Unstable angina,

  - ST-elevation myocardial infarction,

  - Non-ST-elevation myocardial infarction.

- Patients receiving CABG surgery as method of treatment.

- Patients able to give informed consent.

3.3.2 Exclusion Criteria

- Patients with existing organ failures other than congestive cardiac failure (CCF).

- Patients not receiving isolated CABG surgery.

3.4 Study Design

Sixty patients operated in theatre 7 that met the inclusion criteria of the research project was selected to form part of this observational analytical cohort study. Only patients in theatre 7

was recruited for the study due to the fact that the Datex hemodynamic monitoring system was only available in theatre 7, Universitas Academic Hospital.

3.5   Study Layout

3.5.1   Phase 1

Phase 1 consisted of 60 patients diagnosed with ACS and received CABG surgery as mode of treatment. The 60 patients were divided into two groups, 30 patients received CABG surgery on-pump and 30 patients received CABG surgery off-pump (Figure 3.1a). Demographic and clinical data, intra-operative arterial blood gasses (metabolic data), intra-operative hemodynamic data, post-operative arterial blood gasses (metabolic data) and the clinical outcomes/complications were recorded and compared between the 2 groups.

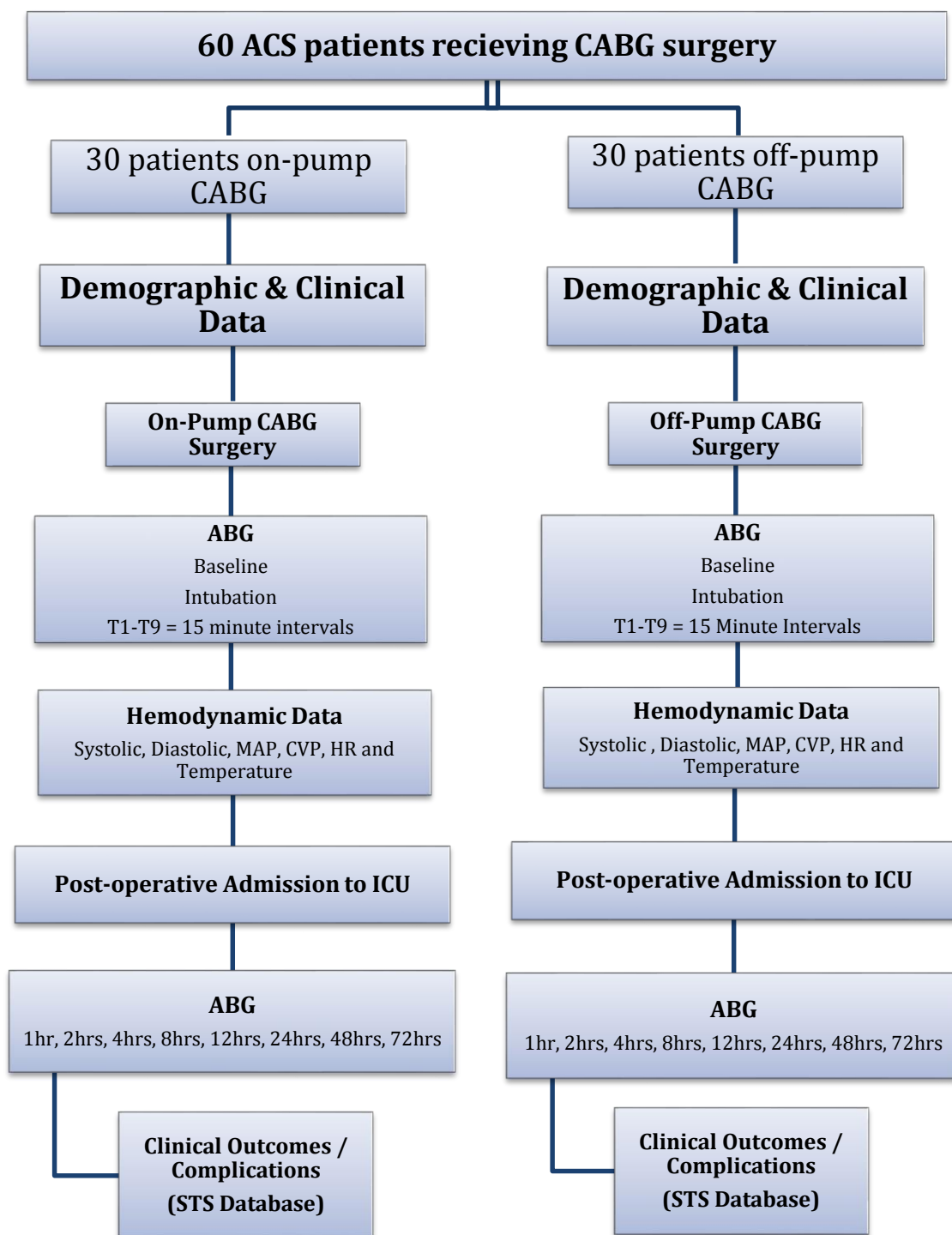**Figure 3.1.a   Schematic Presentation of Study Layout- Phase 1.**

[Acute Coronary Syndrome (ACS); Coronary Artery Bypass Graft surgery (CABG); Arterial Blood Gas (ABG); Central Venous Pressure (CVP); Heart Rate (HR); Haemoglobin (Hb); BP (systolic, diastolic and mean arterial blood pressure) ECG (Electrocardiograph; ICU (intensive care unit), MI (Myocardial Infarction), GIT (Gastrointestinal Tract)).

3.5.1.1 Demographic and Clinical Data

Upon admission each patient's demographic data (EuroSCORE%, ethnicity, gender, age, height, weight, body surface area (BSA) and body surface index (BSI)) and clinical data (smoking, diabetes, renal complications, neurological complications, pulmonary complications, previous non-surgical intervention, dyspnoea, LVEF%, hypertension, ACS and last previous MI) were recorded (Figure 3.1a).

3.5.1.2 Metabolic Data

Intra-operative metabolic data were captured for both the on-pump and off-pump CABG patients. Glucose, lactate, pH, PO_2, PCO_2, HCO_3, BE, Hb, Saturation, K^+, Ca^{++}, Na^+ and Cl^- concentrations were recorded as part of the ABG. ABG's were drawn at baseline and intubation, then at 15 minute time intervals after initiation of CBP for the on-pump group, and 15 minute time intervals after manipulation of the heart for the off-pump group (for the duration of surgery).

The same metabolic data were captured during the post-operative period at the following time intervals: 1 hour, 2 hours, 4 hours, 8 hours, 12 hours, 24 hours, 48 hours and 72 hours after admission to the ICU.

3.5.1.3 Hemodynamic Monitoring

Intra-operatively, hemodynamic data were recorded using the Datex Omeda software program. The recorded data included; blood pressure (BP) (systolic, diastolic and mean arterial pressure (MAP), heart rate (HR), central venous pressure (CVP) and temperature at increments of 1 minute (Figure 3.1a).

3.5.1.4 Clinical Outcomes/Complications

The clinical outcomes/complications (Figure 3.1a) were recorded using the STS database (Appendix E).

3.5.2   Phase 2

Irrespective of surgical technique, the 60 patients were divided into those with lactate levels <5mmol/L or lactate levels >5mmol/L. Comparisons between the two groups were made with reference to the metabolic data, hemodynamic data and post-operative clinical outcomes /complications (Figure 3.1b, refer to section 3.5.1.1, 3.5.1.2 and 3.5.1.3).

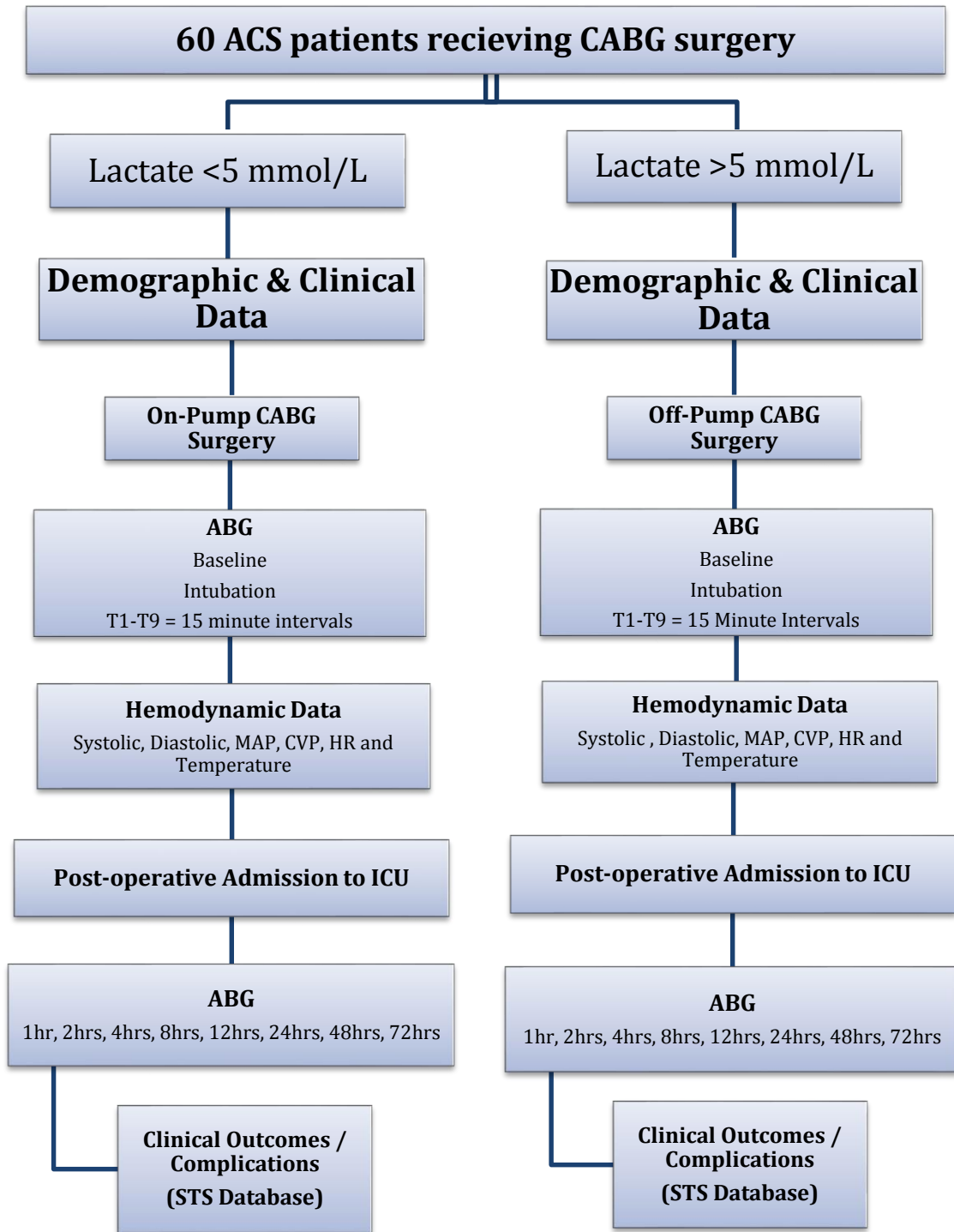**Figure 3.1.b   Schematic Presentation of Study Layout- Phase 2**

[Acute Coronary Syndrome (ACS); Coronary Artery Bypass Graft surgery (CABG); Arterial Blood Gas (ABG); Central Venous Pressure (CVP); Heart Rate (HR); Haemoglobin (Hb); BP (systolic, diastolic and mean arterial blood pressure) ECG (Electrocardiograph; ICU (intensive care unit), MI (Myocardial Infarction), GIT (Gastrointestinal Tract).

3.6 Special Investigations

3.6.1 Demographic and Clinical Data

The following demographic data were recorded for each patient:

- Age (years).

- Gender (M/F).

- Weight (kg).

- Height (cm).

- BMI - *Body Mass Index = Weight(kg) / Height(m)*2 a measure of body fat based on height and weight (Gallagher *et al.,* 1996).

- BSA – *Body Surface Area 0.20247* ^{x} height *(m)$^{0.725}$ x* weight (kg)$^{0.425}$ using the Du Bois formula (Wang *et.,* 1992).

- Euroscore calculated using the EuroSCORE II model (Roques *et al.,* 2003).

- Ethnicity.

The patient's pre-operative risk profile was established using the following clinical data (Figure 3.2).

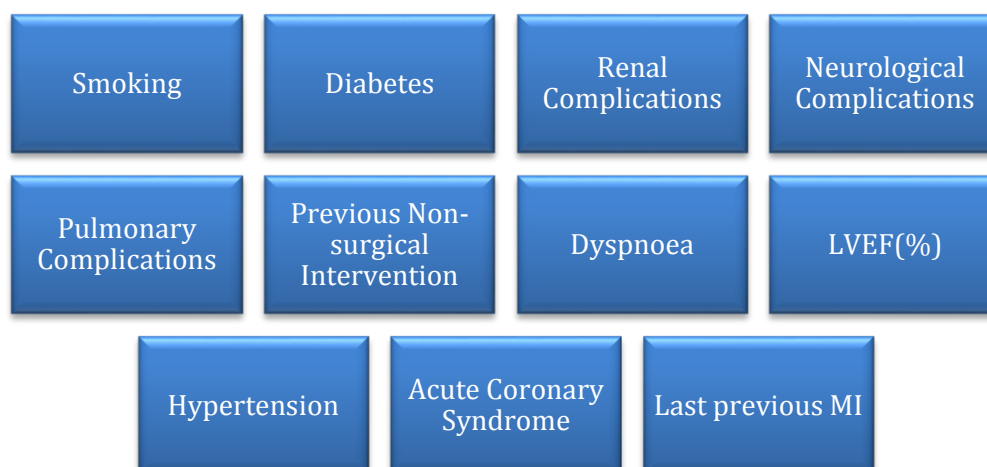| Smoking	Diabetes	Renal Complications	Neurological Complications
Pulmonary Complications	Previous Non-surgical Intervention	Dyspnoea	LVEF(%)
	Hypertension	Acute Coronary Syndrome	Last previous MI

Figure 3.2   Pre-operative risk profile

3.6.2 Arterial Blood Gas Analysis

3.6.2.1 Sample Collection

For each ABG analysis two millilitres of whole blood was drawn in a pre-heparinised syringe (BD Diagnostics) intra-operatively for all patients (Rapidlab 1200, Serial Number 013062). The recorded ABG variables for both groups intra- and post-operatively were pH, pO_2, pCO_2, during HCO_3^-, BE (B), O_2 SAT, Sodium (Na^+), Potassium (K^+), Calcium (Ca^{++}), Chloride (Cl^-), glucose and lactate (Table 3.1).

A) On-pump CABG Surgery

During on-pump CABG surgery, arterial blood was drawn for ABG analysis from an indwelling radial artery catheter before induction of anaesthesia (baseline) and 5 minutes after intubation.

Blood was drawn from the sample port of the oxygenator (Sorin Group Italy, Ref: 050239) after the initiation of bypass and every 15 minutes until termination of CPB.

B) Off-pump CABG Surgery

During off-pump CABG surgery the arterial blood samples were drawn for ABG analysis from an indwelling radial artery catheter before induction of anaesthesia (baseline), 5 minutes after intubation and after repositioning of the heart, every 15 minutes until the last anastomosis was completed.

C)   Post-operative ABG Sampling for both On-pump and Off-pump Groups

Two millilitre of whole blood was drawn from the patient's arterial line in a pre-heparinised syringe (BD Diagnostics) for an arterial blood gas analysis (Rapidlab 1200, Serial Number 013062).

The arterial blood was drawn from the indwelling radial artery catheter during specified time intervals scheduled at 1 hour, 2 hours, 4 hours, 8 hours, 12 hours, 24 hours, 48 hours and 72 hours during the post-operative period in the ICU for both the on- and off-pump groups .

Table 3.1   Metabolic Data and Normal and Abnormal References Ranges

ARTERIAL BLOOD GAS (ABG) VARIABLE (UNIT)	NORMAL REFERENCE RANGE	FOR THE PURPOSE OF THE STUDY ABNORMAL VALUES WERE DEFINED AS:
pH	7.35-7.45	<7.2 / 7.5>
pCO_2 (mmHg)	35-45 mmHg	<30mmHg or >46mmHg
pO_2 (mmHg)	100-250 mmHg	<60mmHg
HCO_3- STD (mmol/L)	22-26 mmol/L	Metabolic Acidosis <22mmol/L; Metabolic Alkalosis >22mmol/L
BE (B) (mmol/L)	-2 mmol/L-+2 mmol/L	Metabolic Acidosis <-2mmol/L; Metabolic Alkalosis >+2mmol/L
tHb (g/dL)	12-14 g/dL	<8g/dL
O_2 Sat (%)	>94%	<85%
Na^+ (mmol/L)	135-145 mmol/L	>145 mmol/L
K^+ (mmol/L)	3.5-5.0 mmol/L	<3mmol/L or >6mmol/L
Ca^{++} (mmol/L)	0.9-1.1 mmol/L	>1.1 mmol/L
Cl^- (mmol/L)	104-112 mmol/L	>112 mmol/L
Glucose (mmol/L)	5 mmol/L	> 10 mmol/L
Lactate (mmol/L)	<2 mmol/L	> 5 mmol/L

3.6.3   Hemodynamic Monitoring

Intra-operative hemodynamic data were recorded electronically at 10 second intervals using the Datex-Ohmeda S/5™ software program (Datex-Ohmeda S/5™ Collect, GE Healthcare software, Ref: L-COLLECT4-01-EN, SN: 6521804, GE Healthcare, Finland).

The Datex-Ohmeda monitor displays a hemodynamic calculation view where values were selected and analysed only at baseline and intubation for both the on-pump and off-pump groups and thereafter at 15 minute intervals from onset of CPB for the on-pump group and for the off-pump group at 15 minute intervals after manipulation of the heart. The system collected trend waveforms and alarm data directly from a Datex-Ohmeda monitor (*(Datex-Ohmeda S/5 ™ Cardiovascular Anaesthetic monitor Serial no: 90027365 and 4416799)* through a PC serial interface cable (RS 232).

The following hemodynamic parameters were recorded for both the on-pump and off-pump groups:

a)   **Arterial blood pressure** (systolic, diastolic and mean BP via an arterial catheter placed into the left radial artery).

b)   **Central venous pressure** (measured in the SVC with a cannula inserted from either the internal jugular or subclavian vein).

c)   **Pulse oximetry** (probe placed on the patient's index finger, measured arterial oxygen saturation and pulse rate).

d)   **Heart rate** (recorded via a 3-lead ECG).

e)   **Temperature.**

Hemodynamic data were collected every minute, but for the purpose of the study, was presented at baseline, intubation and 15 minute intervals from onset of CPB for the on-pump group. Hemodynamic data for the off-pump group was presented at baseline, intubation and 15 minute intervals after manipulation of the heart.

3.6.4   Coronary Artery Bypass Graft (CABG) Surgery

The Cardiologist and Cardiothoracic Surgeon made a collaborative decision regarding the optimal course of treatment for the patient.

The study did not influence the surgeon's decision whether to perform the CABG procedure with or without cardiopulmonary bypass. The surgeon selected the method that was most suited and beneficial to the patient's condition taking all factors into consideration. It was the surgeon's decision whether on-pump or off-pump CABG surgery would yield the best possible outcome for the patient.

3.6.5   Surgical Techniques

3.6.5.1   On-pump CABG Surgery

(A)   Preparation of the perfusion system in theatre

- The Stöckert S5 System (Cardiopulmonary bypass system, Serial no: 48E00380   and 48E00381) was routinely used and the bypass circuit setup included:

- Sorin Biomedica Synthesis oxygenator (Ref: 050239, Sorin Group, Italy).

- Medtronic adult membrane pack (Ref: M273102E, Medtronic Inc. Minneapolis, USA).

- Medtronic Myotherm 4:1 (Ref: M999214E, Medtronic Inc. Minneapolis, USA).

- Medex disposable dome for the Medex transducer (Ref: MX960XYP1, Medex medical LTD, Lancashire) (cardioplegia pressure transducer).

- 1L Balsol Infusion (Ref: FSB001000, Fresenius Kabi for Bodene Limited trading as Intramed, Port Elizabeth, RSA).

- 12.5g Mannitol (Intramed Mannitol 25% m/v, 12.5g, 50ml, Ref: FSM 250050, Fresenius Kabi for Bodene Limited trading as Intramed, Port Elizabeth, RSA).

- 30mg Heparin, Heparin Sodium-Fresenius 1000 i.u. /ml (Ref: J/8.2/405, Fresenius Kabi for Bodene Limited trading as Intramed, Port Elizabeth, RSA).

- 1g Ranzol (Ranbaxy Ranzol Injection Cefazolin Sodium (Sterile) 1m/Intra Venous (I.V.), Ref: 30/20.1.1/0333, Code: MP/DRUGS/28/15/83, Ranbaxy (SA) (Pty) LTD, North Centurion, RSA).

- 500ml Gelofusion (Gelofusion Solution for intra venous (I.V.) infusion, Plasma Substitute Ref: 31/8.4/0360, B. Braun Medical (Pty) LTD, Randburg, RSA).

- Edwards Lifesciences pressure monitoring set (Ref: PX600FP, Edwards Lifesciences, Irvine, USA).

- CritiCare 0.9% Sodium Chloride Injection BP (200ml) (Ref: 32/24/0128, Dismed CritiCare (Pty) LTD, Midrand, RSA).

- 30mg Heparin, Heparin Sodium-Fresenius 1000 i.u/ml (Ref: J/8.2/405, Fresenius Kabi for Bodene Limited trading as Intramed, Port Elizabeth, RSA).

- Two cardioplegic solutions were used at UAH, depending on surgeon's preference:

(D1)   Buckberg solution

- Medsol Cardioplegic Induction Solution (Ref: FSM01850I, Fresenius Kabi for Bodene Limited trading as Intramed, Port Elizabeth, RSA).

- Medsol Cardioplegic Maintenance Solution (Ref: FSM01850M, Fresenius Kabi for Bodene Limited trading as Intramed, Port Elizabeth, RSA).

- Medsol Cardioplegic Reperfusion Solution (Ref: FSM01850R, Fresenius Kabi for Bodene Limited trading as Intramed, Port Elizabeth, RSA).

- 10ml 50% Dextrose added to each bag of cardioplegic solution (Dextose-Fresenium 50% (20ml) (Ref: V/24/222, Fresenius Kabi for Bodene Limited trading as Intramed, Port Elizabeth, RSA).

(D2)   Modified St Thomas solution

- 1000ml cold Ringer-Lactate (Intramed Ringer-Lactate Solution 1000ml Infusion, Ref: FSR001000, Fresenius Kabi for Bodene Limited trading as Intramed, Port Elizabeth, RSA).

- 50ml, 4% Albusol (Human Plasma Albumin, Ref: T/30.3/738, National Bioproducts Institute, Pinetown, RSA).

- 30ml, 8.5% Sodium Bicarbonate (Intramed Sodium Bicarbonate Injection 8.5% (50ml) m/v, Ref: FSS850050, Fresenius Kabi for Bodene Limited trading as   Intramed,   Port Elizabeth, RSA).

- 200mg Lignocaine (Lignocaine HCl-Fresenius, Ref: M/4/254, Fresenius Kabi for Bodene Limited trading as Intramed, Port Elizabeth, RSA).

- 4g Magnesium Sulphate (SABAX Magnesium Sulphate 50% Injection (1g/2ml) iv/imi, Pharmacological Classification A.24 (Mineral Substitutes, Electrolytes, Ref: V/24/253, ADCOCK Ingram Critical Care (Pty) LTD, Johannesburg, RSA).

- 30mmol/L Potassium (SABAX Potassium Chloride 15% Injection, Pharmacological Classification A.24 (Mineral Substitutes, Electrolytes, Ref: V/24/218, ADCOCK Ingram Critical Care (Pty) LTD, Johannesburg, RSA).

(E)   Peri-operative management of the patient

- A three point ECG was connected to the patient's back.

- Peripheral lines and arterial blood pressure lines were inserted.

- Anesthesia commenced.

- Central venous line was inserted.

- Median sternotomy was performed by the surgeon and saphenous vein grafts were harvested from patient's legs by the assistant. Internal Mammary Artery   may   also have been harvested by the surgeon.

- Full systemic heparinization of the patient was achieved by intravenous administration of 4 mg/kg Heparin (Heparin Sodium-Fresenius 1000 i.u/ml, Ref: J/8.2/405, Fresenius Kabi for Bodene Limited trading as Intramed, Port   Elizabeth, RSA).

- 5 minutes after heparin administration activated clotting time (ACT) sample was drawn, and ACT was measured.

- The ascending aorta was cannulated and as soon as an ACT of 480 seconds was achieved, bypass commenced.

- Access to the right atrium was established and venous blood was obtained through cannulation with a two-stage venous cannula via the right atrial appendage.

- Systemic hypothermia of between 28-30^{0}C was achieved and the alpha-stat principle was applied.

- An antegrade cardioplegia cannula was placed in the aortic root proximal to the arterial cannula. This cannula also served as an aortic vent.

- The ascending aorta was cross-clamped between the aortic cannula and the antegrade cardioplegia cannula.

- Infusion of cold blood cardioplegia (at ± 20^{0}C), antegrade into aortic root via cardioplegia cannula and was repeated every 20 minutes.

- Topical ice slush was applied onto the heart.

- Distal venous anastomoses were performed on the coronary artery.

- When last distal anastomosis was performed, rewarming commenced.

- The aortic root was de-aired through the LV vent cannula.

- The aorta cross clamp was removed from the distal ascending aorta, when normothermia was reached.

- Oxygenated blood was flowed into the bypassed vessels using a manifold.

- Proximal anastomosis was performed on the distal ascending aorta utilizing a side-biting clamp.

- Cardiopulmonary bypass was weaned and stopped.

- Protamine was given to reverse Heparin. (Three quarters of heparin dosage = 3mg/kg Protamine Sulphate, (Protamine Sulphate), Ref: 4543/0234, CP   Pharmaceuticals LTD, Wrexham).

- Once haemostasis was achieved, mediastinal and pericardial underwater drains were inserted.

- The sternum was wired and the sternotomy closed.

3.6.5.2   Off-pump CABG Surgery

- A three point ECG was connected to the patient's back.

- Peripheral lines and arterial blood pressure lines were inserted.

- Anaesthesia commenced.

- The central venous line was inserted.

- Patient was draped and autologous cell salvage suction/aspiration line was handed to the scrub sister.

- Surgeon performed median sternotomy and the assistant harvested saphenous veins from the patient's legs. Internal Mammary Artery may also be harvested by surgeon.

- 1mg/kg Heparin was given to the patient to partially heparinize the patient (Heparin Sodium-Fresenius 1000 i.u/ml Ref: J/8.2/405, Fresenius Kabi for Bodene Limited trading as Intramed, Port Elizabeth, RSA).

- The distal venous anastomoses onto the coronary artery were performed using one of 3 stabilizers to stabilize the area.

    - Medtronic Octopus 4 (Ref: 29400, Medtronic Inc. Minneapolis, USA).

    - Medtronic Starfish 2 (Ref: 29800, Medtronic Inc. Minneapolis, USA).

    - Genzyme stabilizer (Ref: TX180010, Thebe Medical, Johannesburg, RSA).

- A coronary shunt may be used by the surgeon.

    - Medtronic Clear view 1.5mm (Ref: 31150, Medtronic Inc. Minneapolis, USA).

- A water-filled glove was placed posterior to the heart and steadily inflated in order to bring the heart more anterior if necessary or a posterior pericardial stitch and vaginal swab could have been used to facilitate better exposure of the coronary arteries.

- Proximal anastomoses were performed on the ascending aorta utilizing a side-biting clamp.

- Protamine was given to reverse Heparin. (Three quarters of heparin dosage = mg/kg Protamine Sulphate dosage).   Prosulf (Protamine Sulphate, Ref: 4543/0234, CP Pharmaceuticals LTD, Wrexham).

- Once haemostasis was achieved, mediastinal and pericardial underwater drains were inserted.

- Sternum was wired and the sternotomy was closed.

3.6.6   Post-operative Complications

The surgical data was captured by a cardiothoracic surgeon in a surgical database. The pre-operative dataset of the surgical registry was designed in accordance with the Society of Cardiothoracic Surgeons of Great Britain and Ireland (SCTS) Adult Cardiac database and the post-operative dataset in accordance with the Society of Thoracic Surgeons (STS) Adult Cardiac Database. Details for the pre-operative and post-operative datasets can be viewed in Appendices C and D.

The STS Adult Cardiac Database (Figure 3.3) was used to assess surgical outcome of patients included in the study (Adapted from: STS Society of thoracic Surgeons. 2008. STS Adult Cardiac Database: Post-Operative Complications [Online]. Version 2.41. Available from: http://www.ctsnet.org [Accessed 20/07/2012]).

Length of Hospital Stay	Re-operation	GIT Complications	Atrial Fibrillation	Sternal Wound Infection
Heart Block	Renal Complications	Re-intubation	Tamponade	Acute Limb Ischemia
Neurological Complications	Ventilator Time	SIRS	Anticoagulant Complication	Post-op Dissection of Major Artery
Pulmonary Complications	Return to ICU	Septicemia	Cardiac Arrest	Multi Organ Failure
	Periop MI	ICU Length of Stay	Other Infection	

Figure 3.3   Post-operative Complications Recorded by STS Adult Cardiac Database.

(Adapted from: STS Society of thoracic Surgeons. 2008. STS Adult Cardiac Database: Post-Operative Complications [Online]. Version 2.41. Available from: http://www.ctsnet.org/file/241DataSpecs.pdf [Accessed 20/07/2012]).

3.7   Statistical Analysis

Data was captured on a Microsoft ® Excel spreadsheet. The statistical analysis was done by a qualified biostatistician using SAS Version 9.2. The data was summarised using descriptive statistics, namely percentages and frequencies for categorical data. Medians and percentiles were used to summarize continuous data.

Analytical statistics compared the frequencies and percentages in different groups by using the Chi-square test to calculate p-values. Medians were compared by using the Kruskal-Wallis test to calculate p-values.   Mean values were compared using the Wilcoxon-Mann-Whitney to calculate p-values.   Significant differences were noted at $p < 0.05$.   The hemodynamic and

metabolic data were plotted over time, and by analysis group, to provide a visual representation of the changes intra- and post-operatively.

Two separate group analyses were performed when analysing the data. The on- and off-pump patients were compared to assess whether the two groups were comparable regarding demographic, risk profiles, intra-and post-operative data and clinical outcomes. Thereafter the data was stratified into two groups, regardless of whether they were operated on- or off-pump, according to whether their lactate level ever peaked above 5 mmol/l during surgery or not. The same set of analyses were performed as for the on- and off-pump comparisons.

A power analysis was calculated using G* Power, version 3.1.7 software (Faul, 2013).

3.8   Ethical Aspects

3.8.1   Ethical Clearance

This study was conducted as part of the project: "Endothelial function as a predictor of post-intervention outcomes" and was granted ethical clearance by the Ethics Committee of the University of the Free State (ETOVS nr 51/07A) (Appendix F). Approval was also granted by the Clinical Head and Director of Finance of Universitas Academic Hospital.

3.9   Safety Variables

3.9.1   Project and Patient Safety

The research project was safe. All the procedures were routine procedures for cardiology and cardiothoracic surgery and the study did not in any means interfere with the desired treatment plan for the patient.

Patients participating in the study were monitored by doctors in the department of cardiothoracic surgery and could discontinue participation at any time without influencing the quality of their care/treatment.

3.9.2   Good Clinical Practice (GCP) / Quality Assurance

All clinical work conducted under this research study was subjected to the South African Good Clinical Practice guidelines (SA GCP) (The Principles of ICH GCP, 2004).

The declaration of Helsinki's basic principle number 3 states that research should be conducted only by scientifically qualified people and under the supervision of adequately qualified people (World Medical Association, 2002). Therefore, the research project was administered by registered Cardiothoracic Surgeons and Clinical Technologists (Registered with the Health Professional Council of South Africa).

3.9.3   Informed Consent and Information Leaflet

Participation was only allowed after informed consent was given. Each patient received an information document that explained the purpose and extent of participation in the research study. Both the informed consent and the information leaflet were approved by the Ethics Committee of the University of the Free State.

3.9.4   Confidentiality

The personal details of every patient participating in the study were kept confidential as far as possible. At no time during the research were any of the patients' identification details made known to any person who was not part of the research team. For the purpose of data collection and statistical analysis patients were identified by their hospital number (UM number).

3.9.5   Financial Implications to the Patient

The majority of the investigations performed during this study were routine medical practice. Financial constraints caused by any additional tests were the responsibility of the Department of Cardiothoracic Surgery. No financial remuneration was claimed or paid to from the patients to participate in the study.

3.9.6   Withdrawal Criteria

Participation in the study was voluntary. Patients had the right to withdraw from the study at any time, without stating reason and without influencing the quality of their health care.

Chapter 4

Results

4.1 Introduction

The metabolic and clinical changes of sixty patients diagnosed with ACS undergoing on- and off-pump CABG surgery were evaluated during the study. Thirty patients underwent on-pump CABG and 30 patients received off-pump CABG surgery. The sixty patients were then further evaluated with respect to lactate levels of <5mmol/L and >5mmol/L. The objectives for the study are defined in Figure 4.1.
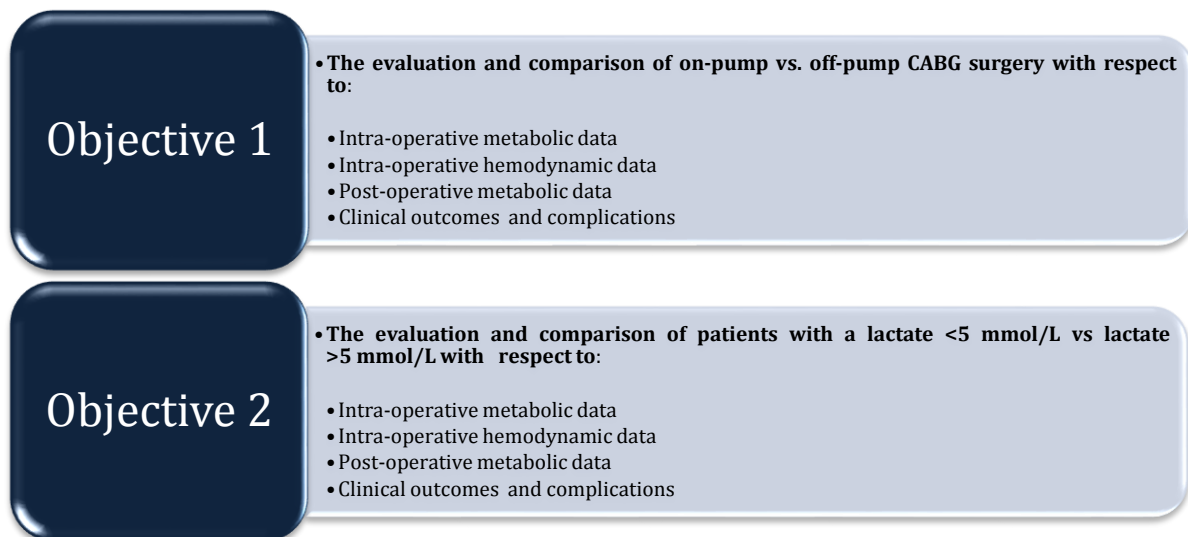
Objective 1
- **The evaluation and comparison of on-pump vs. off-pump CABG surgery with respect to**:
  - Intra-operative metabolic data
  - Intra-operative hemodynamic data
  - Post-operative metabolic data
  - Clinical outcomes and complications

Objective 2
- **The evaluation and comparison of patients with a lactate <5 mmol/L vs lactate >5 mmol/L with respect to**:
  - Intra-operative metabolic data
  - Intra-operative hemodynamic data
  - Post-operative metabolic data
  - Clinical outcomes and complications

Figure 4.1   Schematic presentation of research objectives

4.2   Study Population

4.2.1   Demographic Data

Sixty ACS patients receiving CABG surgery (30 patients on-pump and 30 patients off-pump) participated in the study. The on-pump 27 (90%) and off-pump 23 (77%) CABG groups were both predominantly male (Figure 4.2) (p >0.05).
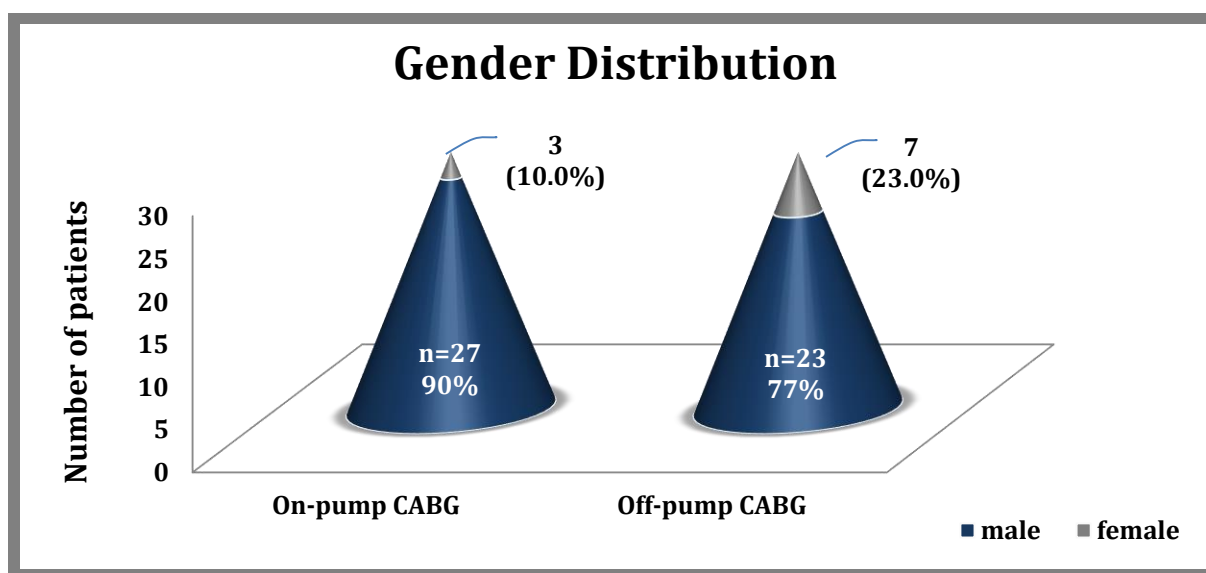

Figure 4.2   Gender distribution for on-pump and off-pump CABG groups.
[n=number of patients; % = percentage of patients].

The majority of patients were Caucasian 50 (83%) followed by Coloured 6 (10%) and Negroid 4 (7%) (Figure 4.3). The on-pump and off-pump groups were similar with respect to ethnicity (p >0.05).
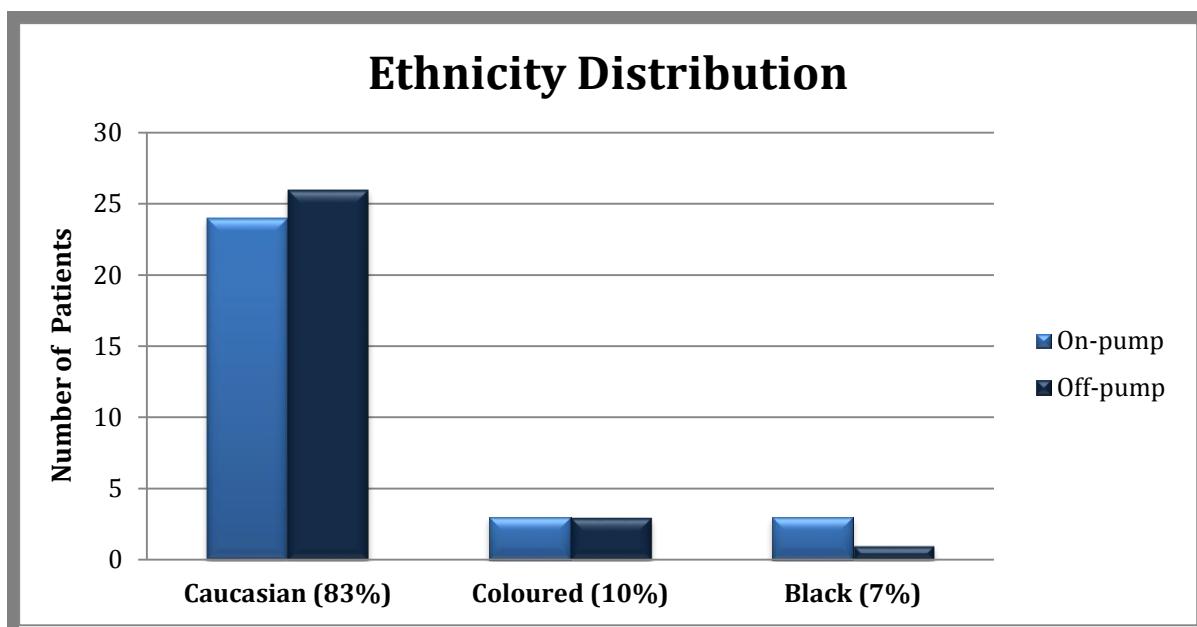
Figure 4.3   Ethnicity distribution for On-pump and Off-pump CABG patients.

[Caucasian on-pump 24 (80.0%); Caucasian off-pump 26 (86.0%); Coloured on-pump 3 (10%); Coloured off-pump 3 (6.0%); Negroid on-pump 3 (10.0%); Negroid off-pump 1 (3.0%); n=number of patients; % = percentage of patients.

Although the groups were small they exhibited similar demographic data (Table 4.1). No statistically significant differences (p >0.05) were reported for the EuroSCORE, age, height, weight, body surface area (BSA) and body mass index (BMI).

Table 4.1   Demographic Data: On-pump vs. Off-pump CABG Groups

VARIABLE (UNIT)	ON-PUMP	OFF-PUMP	p-VALUE
EuroSCORE (%)			
Median	4.0	3.3	
25th percentile	2.6	1.8	**0.19**
75th percentile	7.1	6.3	
Age (years)			
Median	58.0	61.0	
25th percentile	54.0	53.0	**0.37**
75th percentile	67.0	67.0	
Height (cm)			
Median	177.5	176.0	**0.84**
25th percentile	170.0	170.0	

VARIABLE (UNIT)	ON-PUMP	OFF-PUMP	p-VALUE
75th percentile	183.0	184.0	
Weight (kg)			
Median	81.5	90.5	
25th percentile	75.0	75.0	**0.72**
75th percentile	96.0	106.0	
BSA (m^2)			
Median	1.9	2.0	
25th percentile	1.8	1.7	**0.82**
75th percentile	2.1	2.2	
BMI (kg/m^2)			
Median	26.5	29.0	
25th percentile	24.5	25.2	**0.34**
75th percentile	31.0	32.8	

Significant differences were noted at $p < 0.05$. [BSA= Body Surface Area; BMI= Body Mass Index; EuroSCORE: calculated using the EuroSCORE II model].

4.2.2 Pre-operative Clinical Data: On-pump vs. Off-pump CABG Groups

The major pre-operative risk factors recorded for the on- and off-pump CABG groups are summarized in Table 4.2.

The majority of pre-operative risk factors (Table 4.2) showed no statistically significant differences between the two groups (p>0.05).

However, the number of patients that were either smokers or ex-smokers was notable. In the on-pump CABG group 24 (80.0%) of the patients either had a history of smoking or were current smokers and in the off-pump CABG group 26 (87.0%) of patients presented as smokers or ex-smokers.

Six (20.0%) patients in both groups had mild COPD, 3 (10.0%) in the off-pump group presented with mild COPD and asthma, 1 (3.3%) in the on-pump group had moderate COPD and 1 (3.33%) in the off-pump group had severe COPD (Table 4.2). Most patients had no pre-operative COPD, thus, with respect to pulmonary disease the on-pump and off-pump groups were similar.

ACS was classified as UA, STEMI and NONSTEMI. One patient (3.3%) in the on-pump group and 5 (16.7%) patients in the off-pump presented with STEMI. Four patients (13.3%) in the on-

pump group and 3 (10.0%) patients in the off-pump presented with NONSTEMI. The majority of patients presented with UA, 25 (83.3%) for the on-pump group and 22 (73.3%) for the off-pump group with no statistically significant difference (p>0.05) between the groups.

Statistically significant differences between the on-pump and off-pump groups were noted for number of previous MI's (p<0.05) and last previous MI's upon admission to Cardiology (p<0.05) (Table 4.2). In the case of the off-pump group the last previous MI was unknown for 18 (60%) of the patients and thus the difference between the groups may not be notable.

Table 4.2   Pre-operative Clinical Data: On-pump vs. Off-pump Groups

VARIABLE (UNIT)	ON-PUMP n (%)	OFF-PUMP n (%)	p-VALUE
LVEF %			
Median	51.0	56.5	
25th percentile	40.0	48.0	**0.21**
75th percentile	65.0	66.0	
Smoking			
Ex-smoker	6 (20.0%)	12 (40.0%)	
Never	6 (20.0%)	4 (13.3%)	**0.27**
Current	18 (60.0%)	14 (46.7%)	
Renal complications			
No	29 (96.7%)	29 (96.7%)	**1.00**
Yes	1 (3.3%)	1 (3.3%)	
Neurological disease			
No	30 (100%)	29 (96.7%)	**0.49**
Yes CVA with full recovery	-	1 (3.3%)	
Pulmonary disease			
None	23 (76.7%)	20 (66.7%)	
Mild COPD	6 (20.0%)	6 (20.0%)	
Moderate COPD	1 (3.3%)	-	**0.30**
Severe COPD	-	1 (3.3%)	
Asthma + Mild COPD	-	3 (10.0%)	
Previous non-surgical intervention			
Previous PCI	3 (10.0%)	2 (6.7%)	**0.67**
PCI > 24hrs before surgery	1 (3.3%)	-	
Dyspnoea			

VARIABLE (UNIT)	ON-PUMP n (%)	OFF-PUMP n (%)	p-VALUE
NYHA I	8 (26.7%)	3 (10.0%)	0.26
NYHA II	18 (60.0%)	23 (76.7%)	
NYHA III	4 (13.3%)	3 (10.0%)	
NYHA I-IV	-	1 (3.3%)	
Diabetes			
None	24 (80.0%)	19 (63.3%)	0.35
Diet	1 (3.3%)	5 (16.7%)	
Oral Therapy	3 (10.0%)	4 (13.3%)	
Insulin	2 (6.7%)	2 (6.7%)	
Hypertension			
Treated	19 (63.3%)	20 (66.7%)	0.17
Acute Coronary Syndrome			
Unstable Angina	25 (83.3%)	22 (73.3%)	0.18
STEMI	1 (3.3%)	4 (16.7%)	
NONSTEMI	4 (13.3%)	3 (10.0%	
Previous MI			
One	8 (26.7%)	3 (10.0%)	0.04
Two or more	14 (46.7%)	12 (40.0%)	
Last previous MI upon admission to Cardiology			
Unknown	10 (33.3%)	18 (60.0%)	0.03
< 6 hrs	14 (46.7%)	5 (16.7%)	
6-24 hrs	1 (3.3%)	1 (3.3%)	
1-30 days	5 (16.7%)	4 (13.3%)	
31-90 days	-	-	
> 90 days	-	2 (6.7%)	

Significant differences were noted at $p < 0.05$. [%= percentage; n= number of patients in each subcategory; LVEF %= Left Ventricle Ejection Fraction percentage; BSA= Body Surface Area; BMI= Body Mass Index; STEMI= ST segment Elevation Myocardial Infarction; NONSTEMI= Non ST segment Myocardial Infarction; MI= Myocardial Infarction; NYHA= New York Heart Association classification; CVA= Cerebrovascular Accident; COPD= Chronic Obstructive Pulmonary Disease].

The data displayed in Table 4.2 indicates that the on- and off-pump CABG groups were mostly comparable with respect to pre-operative risk factors and co-morbidities.

4.3 Intra-operative Metabolic- and Hemodynamic Data for On-pump and Off-pump CABG Groups

4.3.1 Intra-operative Metabolic Data: On-pump and Off-pump CABG Groups

The metabolic and clinical changes seen in the on- and off-pump CABG groups were compared by analysing the patient's intra-operative arterial blood gasses and hemodynamic profiles. The intra-operative metabolic data for the on-pump CABG group are displayed in Table 4.3 and the off-pump CABG group in Table 4.4. Due to the limited sample size the median, 25th and 75th percentiles were calculated. The median values of metabolic data of both groups were plotted on line graphs to compare the two groups and to observe whether any trends could be identified (Figure 4.4-4.6). Metabolic data were recorded intra-operatively at 15 minute time intervals. The baseline ABG represents the first ABG drawn upon the patient's admission to theatre. The second ABG was drawn 5 minutes after intubation. T1-T9 represents intra-operative ABG's that were drawn at 15 minute time intervals from the onset of surgery.

Table 4.3   Intra-operative Metabolic Data: On-pump CABG Group

VARIABLE (UNIT)	BASELINE	INTUBATION	T1	T2	T3	T4	T5	T6	T7	T8	T9
pH											
Median	7.46	7.41	7.42	7.42	7.41	7.41	7.42	7.42	7.40	7.38	7.39
25th percentile	7.44	7.37	7.36	7.35	7.38	7.37	7.34	7.34	7.33	7.34	7.35
75th percentile	7.48	7.43	7.46	7.47	7.46	7.46	7.45	7.45	7.45	7.42	7.40
pCO$_2$ (mmHg)											
Median	34.4	36.7	34.7	34.1	33.9	35.3	41.8	34.3	35.5	37.0	38.1
25th percentile	31.2	33.9	32.3	32.2	32.5	31.9	32.3	32.3	34.7	35.5	37.6
75th percentile	35.9	43.4	37.7	37.9	37.1	38.1	42.0	39.7	40.6	40.5	43.1
pO$_2$ (mmHg)											
Median	71.2	231.0	225.0	205.1	193.0	189.0	188.4	189.0	182.0	203.3	198.0
25th percentile	66.8	187.1	207.4	184.4	173.4	171.8	157.8	149.0	174.4	144.8	149.1
75th percentile	84.9	313.8	263.7	245.5	216.3	213.3	215.5	220.1	232.6	220.8	201.0
HCO$_3$- std (mmol/L)											
Median	24.4	23.5	23.3	22.9	22.6	22.4	24.7	22.5	22.5	22.5	22.7
25th percentile	24.0	23.0	23.0	22.4	22.3	22.2	22.6	22.2	20.4	20.3	21.1
75th percentile	25.5	24.9	24.2	23.9	23.5	23.7	25.0	23.6	24.4	23.8	23.3
BE (B) (mmol/L)											
Median	0.0	-1.1	-1.6	-1.9	-2.3	-2.6	-2.0	-2.3	-2.4	-2.4	-2.1
25th percentile	-1.3	-1.8	-3.6	-4.3	-4.8	-4.4	-5.3	-5.3	-4.9	-5.0	-3.6
75th percentile	1.3	0.4	-0.4	-0.7	-1.2	-1.0	-1.2	-1.0	-0.6	-0.5	-1.3
t Hb (g/dL)											
Median	14.5	13.8	9.9	9.9	10.0	9.5	10.4	9.2	9.5	9.4	8.9
25th percentile	13.8	13.4	9.1	8.9	9.0	8.8	8.4	8.7	8.6	8.3	8.6
75th percentile	15.4	14.7	11.3	10.8	10.6	10.3	10.9	10.2	10.2	10.0	10.3
O$_2$ Sat (%)											
Median	95.1	99.5	98.6	98.7	99.1	98.7	98.5	98.4	98.7	99.0	98.5
25th percentile	94.2	99.3	96.2	97.3	98.2	97.0	97.0	97.0	96.4	97.9	98.0
75th percentile	96.1	99.7	99.6	99.6	99.5	99.5	99.4	99.5	99.5	99.5	99.4
Na+ (mmol/L)											
Median	138.0	139.0	136.0	136.0	136.0	136.0	135.0	135.0	136.0	137.0	138.0
25th percentile	134.2	133.7	134.8	134.1	134.7	134.9	134.0	133.1	134.8	134.5	135.4
75th percentile	139.7	140.0	137.7	138.0	137.9	137.2	137.8	138.0	138.0	138.3	138.6
K+ (mmol/L)											
Median	3.9	3.8	3.4	3.6	3.6	3.9	3.9	4.0	4.2	4.1	3.9
25th percentile	3.4	3.7	3.3	3.4	3.4	3.6	3.7	3.8	3.9	3.7	3.7
75th percentile	4.1	4.0	3.9	3.7	3.7	4.0	4.0	4.3	4.3	4.2	4.1
Ca++ (mmol/L)											
Median	1.2	1.1	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0

VARIABLE (UNIT)	BASELINE	INTUBATION	T1	T2	T3	T4	T5	T6	T7	T8	T9
25th percentile	1.1	1.1	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
75th percentile	1.2	1.1	1.0	1.1	1.0	1.1	1.1	1.1	1.0	1.0	1.1
Cl⁻(mmol/L)											
Median	107.0	109.0	111.0	112.0	112.0	112.0	112.0	112.0	111.0	111.0	112.0
25th percentile	104.0	101.0	108.0	110.0	104.0	106.0	108.0	107.0	108.0	104.0	105.0
75th percentile	110.0	111.0	112.0	113.0	113.0	114.0	113.0	113.0	113.0	112.0	113.0
Glucose (mmol/L)											
Median	5.6	5.6	6.3	6.9	7.5	7.8	7.8	7.8	8.8	9.5	9.5
25th percentile	4.8	4.9	5.1	5.5	6.1	6.6	6.7	7.1	7.8	7.0	7.5
75th percentile	6.2	6.3	7.6	8.9	10.0	10.4	10.8	11.2	11.3	11.5	12.8
Lactate (mmol/L)											
Median	1.2	1.3	2.8	3.6	4.0	4.1	4.1	4.1	3.9	3.8	3.5
25th percentile	0.9	1.0	2.1	2.6	3.2	2.9	3.2	3.4	3.0	2.6	3.0
75th percentile	1.4	1.5	4.2	4.7	5.6	5.4	5.6	5.6	6.1	6.5	7.3

pH= measure of concentration of hydrogen ions, pCO_2= Carbon Dioxide, O_2= Oxygen, HCO_3- & BE (B)= acid-base balance, tHb= Haemoglobin, O_2 Sat (%)= Saturation, Na^+= Sodium, K^+= Potassium, Ca^{++}= Calcium and Cl^-= Chloride. [T1=15 minutes; T2= 30 minutes; T3= 45 minutes; T4= 60 minutes; T5= 75 minutes; T6= 90 minutes; T7= 105 minutes; T8= 120 minutes; T9= 135 minutes].

Table 4.4   Intra-operative Metabolic Data: Off-pump CABG Group

VARIABLE (UNIT)	BASELINE	INTUBATION	T1	T2	T3	T4	T5	T6	T7	T8	T9
pH											
Median	7.45	7.41	7.37	7.38	7.38	7.38	7.35	7.38	7.38	7.37	7.37
25th percentile	7.42	7.38	7.34	7.34	7.35	7.33	7.34	7.32	7.31	7.34	7.32
75th percentile	7.48	7.45	7.42	7.42	7.41	7.40	7.40	7.40	7.40	7.40	7.41
pCO$_2$ (mmHg)											
Median	35.9	37.8	37.2	38.0	38.0	39.6	37.6	37.7	37.2	41.8	41.9
25th percentile	32.3	33.0	35.4	35.2	35.4	36.5	36.5	34.7	35.2	37.7	34.7
75th percentile	39.1	43.0	40.4	41.8	40.9	41.8	41.4	43.2	44.7	43.8	48.7
pO$_2$ (mmHg)											
Median	71.7	229.0	151.0	169.0	165.0	143.0	173.0	167.0	157.0	134.0	134.0
25th percentile	66.1	130.6	113.9	139.0	133.8	118.0	91.9	120.0	82.0	94.4	84.6
75th percentile	126.1	289.9	189.1	200.8	193.3	177.6	189.5	177.6	184.3	188.7	199.7
HCO$_3$- std (mmol/L)											
Median	24.6	23.9	21.9	21.5	22.4	22.2	20.3	22.0	21.7	22.2	22.5
25th percentile	23.7	22.4	20.3	21.0	20.7	20.2	20.0	20.5	21.1	21.5	21.6
75th percentile	25.5	24.8	24.1	24.7	23.5	23.9	23.4	22.9	23.3	23.7	24.1
BE (B) (mmol/L)											
Median	0.4	-0.7	-3.2	-3.7	-2.5	-2.8	-3.8	-3.0	-3.2	-2.8	-2.4
25th percentile	-0.9	-2.2	-5.1	-4.2	-4.6	-5.2	-4.0	-4.9	-4.0	-3.6	-3.5
75th percentile	1.3	0.3	-0.5	0.2	-1.2	-0.7	-1.3	-1.7	-1.5	-0.9	-0.5
t Hb (g/dL)											
Median	13.2	12.7	11.8	11.4	11.1	11.1	10.8	10.9	11.0	11.9	10.9
25th percentile	12.3	11.5	10.5	10.4	10.4	10.5	10.3	9.9	9.8	9.6	10.0
75th percentile	14.9	13.9	13.0	12.4	12.7	12.9	12.9	13.4	13.2	13.0	13.0
O$_2$ Sat (%)											
Median	95.8	99.5	99.6	98.4	99.7	98.4	98.8	98.6	98.7	99.7	98.7
25th percentile	93.3	98.1	96.7	97.7	98.1	97.3	97.2	96.7	93.7	96.2	93.8
75th percentile	96.6	99.7	99.9	99.3	99.8	99.0	99.2	99.2	99.1	99.9	99.2
Na$^+$ (mmol/L)											
Median	138.0	139.0	139.0	138.0	138.0	138.0	137.0	138.0	138.0	138.0	138.0
25th percentile	136.0	136.4	135.8	135.7	135.1	136.0	136.0	136.2	135.9	134.2	136.0
75th percentile	138.9	139.7	140.0	139.2	139.4	139.8	139.7	139.0	139.5	139.1	139.9
K$^+$ (mmol/L)											
Median	3.8	3.7	3.7	3.9	3.9	3.9	3.9	3.8	3.9	4.1	3.8
25th percentile	3.7	3.6	3.5	3.4	3.6	3.4	3.9	3.7	3.8	3.7	3.4
75th percentile	4.0	4.0	4.0	4.0	4.0	4.1	4.3	4.2	4.3	4.4	4.1
Ca^{++} (mmol/L)											
Median	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.0	1.0
25th percentile	1.0	1.0	0.9	1.0	1.0	1.0	0.9	0.9	0.9	1.0	0.9

VARIABLE (UNIT)	BASELINE	INTUBATION	T1	T2	T3	T4	T5	T6	T7	T8	T9
75th percentile	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1
Cl⁻(mmol/L)											
Median	109.0	110.0	112.0	112.0	112.0	112.0	112.0	112.0	112.0	111.0	112.0
25th percentile	107.0	106.0	110.0	110.0	109.2	110.0	110.0	110.0	109.0	108.0	111.0
75th percentile	109.1	111.0	113.0	113.0	114.0	113.0	113.0	114.0	112.5	112.0	112.5
Glucose (mmol/L)											
Median	5.2	5.4	6.5	7.2	7.6	8.1	7.9	7.9	6.8	6.9	7.3
25th percentile	5.0	5.0	5.0	5.3	5.9	5.7	5.7	5.5	6.1	6.6	5.1
75th percentile	6.1	6.8	8.9	8.8	8.9	9.8	11.4	11.5	13.4	12.7	11.8
Lactate (mmol/L)											
Median	1.1	1.2	1.8	2.1	2.3	2.8	2.8	2.9	2.7	2.5	2.8
25th percentile	0.8	0.9	1.4	1.6	1.8	1.9	1.9	1.8	1.7	2.0	1.8
75th percentile	1.4	1.6	3.1	3.2	3.6	3.8	4.0	4.5	3.6	3.7	4.2

pH= measure of concentration of hydrogen ions, pCO_2= Carbon Dioxide, O_2= Oxygen, HCO_3^- & BE (B)= acid-base balance, tHb= Haemoglobin, O_2 Sat (%)= Saturation, Na^+= Sodium, K^+= Potassium, Ca^{++}= Calcium and Cl^-= Chloride. [T1= 15 minutes; T2= 30 minutes; T3= 45 minutes; T4= 60 minutes; T5= 75 minutes; T6= 90 minutes; T7= 105 minutes; T8= 120 minutes; T9= 135 minutes].
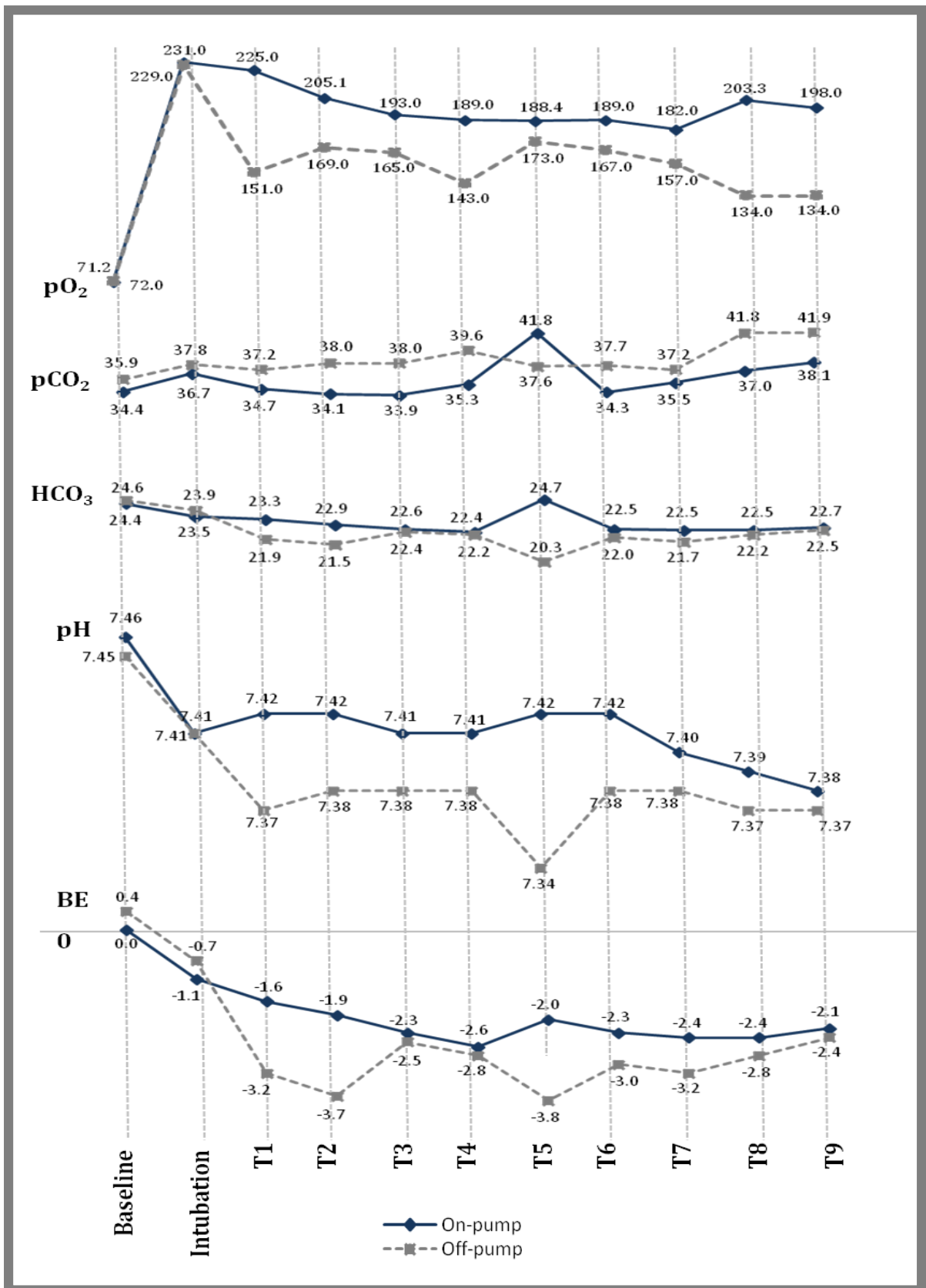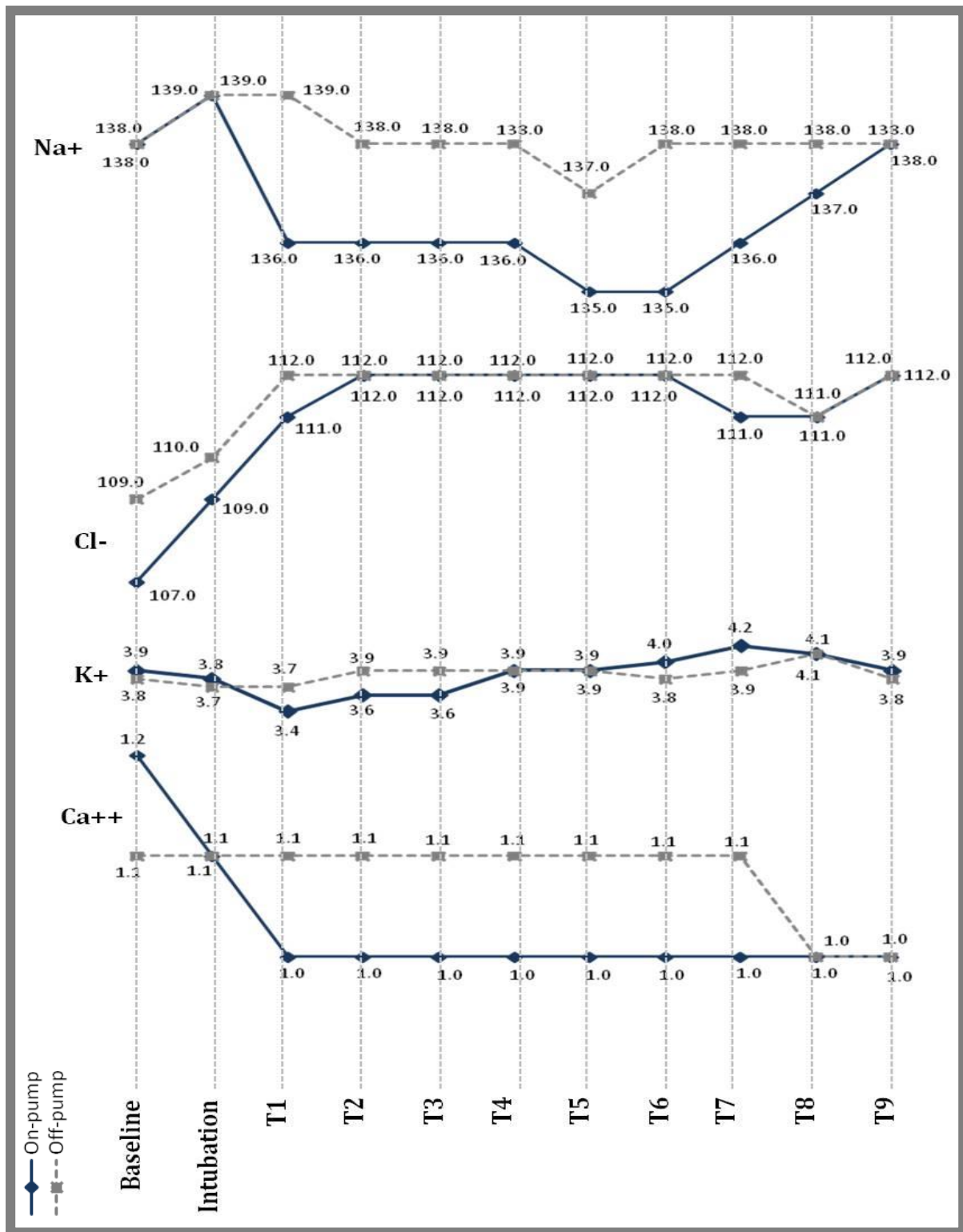
Figure 4.4   Medians for acid-base balance for the on-pump and off-pump CABG groups.

[T1=15 minutes; T2=30 minutes; T3= 45 minutes; T4= 60 minutes; T5= 75 minutes; T6= 90 minutes; T7= 105 minutes; T8= 120 minutes; T9= 135 minutes].
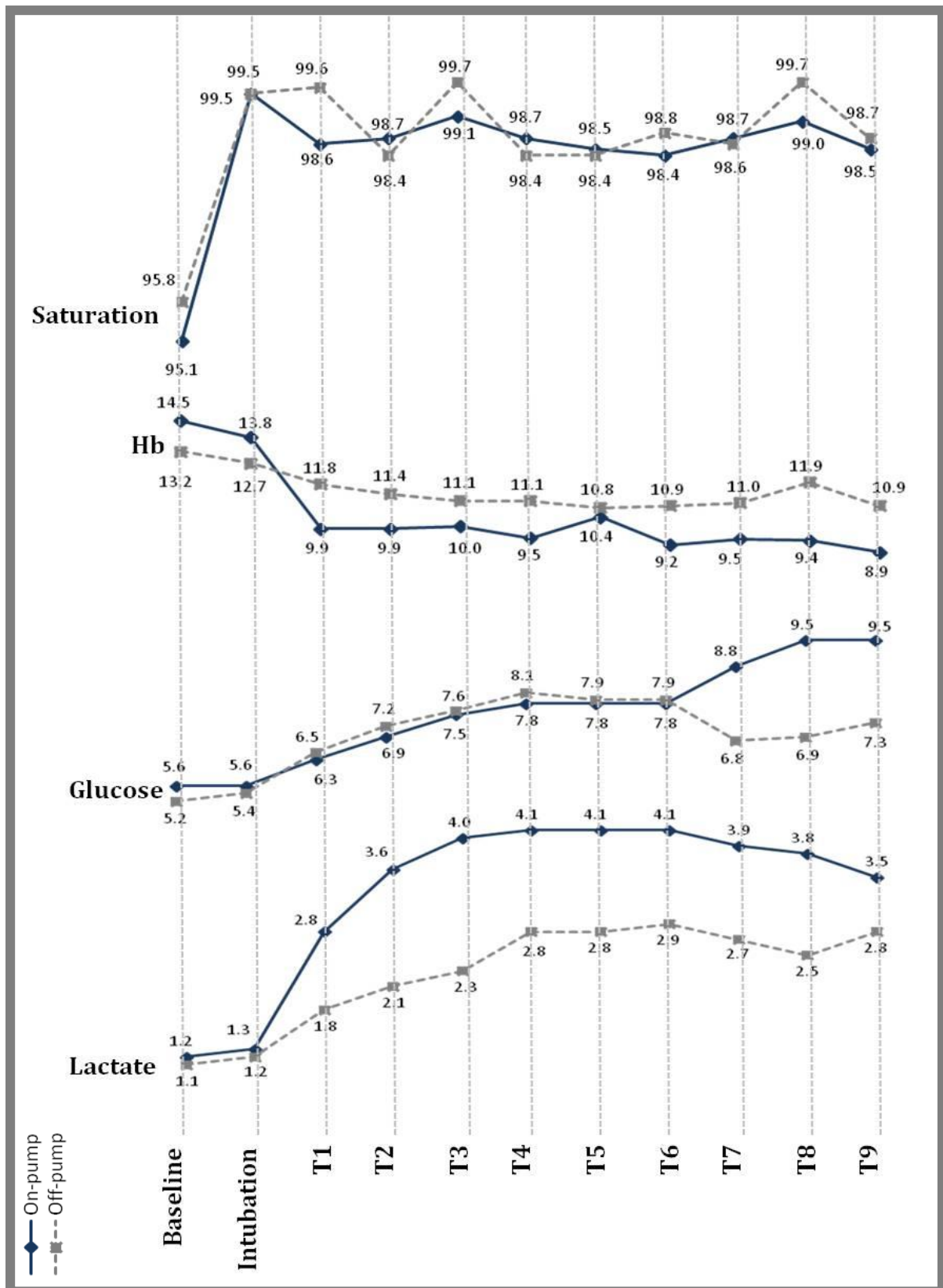
Figure 4.5 **Medians for metabolites: saturation (%) and haemoglobin (Hb), glucose and lactate for the on-pump and off-pump groups.**

[T1=15 minutes; T2= 30 minutes; T3= 45 minutes; T4= 60 minutes; T5= 75 minutes; T6= 90 minutes; T7= 105 minutes; T8= 120 minutes; T9= 135 minutes].

Figure 4.6   Medians for Electrolytes: Sodium (Na+), Chloride (Cl-), Potassium (K+) and Calcium (Ca++) for the on-pump and off-pump groups.

[T1=15 minutes; T2= 30 minutes; T3= 45 minutes; T4= 60 minutes; T5= 75 minutes; T6= 90 minutes; T7= 105 minutes; T8= 120 minutes; T9= 135 minutes].

4.3.1.1 P-values for Intra-operative Metabolic Data: On-pump vs. Off-pump CABG Groups

There were no statistically significant differences ($p > 0.05$) for the acid-base variables, pH, pO_2 and pCO_2 (Table 4.5).

The other variables for acid-base balance; HCO_3- and BE (B), showed statistically significant ($p < 0.05$) differences during most of the surgery.

The metabolites, O_2 Sat (%) and glucose showed no statistically significant differences ($p > 0.05$), however, tHb (g/dL) and lactate showed statistically significant differences ($p < 0.05$) during most of the surgery.

The electrolytes, K^+, Ca^{++}, Na^+ and Cl^-, indicated no statistically significant differences ($p > 0.05$). Overall the groups were comparable with only a few statistically significant differences observed between the two groups.

Table 4.5   P-values for Intra-operative Metabolic Data: On-pump vs. Off-pump CABG Groups

VARIABLE (UNIT)	BASELINE	INTUBATION	T1	T2	T3	T4	T5	T6	T7	T8	T9
pH	0.68	0.14	5.15	4.70	6.67	4.52	1.49	0.47	1.34	0.47	0.12
pCO_2 (mmHg)	0.96	0.22	4.72	7.20	9.44	14.7	11.9	0.92	1.65	3.58	0.87
pO_2 (mmHg)	0.63	0.89	17.6	7.80	4.76	11.7	5.19	4.17	12.0	3.34	0.63
HCO_3- STD mmol/L	0.03	0.19	1.34	0.00	0.00	0.04	0.03	1.11	0.34	0.02	0.40
BE (B) (mmol/L)	0.10	0.01	0.96	0.00	0.00	0.04	0.02	0.91	0.24	0.00	0.26
tHb (g/dL)	1.23	1.28	0.00	0.00	0.00	<0.0	<0.0	0.00	0.00	0.00	0.09
O_2 SAT (%)	0.06	1.84	8.37	4.50	1.33	2.32	1.63	7.40	6.03	9.02	1.59
Na^+ (mmol/L)	1.34	1.70	1.00	2.00	1.83	3.00	0.78	0.90	0.49	1.01	1.51
K^+ (mmol/L)	0.63	0.78	0.59	0.74	1.74	1.98	1.00	1.51	1.41	1.52	0.99
Ca^{++} (mmol/L)	0.98	1.00	1.55	1.08	1.01	0.88	1.74	2.00	4.79	0.19	0.48
Cl^- (mmol/L)	0.32	0.10	0.66	0.49	0.97	0.53	0.62	0.42	0.88	0.71	0.70

VARIABLE (UNIT)	BASELINE	INTUBATION	T1	T2	T3	T4	T5	T6	T7	T8	T9
Glucose (mmol/L)	0.10	0.11	0.73	0.17	0.06	0.19	0.15	1.13	0.56	0.65	2.32
Lactate (mmol/L)	0.63	0.06	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.11	0.07

pH= measure of concentration of hydrogen ions, pCO_2= Carbon Dioxide, O_2= Oxygen, HCO_3^- & BE (B)= acid-base balance, tHb= Haemoglobin, O_2 Sat (%)= Saturation, Na^+= Sodium, K^+= Potassium, Ca^{++}= Calcium and Cl^-= Chloride. [T1=15 minutes; T2= 30 minutes; T3= 45 minutes; T4= 60 minutes; T5= 75 minutes; T6= 90 minutes; T7= 105 minutes; T8= 120 minutes; T9= 135 minutes]. The p-values were calculated using the Kruskal–Wallis test for the comparison of medians.

4.3.2 Post-hoc Power Analysis: Mean Intra-operative and Post-operative Lactate Levels

Table 4.6 summarizes the difference between the on-pump and off-pump groups with respect to the mean intra-operative lactate levels and the mean post-operative lactate levels.

Table 4.6   Post-hoc Power Analysis: Mean Intra-operative and Post-operative Lactate Levels for On-pump and Off-pump CABG Groups

VARIABLE (UNIT)	ON-PUMP	OFF-PUMP	DIFFERENCE (ON-PUMP – OFF-PUMP)
Mean intra-operative lactate level (mmol/L)	3.7	2.4	1.3 (p = 0.00)
Mean post-operative lactate level (mmol/L)	4.2	2.9	1.3 (p = 0.00)

p-value was calculated using the Wilcoxon-Mann-Whitney test for the comparison of means.

The differences between the groups, with respect to the mean intra-operative lactate levels and the mean post-operative lactate levels, were statistically significant. The p-values were (p= 0.00

and p= 0.00) for the mean intra-operative lactate levels and the mean post-operative lactate levels, respectively.

The usefulness of post hoc power analyses is disputed, however since this was a pilot study a post hoc analysis was done, on what was considered to be the primary comparison in the study, in order to assess if the study could be considered reasonably powered to show any differences. Cohen, 1988 suggests that a minimum power of 80% is needed to speculate whether a study carries any statistical value.

Our study had a modest sample size (n=60), which may have played a role in limiting the significance of some of the statistical comparisons conducted. However, a post-hoc power analysis, on the difference between the on-pump and off-pump patients with respect to the mean lactate levels during surgery, revealed that this study had a power of more than the recommended 80% (d=0.88), indicating that there was a strong probability of detecting an effect when it exists in our sample size.

4.3.3 Intra-operative Hemodynamic Data and Temperature: On-pump and Off-pump CABG Groups

The intra-operative hemodynamic data captured for the on- and off-pump groups are presented in Tables 4.7 and 4.8, respectively.

The median values of hemodynamic data, for the on- and off-pump groups, were plotted on a line graph to observe trends between the 2 groups with reference to hemodynamic instability (Figure 4.7). Hemodynamic data were recorded at 5 minute time intervals but for the purpose of this study hemodynamic data was only displayed at baseline, intubation and T1-T9 (15 minute intervals).

Table 4.7   Intra-operative Hemodynamic Data and Temperature: On-pump CABG Group

VARIABLE (UNIT)	BASELINE	INTUBATION	T1	T2	T3	T4	T5	T6	T7	T8	T9
Systolic Pressure (mmHg)											
Median	102.6	101.4	124.1	78.4	68.1	66.5	68.9	70.4	68.2	67.9	64.1
25th percentile	101.4	100.9	95.6	74.6	64.6	65.3	64.2	58.9	58.9	57.0	60.0
75th percentile	147.7	149.2	124.6	114.0	107.1	108.0	95.2	84.3	98.5	118.0	109.4
Diastolic Pressure (mmHg)											
Median	52.1	55.9	57.6	50.4	66.6	62.6	64.5	65.2	61.1	64.1	57.8
25th percentile	50.0	51.5	49.3	50.0	60.1	62.4	63.5	52.9	58.4	57.0	54.0
75th percentile	56.3	58.0	57.8	66.7	68.0	65.1	66.9	69.9	68.3	68.0	67.9
Mean Arterial Pressure (mmHg)											
Median	88.3	87.3	95.2	71.8	67.6	63.7	67.9	69.3	59.8	64.1	57.8
25th percentile	76.3	73.1	69.4	67.4	60.5	54.7	58.6	52.9	54.7	63.3	54.1
75th percentile	108.8	106.0	96.1.0	87.6	97.0	94.0	78.7	70.9	71.4	81.0	75.5
CVP (mmHg)											
Median	6.0	6.2	7.4	4.2	3.2	1.6	1.3	1.2	1.3	2.9	2.6
25th percentile	5.4	5.0	3.2	3.0	1.3	1.3	1.0	1.0	2.0	2.2	2.0
75th percentile	6.8	7.9	8.0	4.8	4.6	2.7	2.9	2.7	3.1	3.6	3.6
HR (beats/min)											
Median	67.0	68.0	70.0	71.0	0.0	0.0	0.0	47.0	56.0	40.5	37.0
25th percentile	64.0	66.0	61.0	0.0	0.0	0.0	0.0	41.0	37.0	31.0	29.0
75th percentile	69.0	72.0	77.0	72.0	68.0	70.0	71.0	78.0	82.0	81.0	89.0
Temperature (°C)											
Median	35.9	35.9	35.8	35.2	32.3	30.1	32.2	32.2	35.4	36.1	34.3
25th percentile	35.1	35.5	35.1	31.2	29.7	29.5	30.5	30.6	35.0	34.2	34.0
75th percentile	36.0	36.0	35.8	35.7	33.0	31.1	33.7	35.7	36.3	36.2	36.9

CVP= central venous pressure, HR= heart rate. Temperature was measured in degrees Celsius (°C). [T1=15 minutes; T2= 30 minutes; T3= 45 minutes; T4= 60 minutes; T5= 75 minutes; T6= 90 minutes; T7= 105 minutes; T8= 120 minutes; T9= 135 minutes].

Table 4.8 **Intra-operative Hemodynamic Data and Temperature: Off-pump CABG Group**

VARIABLE (UNIT)	BASELINE	INTUBATION	T1	T2	T3	T4	T5	T6	T7	T8	T9
Systolic Pressure (mmHg)											
Median	162.4	170.4	150.0	112.4	107.7	102.4	104.6	96.5	121.5	103.3	115.0
25th percentile	97.5	101.0	93.9	102.1	106.3	95.5	91.6	96.1	95.7	91.6	77.7
75th percentile	179.0	183.0	167.0	144.2	139.8	113.0	124.5	111.0	138.2	124.9	124.5
Diastolic Pressure (mmHg)											
Median	72.0	82.0	68.6	54.8	57.2	56.6	55.2	53.5	55.7	53.1	50.9
25th percentile	68.4	57.2	54.0	50.7	51.1	50.0	49.1	51.5	49.7	44.2	40.2
75th percentile	89.1	83.1	75.3	63.0	60.9	64.2	70.2	71.4	60.8	71.2	55.0
Mean Arterial Pressure (mmHg)											
Median	112.9	116.9	95.4	88.5	80.2	77.8	74.9	67.6	78.2	71.9	75.9
25th percentile	64.2	76.2	77.9	71.3	67.7	70.9	70.9	64.2	68.3	68.0	65.0
75th percentile	133.8	117.8	103.4	95.9	95.7	94.3	94.3	86.7	86.9	87.0	81.1
CVP (mmHg)											
Median	4.0	3.8	2.9	8.9	9.4	9.5	8.5	8.1	7.7	14.4	6.8
25th percentile	0.7	2.1	2.3	6.7	9.2	8.3	6.8	5.4	4.1	5.5	4.8
75th percentile	5.0	6.9	11.0	14.2	14.9	12.7	11.4	9.8	13.1	15.7	9.4
HR (beats/min)											
Median	67.0	68.0	56.0	71.0	62.0	70.0	68.0	74.0	73.0	70.0	57.0
25th percentile	61.0	62.0	54.0	53.0	58.0	55.0	58.0	65.0	62.0	53.0	55.0
75th percentile	75.0	74.0	78.0	74.0	80.0	77.0	84.0	81.0	90.0	80.0	75.0
Temperature (˚C)											
Median	36.7	36.5	36.4	36.1	35.8	35.8	35.9	35.7	35.9	35.7	35.7
25th percentile	36.3	36.1	35.9	35.5	35.6	35.7	35.3	35.6	35.4	35.4	35.3
75th percentile	36.9	36.5	36.5	36.1	36.8	36.1	36.2	36.2	36.9	36.7	36.7

CVP= central venous pressure, HR= heart rate. Temperature was measured in degrees Celsius (°C). [T1=15 minutes; T2= 30 minutes; T3= 45 minutes; T4= 60 minutes; T5= 75 minutes; T6= 90 minutes; T7= 105 minutes; T8= 120 minutes; T9= 135 minutes].
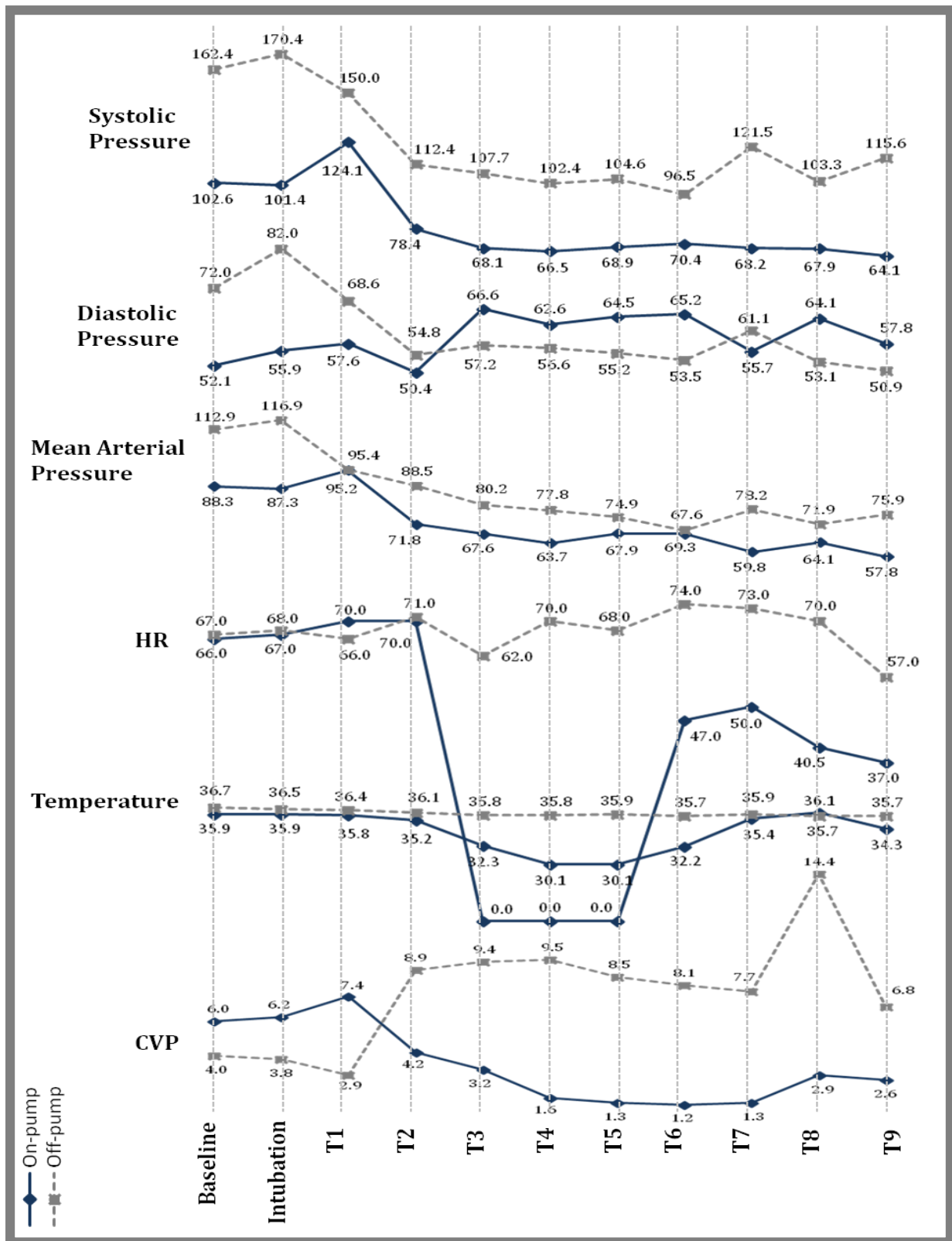
Figure 4.7   Medians for hemodynamic data and temperature during on-pump and off-pump CABG surgery.

[CVP= central venous pressure, HR= heart rate. Temperature was measured in degrees Celsius (°C). [T1=15 minutes; T2= 30 minutes; T3= 45 minutes; T4= 60 minutes; T5= 75 minutes; T6= 90 minutes; T7= 105 minutes; T8= 120 minutes; T9= 135 minutes].

4.3.3.1 P-values for Intra-operative Hemodynamic Data and Temperature: On-pump vs. Off-pump CABG Groups

Statistically significant differences between the on- and off pump groups were noted for systolic pressures, diastolic pressures, mean arterial pressures, HR, CVP and body temperature for most of the duration of surgery (p<0.05) (Table 4.9).

Table 4.9   P-values for Intra-operative Hemodynamic Data and Temperature: On-pump vs. Off-pump Groups

VARIABLE (UNIT)	BASELINE	INTUBATION	T1	T2	T3	T4	T5	T6	T7	T8	T9
Systolic Pressure (mmHg)											
	0.60	0.40	0.02	<0.01	<0.01	<0.01	<0.01	<0.01	0.00	0.00	0.12
Diastolic Pressure (mmHg)											
	6.03	10.29	0.01	0.01	0.00	0.00	<0.01	0.02	0.00	<0.01	0.79
Mean Arterial Pressure (mmHg)											
	0.22	0.10	0.02	0.00	0.01	0.01	0.00	<0.01	0.00	0.00	0.34
HR (beats/min)											
	0.54	0.20	0.07	0.01	0.00	0.00	0.00	0.01	0.04	0.04	0.66
CVP (mmHg)											
	0.08	0.86	0.06	0.00	0.02	0.04	<0.01	0.00	<0.01	0.20	0.41
Temperature (°C)											
	6.21	1.18	0.12	0.02	0.01	0.05	0.03	0.01	0.09	0.49	0.25

CVP= central venous pressure, HR= heart rate, temperature was measured in degrees Celsius (°C). [T1=15 minutes; T2= 30 minutes; T3= 45 minutes; T4= 60 minutes; T5= 75 minutes; T6= 90 minutes; T7= 105 minutes; T8= 120 minutes; T9= 135 minutes]. The p-values were calculated with the Kruskal-Wallis test where used for the comparison of medians.

4.4 Post-operative Metabolic Data: On-pump and Off-pump CABG Groups

4.4.1 Post-operative Metabolic Data: On-pump CABG Group

Metabolic changes in the on- and off-pump CABG groups were observed by comparing metabolic data during the post-operative period (from 1hr - 72hrs upon admission to ICU) (Table 4.10 and Table 4.11). The ABG's were drawn post-operatively at specified time intervals; 1 hr, 2 hrs, 4 hrs, 8 hrs, 12 hrs, 24 hrs, 48 hrs and 72 hrs.

Table 4.10 **Post-operative Metabolic Data: On-pump CABG Group**

VARIABLE (UNIT)	1HR POST OPERATIVE	2HRS POST OPERATIVE	4HRS POST OPERATIVE	8HRS POST OPERATIVE	12HRS POST OPERATIVE	24HRS POST OPERATIVE	48HRS POST OPERATIVE	72HRS POST OPERATIVE
pH								
Median	7.29	7.33	7.33	7.38	7.43	7.47	7.49	7.49
25th percentile	7.26	7.26	7.31	7.38	7.38	7.45	7.47	7.44
75th percentile	7.34	7.36	7.39	7.42	7.45	7.49	7.51	7.51
pCO$_2$ (mmHg)								
Median	42.3	41.0	35.2	34.3	33.9	33.8	33.6	34.8
25th percentile	39.0	35.7	33.2	31.9	31.8	31.3	30.6	32.5
75th percentile	46.2	43.4	40.3	38.6	36.6	36.4	39.2	37.4
pO$_2$(mmHg)								
Median	114.7	97.0	97.1	91.6	85.2	75.7	70.2	69.7
25th percentile	96.6	88.8	81.8	83.0	81.6	63.5	59.6	46.9
75th percentile	136.5	117.0	114.6	105.2	106.1	83.9	81.0	82.1
HCO$_3$- STD (mmol/L)								
Median	19.3	19.8	20.2	21.3	22.7	25.4	26.2	26.2
25th percentile	17.9	17.7	18.0	19.2	20.3	23.3	25.2	25.4
75th percentile	21.2	21.5	21.5	22.5	24.6	26.8	27.0	27.2
BE (B) (mmol/L)								
Median	-6.4	-5.7	-5.2	-3.8	-2.2	1.0	1.9	2.0
25th percentile	-8.0	-7.9	-7.9	-6.4	-5.0	-1.3	1.1	1.1

VARIABLE (UNIT)	1HR POST OPERATIVE	2HRS POST OPERATIVE	4HRS POST OPERATIVE	8HRS POST OPERATIVE	12HRS POST OPERATIVE	24HRS POST OPERATIVE	48HRS POST OPERATIVE	72HRS POST OPERATIVE
75th percentile	-3.4	-3.5	-3.6	-2.4	0.2	2.8	2.8	3.2
tHb (g/dL)								
Median	12.5	14.2	15.0	14.1	12.0	9.7	7.8	7.5
25th percentile	10.2	11.1	11.0	10.4	10.8	9.3	6.4	6.0
75th percentile	13.7	15.5	18.8	15.2	13.4	12.6	11.5	12.0
O₂ Sat (%)								
Median	97.8	97.0	96.8	97.1	96.7	95.8	95.0	96.0
25th percentile	96.2	95.7	95.4	95.6	95.6	93.4	93.5	89.5
75th percentile	98.2	97.8	97.8	97.5	97.8	96.8	96.6	97.1
Na⁺ (mmol/L)								
Median	139.0	138.5	138.3	137.6	138.2	138.1	134.6	133.6
25th percentile	136.1	137.4	138.0	136.5	138.0	137.1	134.0	133.0
75th percentile	139.0	139.0	138.6	138.1	138.5	138.7	136.0	135.9
K⁺ (mmol/L)								
Median	3.5	3.7	4.3	4.1	4.2	4.1	4.2	4.1
25th percentile	3.4	3.5	4.0	4.0	4.0	3.5	4.0	4.0
75th percentile	3.7	3.9	4.3	4.5	4.5	4.3	4.3	4.4
Ca⁺⁺ (mmol/L)								
Median	1.0	1.0	1.0	1.0	1.0	1.0	1.1	1.1
25th percentile	1.0	1.0	1.0	0.9	0.9	1.0	1.0	1.1
75th percentile	1.0	1.0	1.0	1.0	1.0	1.1	1.1	1.1
Cl⁻ (mmol/L)								
Median	111.0	110.0	111.0	110.5	111.0	109.5	106.0	105.0
25th percentile	110.0	109.0	110.0	110.0	110.0	109.0	104.0	104.0
75th percentile	111.5	111.0	111.5	111.0	112.0	110.0	108.0	108.0
Glucose (mmol/L)								
Median	11.1	11.7	11.9	11.8	11.5	11.1	10.6	10.6
25th percentile	10.4	11.5	11.8	11.7	10.9	8.1	6.7	6.1
75th percentile	15.2	15.8	16.8	15.8	13.4	12.4	10.9	11.1
Lactate (mmol/L)								
Median	6.3	6.4	6.3	5.9	3.9	1.9	1.5	1.2
25th percentile	3.0	3.2	3.0	3.0	2.3	1.3	1.0	0.9
75th percentile	8.6	8.6	8.8	8.3	6.2	2.7	1.7	1.5

pH= measure of concentration of hydrogen ions, pCO_2= Carbon Dioxide, O_2= Oxygen, HCO_3- & BE (B)= acid-base balance, tHb= Haemoglobin, O_2 Sat (%)= Saturation, Na^+= Sodium, K^+= Potassium, Ca^{++}= Calcium and Cl^-= Chloride.

[Data taken at specified times after admission in ICU at 1-, 2-, 4-, 8-, 12-, 24-, 48- and 72 hours during the post-operative period].

Table 4.11   Post-operative Metabolic Data: Off-pump CABG Group

VARIABLE (UNIT)	1HR POST OPERATIVE	2HRS POST OPERATIVE	4HRS POST OPERATIVE	8HRS POST OPERATIVE	12HRS POST OPERATIVE	24HRS POST OPERATIVE	48HRS POST OPERATIVE	72HRS POST OPERATIVE
pH								
Median	7.36	7.35	7.38	7.40	7.43	7.47	7.46	7.45
25th percentile	7.31	7.32	7.35	7.36	7.38	7.43	7.43	7.42
75th percentile	7.39	7.40	7.42	7.44	7.45	7.48	7.48	7.46
pCO_2 (mmHg)								
Median	40.9	37.7	35.9	33.8	33.1	32.5	33.5	37.8
25th percentile	35.9	34.2	33.5	31.0	29.6	29.9	31.0	32.0
75th percentile	43.2	42.4	38.9	37.4	35.6	37.7	37.6	42.7
pO_2 (mmHg)								
Median	120.5	97.5	96.7	91.8	75.1	73.7	74.7	69.7
25th percentile	86.8	81.9	85.0	71.0	67.9	67.0	64.5	60.8
75th percentile	140.9	126.4	121.2	111.9	94.0	80.4	88.5	85.5
HCO_3^- STD (mmol/L)								
Median	21.9	21.5	21.7	21.6	23.2	23.7	24.7	24.9
25th percentile	20.2	19.6	20.0	20.4	20.8	22.4	23.5	23.3
75th percentile	22.6	22.8	23.8	23.9	24.1	25.8	25.9	26.8
BE (B) (mmol/L)								
Median	-2.9	-3.4	-2.7	-2.7	-0.7	-0.3	0.4	1.1
25th percentile	-5.1	-5.7	-5.0	-4.8	-4.2	-1.9	-1.0	-1.4
75th percentile	-1.2	-1.5	-0.1	1.1	1.4	2.2	2.4	3.1
tHb (g/dL)								
Median	9.4	11.5	12.5	11.2	10.6	8.4	7.6	7.5
25th percentile	8.0	10.5	11.2	10.1	9.4	7.1	5.5	5.8
75th percentile	12.9	12.9	12.8	12.5	12.8	12.3	12.5	13.2
O_2 Sat (%)								
Median	97.8	97.3	97.0	96.8	95.7	95.7	96.2	95.2
25th percentile	96.2	95.6	96.1	95.1	94.0	94.6	93.0	92.6
75th percentile	98.7	98.3	98.4	98.0	97.7	97.5	97.0	96.7
Na^+ (mmol/L)								
Median	138.7	138.8	137.9	137.2	137.6	136.9	135.7	135.0
25th percentile	134.8	134.7	137.7	134.9	133.7	135.0	135.2	134.8
75th percentile	139.2	139.0	138.0	138.2	138.0	137.4	136.7	136.8
K^+ (mmol/L)								
Median	3.8	4.0	4.2	4.1	4.2	4.2	4.2	4.2
25th percentile	3.5	3.6	4.0	3.0	3.0	4.1	4.0	4.0
75th percentile	3.9	4.2	4.2	4.1	4.3	4.4	4.4	4.8

VARIABLE (UNIT)	1HR POST OPERATIVE	2HRS POST OPERATIVE	4HRS POST OPERATIVE	8HRS POST OPERATIVE	12HRS POST OPERATIVE	24HRS POST OPERATIVE	48HRS POST OPERATIVE	72HRS POST OPERATIVE
Ca^{++} (mmol/L)								
Median	1.0	1.0	1.0	1.0	1.0	1.1	1.1	1.1
25th percentile	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.1
75th percentile	1.1	1.1	1.1	1.0	1.1	1.1	1.1	1.1
Cl^- (mmol/L)								
Median	110.0	110.0	109.0	111.0	110.0	109.5	107.0	106.5
25th percentile	109.0	109.0	107.0	110.0	108.0	108.0	106.0	106.0
75th percentile	111.0	111.0	110.0	112.0	111.0	111.0	111.0	112.0
Glucose (mmol/L)								
Median	11.9	11.9	11.9	11.6	11.7	11.6	11.5	12.1
25th percentile	7.5	8.3	9.6	9.3	8.7	7.2	7.1	6.3
75th percentile	12.5	13.3	14.6	12.9	12.8	12.3	13.4	12.9
Lactate (mmol/L)								
Median	2.7	2.8	2.8	2.6	2.1	1.6	1.3	1.2
25th percentile	1.6	1.9	1.8	1.6	1.3	1.3	1.0	0.9
75th percentile	5.5	4.8	5.7	4.9	4.8	2.5	1.7	1.5

pH= measure of concentration of hydrogen ions, pCO_2= Carbon Dioxide, O_2= Oxygen, HCO_3- & BE (B)= acid-base balance, tHb= Haemoglobin, O_2 Sat (%)= Saturation, Na^+= Sodium, K^+= Potassium, Ca^{++}= Calcium and Cl^-= Chloride. [Data taken at specified times after admission in ICU at 1-, 2-, 4-, 8-, 12-, 24-, 48- and 72 hours during the post-operative period].

The medians of post-operative metabolic data for the on-pump and off-pump groups were plotted on line graphs to observe whether any trends could be identified in the 2 groups (Figure 4.8 - 4.10).

Figure 4.8 depicts the trends that were seen for all acid-base values during the first 72 hours post-operatively.

The trends in the on-pump and off-pump groups with respect to metabolites; saturation (%) and haemoglobin (Hb) are illustrated in Figure 4.9, followed by the electrolyte levels in Figure 4.10.
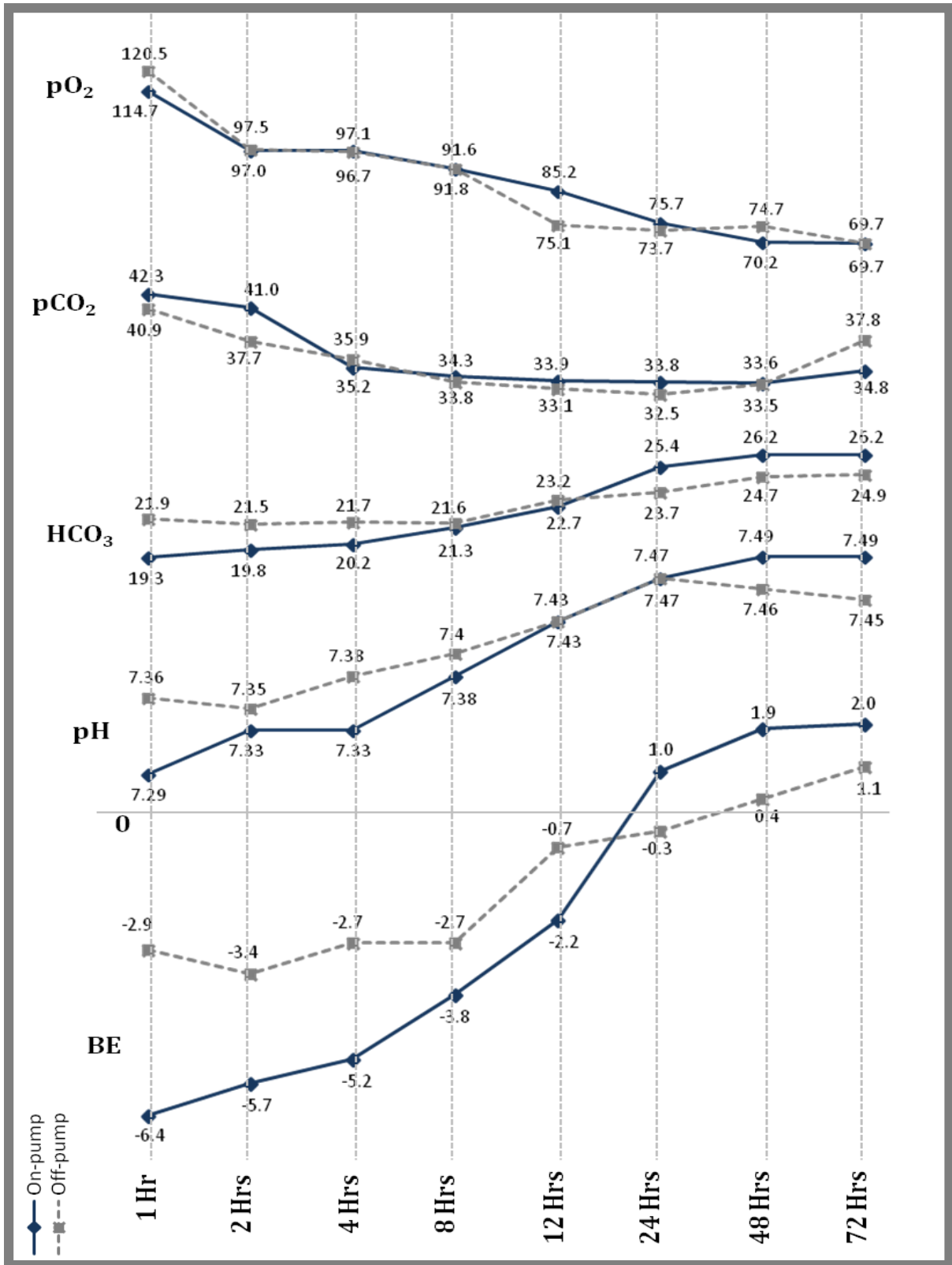
Figure 4.8   Medians for acid-base balance for on-pump and off-pump CABG groups during the first 72 hours post-operatively.

[T1=15 minutes; T2=30 minutes; T3= 45 minutes; T4= 60 minutes; T5= 75 minutes; T6= 90minutes; T7= 105 minutes; T8= 120 minutes; T9= 135 minutes].
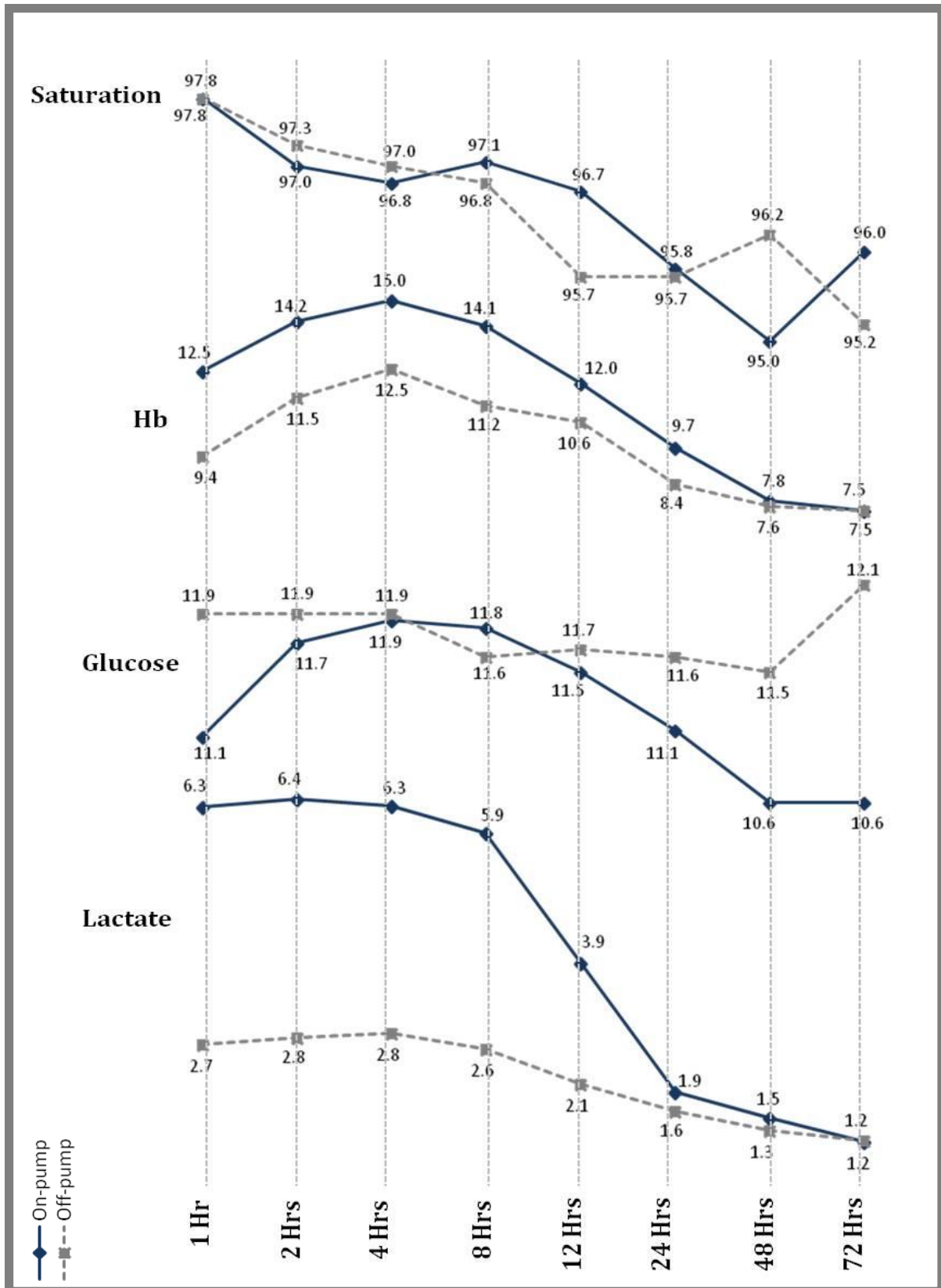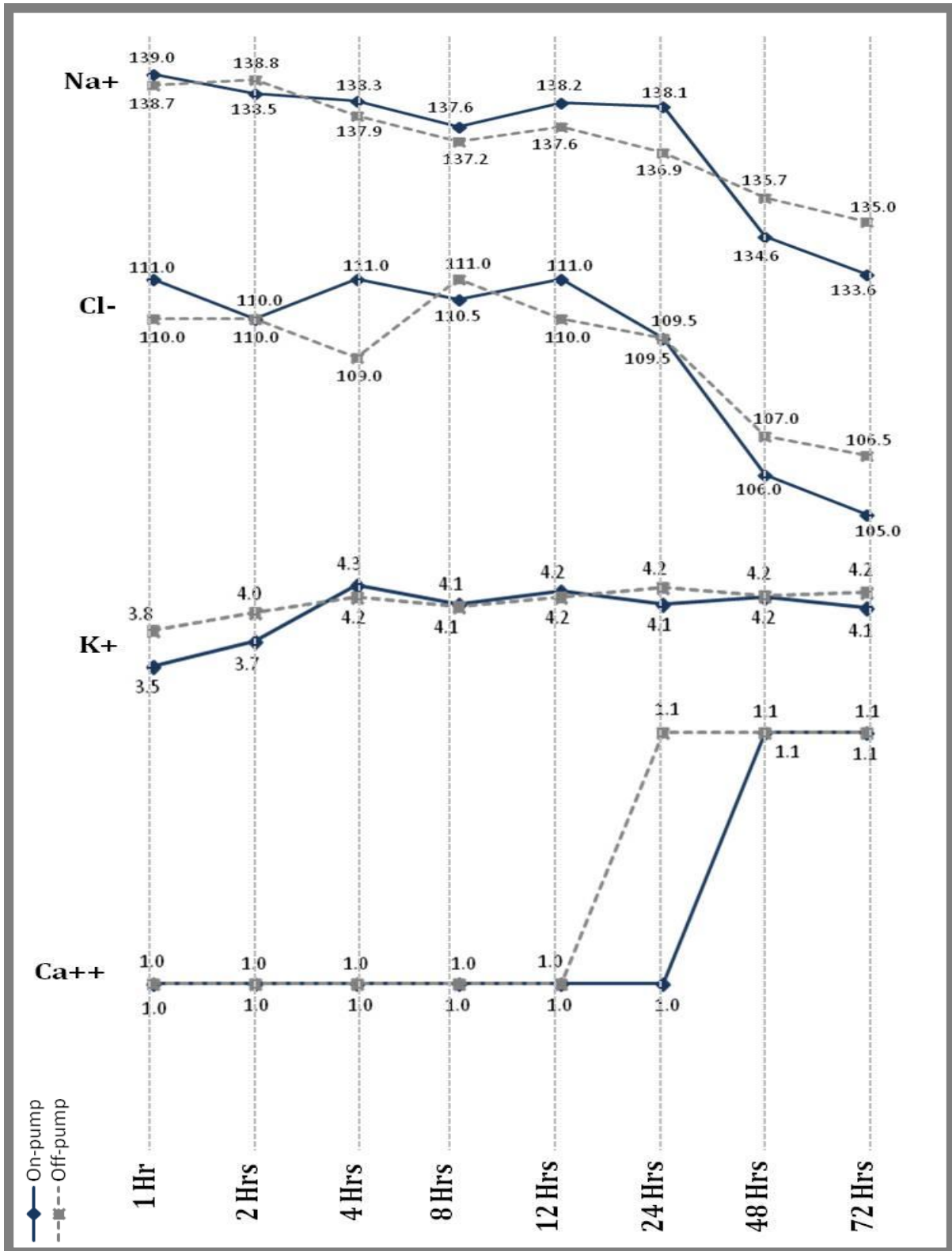
Figure 4.9 **Medians for metabolites, saturation (%) and haemoglobin (Hb) for on-pump and off-pump groups during the first 72 hours post-operatively.**

[T1=15 minutes; T2=30 minutes; T3= 45 minutes; T4= 60 minutes; T5= 75 minutes; T6= 90 minutes; T7= 105 minutes; T8= 120 minutes; T9= 135 minutes].

Figure 4.10 **Medians for electrolytes, Sodium (Na+), Potassium (K+), Calcium (Ca++) and chloride (Cl-) for on-pump and off-pump group up to 72 hours post-operatively.**

[T1=15 minutes; T2=30 minutes; T3= 45 minutes; T4= 60 minutes; T5= 75 minutes; T6= 90minutes; T7= 105 minutes; T8= 120 minutes; T9= 135 minutes].

4.4.2 P-values for Post-operative Metabolic Data: On-pump vs. Off-pump CABG Groups

Post-operative metabolic data were summarised up to 72 hrs after admission to ICU for the on-pump vs. off-pump surgery group in Table 4.12.

Variables for the acid-base balance, pO_2 and pCO_2, showed no statistically significant ($p > 0.05$) differences between the two groups. Other variables for acid-base balance, pH, HCO_3^- and BE (B), ($p < 0.05$), showed statistically significant differences ($p < 0.05$) from admission to ICU until 4 hours post-operatively.

The metabolites O_2 SAT% and tHb (g/dL) showed no statistically significant differences ($p > 0.05$). However, glucose levels and lactate levels showed statistically significant differences ($p < 0.05$) from admission to ICU until 12 hours post-operatively.

The electrolytes K^+, Ca^{++}, Na^+ and Cl^- indicated no statistically significant differences ($p > 0.05$).

Table 4.12   P-values for Post-operative Metabolic Data: On-pump vs. Off-pump CABG Group

VARIABLE (UNIT)	1 HR POST-OPERATIVE	2 HRS POST-OPERATIVE	4 HRS POST-OPERATIVE	8 HRS POST-OPERATIVE	12 HRS POST-OPERATIVE	24 HRS POST-OPERATIVE	48 HRS POST-OPERATIVE	72 HRS POST-OPERATIVE
pH	0.00	0.04	0.01	0.10	0.08	0.09	0.06	0.14
pCO_2 (mmHg)	0.16	0.26	0.68	0.24	0.48	0.61	0.91	0.31
pO_2 (mmHg)	0.72	0.90	0.67	0.86	0.07	0.86	0.20	0.90
HCO_3^- STD (mmol/L)	0.00	0.03	0.02	0.34	0.09	0.05	0.30	0.06
BE (B) (mmol/L)	0.00	0.00	0.00	0.09	0.23	0.42	0.07	0.07
tHb (g/dL)	0.12	0.78	0.98	0.58	0.48	0.42	0.09	0.10
O_2 SAT (%)	0.57	0.68	0.26	0.72	0.14	0.74	0.64	0.58
Na^+ (mmol/L)	1.74	1.50	1.04	1.0	1.31	2.0	0.81	0.60
K^+ (mmol/L)	0.63	0.78	0.59	0.74	1.74	1.98	1.0	1.51
Ca^{++} (mmol/L)	0.98	1.0	1.27	1.48	1.71	0.58	1.44	1.0
Cl^- (mmol/L)	0.28	0.70	0.98	1.0	0.76	0.93	0.72	0.54
Glucose (mmol/L)	0.00	0.00	0.00	0.00	0.02	0.14	0.93	0.39
Lactate (mmol/L)	0.00	0.00	0.00	0.00	0.04	0.40	0.88	0.84

pH= measure of concentration of hydrogen ions, pCO_2= Carbon Dioxide, O_2= Oxygen, HCO_3^- & BE (B)= acid-base balance, tHb= Haemoglobin, O_2 Sat (%)= Saturation, Na^+= Sodium, K^+= Potassium, Ca^{++}= Calcium and Cl^-= Chloride. The p-values were calculated with the Kruskal-Wallis test for the comparison of medians. [Data taken at specified times after admission in ICU at 1-, 2-, 4-, 8-, 12-, 24-, 48- and 72 hours during the post-operative period].

4.4.3   The Clinical Outcomes/Complications: On-pump and Off-pump CABG Groups

Post-operative clinical outcomes and complications were summarised for the on-pump and off-pump surgery group in Table 4.13.

The on-pump group had none of the following clinical outcomes or complications: mortality, return to ICU, post-operative MI, neurological complications, renal complications, multi organ failure, post-operative dissection of major arteries, acute limb ischemia, heart block, cardiac arrest, anticoagulant complications or tamponade.

Clinical outcomes noted for the on-pump group were as follow: re-intubation 1 (3.3%), re-operation 1 (3.3%), pulmonary complications 1 (3.3%), GIT complications 1 (3.3%), AF 1 (3.3%), sternal wound infection 1 (3.3%) and septicaemia 1 (3.3%).

The off-pump group had none of the following clinical outcomes or complications: re-intubation, post-operative MI, neurological complications, dissection of major arteries, acute limb ischemia heart block, cardiac arrest, anticoagulant complications, tamponade or sternal wound infection.

For the off-pump group 2 (7.0%) patients died, 1 (3.3%) patient was returned to the ICU, re-operation 1 (3.3%), pulmonary complication 1 (3.3%), renal complication 1 (3.3%), GIT complication, multi organ failure 1 (3.3%), AF 1 (3.3%) and septicaemia 1 (3.3%).

Length of hospital stay and length of ICU stay indicated no statistically significant difference ($p > 0.05$), however, a statistically significant difference was noted for ventilation time of $p < 0.05$.

Table 4.13   Clinical Outcomes/Complications: On-pump vs. Off-pump CABG Group

VARIABLES (UNITS)	ON-PUMP n (%)	OFF-PUMP n (%)	p-VALUES
Mortality			
Yes	-	2 (7.0%)	-
No	30 (100.0%)	28 (93.0%)	
Return to ICU			
Yes	-	1 (3.3%)	-
No	30 (100.0%)	29 (96.7%)	
Re-intubation			
Yes	1 (3.3%)	-	-
No	29 (96.7%)	30 (100.0%)	
Re-operation			
Yes	1 (3.3%)	1 (3.3%)	-
No	29 (96.7%)	29 (96.7%)	
Post-operative MI			
Yes	-	-	-
No	30 (100.0%)	30 (100.0%)	
Pulmonary complications			
Yes	1 (3.3%)	1 (3.3%)	-
No	29 (96.7%)	29 (96.7%)	
Neurological complications			
Yes	-	-	-
No	30 (100%)	30 (100.0%)	
Renal complications			
Yes	-	1 (3.3%)	-
N	30 (100.0%)	29 (96.7%)	
GIT complications			
Yes	1 (3.3%)	1 (3.3%)	-
No	29 (96.7%)	29 (96.7%)	
Multi organ failure			
Yes	-	1 (3.3%)	-
No	30 (100.0%)	29 (96.7%)	
Post-operative dissection of major arteries			
Yes	-	-	-
No	30 (100.0%)	30 (100.0%)	
Acute limb ischemia			
Yes	-	-	-
No	30 (100.0%)	30 (100.0%)	
Heart block			
Yes	-	-	-
No	30 (100.0%)	30 (100.0%)	
Atrial fibrillation			
Yes	1 (3.3%)	1 (3.3%)	-
No	29 (96.7%)	29 (96.7%)	
Cardiac arrest			
Yes	-	-	-
No	30 (100.0%)	30 (100.0%)	

Anticoagulant complications			
Yes	-	-	-
No	30 (100.0%)	30 (100.0%)	
Tamponade			
Yes	-	-	-
No	30 (100.0%)	30 (100.0%)	
Sternal wound infection			
Yes	1 (3.0%)	-	-
No	29 (96.7%)	30 (100.0%)	
Septicaemia			
Yes	1 (3.3.0%)	1 (3.3%)	-
No	29 (96.7%)	29 (96.7%)	
Post-operative blood transfusion			
Yes	15 (50.0%)	8 (26.0%)	-
No	15 (50.0%)	22 (73%)	
Length of hospital stay (days)			
Median	8.65	7.46	**0.29**
25th percentile	5.41	6.21	
75th percentile	13.79	11.31	
Length of ICU stay (days)			
Median	3.18	3.67	**0.82**
25th percentile	2.64	2.52	
75th percentile	6.72	7.35	
Ventilation time (hours)			
Median	13.07	10.45	**0.03**
25th percentile	6.00	7.46	
75th percentile	30.04	20.27	

ICU= Intensive Care Unit; MI= Myocardial Infarction; GIT= Gastrointestinal Tract. P-values were calculated using the Kruskal-Wallis test for the comparison of medians.

4.5 Data for the Lactate <5 mmol/L Group and Lactate >5 mmol/L Group

4.5.1 Division of Lactate <5 mmol/L Group and Lactate >5mmol/L Group

The sixty recruited patients were divided into two groups according to peri-operative and post-operative lactate values irrespective of surgical technique.

If a patient's lactate level remained <5mmol/L intra- and post-operatively the patient fell in the lactate group 1 (lactate <5mmol/L). If a patient's lactate level increased >5mmol/L at any time

intra- or post-operatively the patient fell in the lactate group 2 (lactate >5mmol/L) (Figure 4.11).
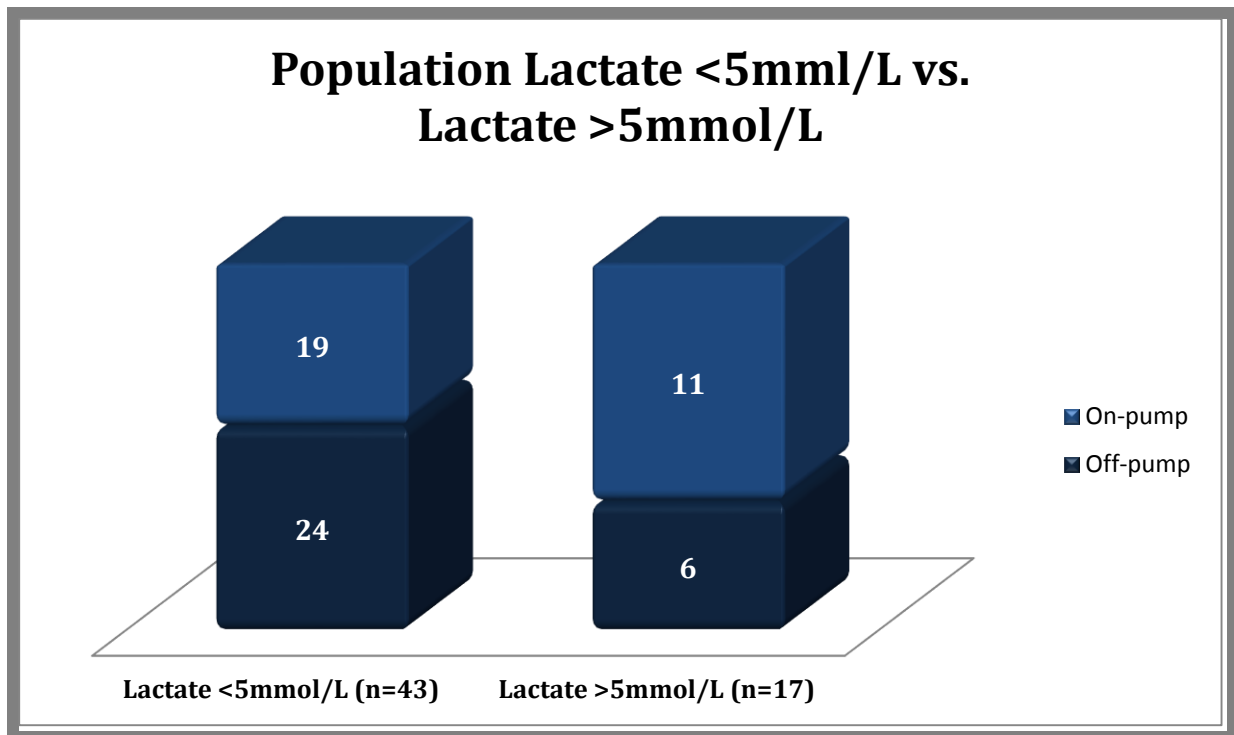
Figure 4.11 Lactate<5 mmol/L and Lactate >5mmol/L irrespective of surgical technique.

[n= number of patients].

4.5.1.1   Association between Lactate Group and Surgical Technique

This evaluation was done to determine whether the odds of a certain event or outcome will be the same for the 2 lactate groups. In this case, whether the odds of a lactate levels of >5mmol/L will be the same for both the on-pump and off-pump group. This test indicated a likelihood of the on-pump group having lactate of >5mmol/L was 2.3 times more likely than the off-pump group. However, this difference was not statistically significant (Table 4.14).

Table 4.14 Odds Ratio for Lactate Group vs. Surgical Technique

LACTATE GROUP AND SURGICAL TECHNIQUE				ODDS RATIO	p-VALUE
Surgical Technique	Lactate < 5 mmol/L Frequency (%)	Lactate > 5 mmol/L Frequency (%)	Total		
Off-pump CABG	24 (40.0)	6 (10.0)	30(50.0)		
On-pump CABG	19 (31.7)	11 (18.3)	30 (50.0)		
Total	43 (71.7)	17 (28.3)	60 (100.0)	2.3	0.15

p-values were calculated using the Chi-square test for the difference in proportions between the lactate groups.

4.5.2 Demographic and Clinical Data for Lactate <5 mmol/L and Lactate >5mmol/L

The demographic data revealed no statistically significant differences between the lactate <5 mmol/L group and lactate >5mmol/L group. Although the groups were unbalanced in size, the groups were comparable with respect to demographic and baseline clinical data (Table 4.15).

Table 4.15   Demographic Data: Lactate <5 mmol/L and Lactate >5mmol/L

VARIABLE (UNIT)	LACTATE <5mmol/L	LACTATE >5mmol/L	p-VALUE
EuroSCORE (%)			
Median	4.0	4.0	
25th percentile	1.6	2.6	**0.19**
75th percentile	7.5	6.3	
Age (years)			
Median	62.0	57.0	
25th percentile	53.0	54.0	**0.37**
75th percentile	68.0	64.0	
Height (cm)			
Median	175.0	178.0	
25th percentile	169.0	171.0	**0.84**
75th percentile	184.0	184.0	

VARIABLE (UNIT)	LACTATE <5mmol/L	LACTATE >5mmol/L	p-VALUE
Weight (kg)			
Median	82.0	96.0	
25th percentile	72.0	83.0	**0.72**
75th percentile	102.0	106.0	
BSA (m^2)			
Median	1.9	2.0	
25th percentile	1.8	1.7	**0.82**
75th percentile	2.2	2.1	
BMI (kg/m^2)			
Median	27.5	31.0	
25th percentile	24.1	25.6	**0.34**
75th percentile	30.4	32.8	

Significant differences were noted at p < 0.05. [BSA= Body Surface Area; BMI= Body Mass Index; EuroSCORE = calculated using the EuroSCORE II model]. p-values were calculated using the Kruskal-Wallis test for the comparison of medians.

4.5.3 Pre-operative Clinical Data: Lactate <5mmol/L vs. Lactate >5mmol/L

Pre-operative risk factors were summarized by lactate group in Table 4.16. Pre-operative risk factors such as; LVEF%, renal complications, neurological complications, pulmonary complications, previous non-surgical intervention, dyspnoea, diabetes, hypertension and ACS showed no significant differences between the two groups (p>0.05).

There was a statistically significant difference between the lactate groups with respect to the number of previous MI's. Last previous MI data showed statistically significance (p<0.05), however much of the data was not available for the lactate <5mmol/L group.

Table 4.16   Pre-operative Clinical Data: Lactate <5mmol/L vs. Lactate >5mmol/L

VARIABLE (UNIT)	LACTATE <5 mmol/L n (%)	LACTATE >5 mmol/L n (%)	p-VALUE
LVEF %			
Median	53.0	53.0	
25th percentile	45.0	48.0	0.15
75th percentile	66.0	60.0	
Renal complications			
No	41(95.0%)	17(100.0%)	1.00
Yes	2(4.0%)	-	
Neurological disease			
No	43(100.0%)	17(100.0%)	0.98
Yes CVA with full recovery	-	-	
Pulmonary disease			
Mild COPD	4(9.0%)	3(17.0%)	2.72
Moderate COPD	1(2.0%)	-	
Previous Non-Surgical Intervention			
Previous PCI	2 (4.0%)	2 (11.0%)	0.82
PCI > 24hrs before surgery	1(2.0%)	-	
Dyspnoea			
NYHA I	8 (18.0%)	1 (5.0%)	
NYHA II	19 (44.0%)	11 (64.6%)	0.56
NYHA III	4 (9.0%)	3 (17.0%)	
NYHA VI	-	1 (5.0%)	
Diabetes			
None	31(72.0%)	12(70.0%)	
Diet	5 (12.0%)	1 (6.0%)	0.56
Oral therapy	4 (9.0%)	3 (18.0%)	
Insulin	3 (7.0%)	1 (6.0%)	
Hypertension			
Treated	18 (60.0%)	20 (66.67%)	0.74
Acute Coronary Syndrome			
Unstable Angina	17 (39.0%)	5 (29.0%)	
STEMI	11 (25.0%)	4 (23.0%)	0.48
NONSTEMI	14 (32.0%)	8 (47.0%)	

VARIABLE (UNIT)	LACTATE <5 mmol/L n (%)	LACTATE >5 mmol/L n (%)	p-VALUE
Previous MI			
One	8 (18.0%)	3 (17.0%)	0.05
Two or more	14 (32.0%)	12 (70.00%)	
Last Previous MI Upon Admission To Cardiology			
Unknown	18(41.0%)	3 (18.0%)	0.01
< 6hrs	16 (37.0%)	5 (29.0%)	
6 – 24hrs	4 (9.0%)	3 (18.0%)	
1 – 30 days	5 (11.0%)	4 (23.0%)	
31 – 90 days	-	-	
> 90 days	-	2 (12.0%)	

Significant differences were noted at $p < 0.05$. [LVEF %= Left Ventricle Ejection Fraction percentage; STEMI= ST segment Elevation Myocardial Infarction; NONSTEMI= Non ST segment Myocardial Infarction; MI= Myocardial Infarction; CVA= Cerebrovascular Accident; COPD= Chronic Obstructive Pulmonary Disease]. p-values for the comparison of categorical data was calculated using the Chi-square.

4.5.4 Intra-operative Metabolic Data: Lactate <5 mmol/L and Lactate >5mmol/L

The metabolic changes seen in lactate <5mmol/L and lactate >5mmol/L were compared by analysing the patient's intra-operative metabolic data and hemodynamic profiles. The intra-operative metabolic data were displayed in Table 4.17 and Table 4.18 for lactate <5mmol/L and lactate >5mmol/L respectively.

The metabolic data were recorded intra-operatively at baseline, intubation and at 15 minute time intervals thereafter. The baseline ABG represents the first ABG drawn upon the patient's admission to theatre. The second ABG was drawn 5 minutes after intubation. T1-T9 represents intra-operative ABG's that were drawn at 15 minute intervals from the onset of surgery.

Table 4.17   Intra-operative Metabolic Data: Lactate <5 mmol/L

VARIABLE (UNIT)	BASELINE	INTUBATION	T1	T2	T3	T4	T5	T6	T7	T8	T9
pH											
Median	7.45	7.41	7.41	7.42	7.41	7.40	7.39	7.39	7.39	7.38	7.40
25th percentile	7.43	7.39	7.36	7.36	7.37	7.37	7.37	7.36	7.36	7.36	7.35
75th percentile	7.47	7.45	7.45	7.45	7.44	7.43	7.45	7.41	7.42	7.41	7.41
pCO$_2$ (mmHg)											
Median	34.8	36.5	36.3	36.8	36.5	36.6	39.5	39.2	35.7	36.7	36.8
25th percentile	31.8	33.0	33.0	32.7	34.2	32.6	35.8	35.3	35.1	34.5	34.3
75th percentile	37.8	43.0	39.8	39.5	40.6	40.3	39.8	37.8	39.6	41.8	41.9
pO$_2$ (mmHg)											
Median	73.5	163.2	251.3	188.1	195.0	186.4	175.8	175.0	175.7	196.8	172.1
25th percentile	66.8	126.4	129.2	157.4	154.7	143.1	143.7	154.0	145.3	122.4	116.3
75th percentile	126.1	297.0	297.5	229.7	212.6	209.4	198.2	215.0	200.8	213.7	213.3
HCO$_3$- std (mmol/L)											
Median	24.7	23.9	22.9	23.4	23.3	22.9	23.1	22.6	22.9	22.8	23.2
25th percentile	23.5	22.5	21.5	21.1	21.4	21.8	22.1	22.0	22.3	22.0	21.8
75th percentile	25.5	25.0	24.3	24.5	24.0	24.0	23.7	24.2	24.1	24.1	23.6
BE (B) (mmol/L)											
Median	0.1	-0.7	-1.9	-1.4	-1.4	-2.0	-1.7	-2.3	-2.0	-2.1	-1.6
25th percentile	-1.1	-2.2	-3.4	-3.6	-4.0	-3.7	-3.2	-2.9	-3.0	-2.7	-2.9
75th percentile	1.3	0.5	-0.4	-0.2	0.0	-0.6	-0.6	-0.9	-0.5	-6.2	-6.2
t Hb (g/dL)											
Median	13.2	11.6	11.3	10.7	10.5	10.5	10.4	10.1	10.1	9.5	9.1
25th percentile	12.4	11.2	9.9	9.9	9.5	9.3	8.9	8.8	9.0	8.7	8.5
75th percentile	14.6	13.9	12.4	11.4	11.4	11.3	11.1	10.8	11.6	10.6	10.3
O$_2$ Sat (%)											
Median	95.3	99.5	98.9	99.3	99.3	99.2	99.2	99.2	99.2	99.3	99.0
25th percentile	94.2	99.1	98.2	98.3	98.7	98.6	98.2	98.4	98.6	98.5	96.5
75th percentile	97.1	99.7	99.3	99.5	99.5	99.4	99.4	99.4	99.4	99.4	99.4
Na$^+$ (mmol/L)											
Median	138.0	139.7	137.3	137.2	137.9	136.4	136.7	136.8	136.7	136.9	137.1
25th percentile	136.0	136.2	135.1	135.8	136.0	134.2	135.7	135.9	136.0	136.4	136.7
75th percentile	139.0	139.8	139.7	139.5	139.7 616	140.0	139.2	139.2	139.7	139.1	140.9

VARIABLE (UNIT)	BASELINE	INTUBATION	T1	T2	T3	T4	T5	T6	T7	T8	T9
K⁺ (mmol/L)											
Median	3.8	3.7	3.6	3.7	3.9	3.9	4.0	4.1	4.2	4.3	4.2
25th percentile	3.1	3.7	3.4	3.3	3.5	3.9	3.8	3.2	3.9	3.6	3.7
75th percentile	4.2	4.7	4.5	4.6	4.4	4.4	4.5	4.5	4.34	4.4	4.4
Ca⁺⁺ (mmol/L)											
Median	1.2	1.1	1.1	1.1	1.0	1.0	1.0	1.0	1.0	1.0	1.0
25th percentile	1.0	0.9	1.0	0.9	1.0	0.9	0.9	0.9	0.9	1.0	1.0
75th percentile	1.2	1.2	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1
Cl⁻ (mmol/L)											
Median	107.0	110.0	111.0	111.0	112.0	112.0	112.0	112.0	111.0	112.0	110.5
25th percentile	96.0	98.0	99.0	101.0	101.0	101.0	104.0	104.0	105.0	104.0	114.0
75th percentile	115.0	124.0	124.0	125.0	120.0	118.0	121.0	117.0	115.0	112.0	115.0
Glucose (mmol/L)											
Median	5.2	5.4	5.6	5.7	6.7	7.0	6.9	7.2	7.0	8.0	8.2
25th percentile	4.9	4.9	4.8	4.5	5.8	5.9	5.8	5.8	6.2	6.6	6.1
75th percentile	6.1	6.4	7.9	8.0	8.2	8.8	9.0	9.7	10.3	10.3	9.6
Lactate (mmol/L)											
Median	1.2	1.6	1.9	2.2	2.5	2.8	3.0	2.9	2.8	2.8	2.8
25th percentile	0.9	1.1	1.4	1.6	1.77	1.9	2.2	2.0	2.0	2.0	2.2
75th percentile	1.5	2.4	2.8	3.2	3.4	3.5	3.8	3.5	3.6	3.5	3.8

pH= measure of concentration of hydrogen ions, pCO_2= Carbon Dioxide, O_2= Oxygen, HCO_3^- & BE (B)= acid-base balance, tHb= Haemoglobin, O_2 Sat (%)= Saturation, Na^+= Sodium, K^+= Potassium, Ca^{++}= Calcium and Cl^-= Chloride. [T1=15 minutes; T2= 30 minutes; T3= 45 minutes; T4= 60 minutes; T5= 75 minutes; T6= 90 minutes; T7= 105 minutes; T8= 120 minutes; T9= 135 minutes].

Table 4.18   Intra-operative Metabolic Data: Lactate >5 mmol/L

| VARIABLE (UNIT)	BASELINE	INTUBATION	T1	T2	T3	T4	T5	T6	T7	T8	T9
pH											
Median	7.45	7.39	7.36	7.36	7.34	7.37	7.32	7.33	7.33	7.33	7.33
25th percentile	7.43	7.36	7.33	7.30	7.31	7.31	7.29	7.29	7.30	7.27	7.24
75th percentile	7.47	7.41	7.41	7.45	7.38	7.38	7.38	7.36	7.35	7.37	7.36
pCO$_2$ (mmHg)											
Median	34.0	37.3	38.0	36.2	36.7	35.3	38.5	36.1	35.4	38.9	39.1
25th percentile	32.2	35.8	33.6	35.5	33.5	34.3	33.5	32.5	34.1	37.2	36.4
75th percentile	39.3	46.0	41.6	38.3	40.1	39.3	41.3	45.4	44.9	44.8	48.4
pO$_2$ (mmHg)											
Median	69.8	190.0	203.0	214.0	203.0	173.0	172.0	175.0	151.0	173.0	164.0
25th percentile	61.3	154.6	179.1	160.5	136.0	142.0	131.5	110.7	105.5	158.2	125.0
75th percentile	72.7	190.1	263.7	241.2	213.9	193.9	217.8	196.1	227.4	216.8	172.0
HCO$_3$- std (mmol/L)											
Median	24.6	23.4	21.8	21.0	20.3	20.5	20.1	19.8	20.0	20.3	20.9
25th percentile	23.9	22.9	20.6	19.0	19.0	18.8	18.7	18.3	19.4	18.9	18.7
75th percentile	25.6	24.2	22.9	21.3	22.4	22.0	21.9	21.7	22.2	21.8	21.7
BE (B) (mmol/L)											
Median	0.2	-1.3	-3.3	-4.2	-5.0	-4.8	-5.2	-5.7	-5.4	-5.1	-4.4
25th percentile	-1.0	-1.9	-5.1	-6.8	-6.6	-7.0	-6.9	-7.5	-6.1	-6.7	-6.0
75th percentile	1.4	-0.4	-2.5	-3.8	-2.5	-3.0	-3.0	-3.4	-2.8	-3.2	-3.9
t Hb (g/dL)											
Median	15.2	14.7	11.9	10.4	10.4	10.4	10.2	10.1	10.0	10.0	9.7
25th percentile	14.5	13.4	9.7	9.3	9.2	8.5	9.0	9.1	8.4	7.9	8.1
75th percentile	16.2	15.4	12.0	12.0	11.0	10.4	10.4	10.4	11.0	14.7	11.1
O$_2$ Sat (%)											
Median	94.9	99.4	99.3	99.4	99.5	99.2	99.1	99.2	98.8	99.1	99.0
25th percentile	92.9	98.9	98.6	98.4	98.6	98.3	97.2	97.4	97.2	95.3	96.3
75th percentile	99.7	99.6	99.5	99.4	99.5	99.4	99.4	99.4	99.3	99.4	99.5
Na$^+$ (mmol/L)											
Median	138.5	138.0	137.3	137.1	137.3	137.0	137.0	137.4	137.6	137.1	138.0
25th percentile	134.3	133.1	127.9	129.7	129.3	126.8	125.7	125.6	127.2	128.6	132.0
75th percentile	142.2	143.2	139.5	142.3	141.2	144.2	142.8	142.8	145.3	144.5	145.5

VARIABLE (UNIT)	BASELINE	INTUBATION	T1	T2	T3	T4	T5	T6	T7	T8	T9
K^+ (mmol/L)											
Median	4.0	3.8	3.4	3.0	3.4	3.5	3.5	3.7	3.9	3.8	3.2
25th percentile	3.0	2.2	2.8	2.3	2.4	2.2	2.9	2.7	2.9	3.2	2.9
75th percentile	4.5	4.6	4.4	5.5	5.3	5.7	6.1	6.1	5.2	5.1	4.3
Ca^{++} (mmol/L)											
Median	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.0	1.1	1.0
25th percentile	1.0	0.9	0.8	0.9	0.9	0.9	0.8	0.8	0.7	0.8	0.9
75th percentile	1.2	1.2	1.2	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.0
Cl^- (mmol/L)											
Median	109.0	110.0	112.0	112.0	112.0	112.0	112.0	112.0	112.0	111.5	111.5
25th percentile	92.0	93.0	99.0	98.0	107.0	99.0	98.0	98.0	97.0	107.0	105.0
75th percentile	118.0	118.0	115.0	117.0	117.0	116.0	118.0	116.0	116.0	115.0	113.0
Glucose (mmol/L)											
Median	5.8	5.7	6.8	8.7	10.1	10.9	10.4	11.5	12.2	13.1	12.7
25th percentile	5.0	5.2	6.2	6.2	7.6	8.2	8.8	8.6	10.0	9.6	9.6
75th percentile	6.2	6.2	8.8	11.2	12.5	13.6	14.6	14.8	16.1	16.6	16.5
Lactate (mmol/L)											
Median	1.2	1.4	2.9	4.7	5.2	5.7	5.7	5.7	5.8	6.1	6.5
25th percentile	1.0	1.0	2.6	3.4	4.2	4.5	4.4	4.9	5.2	5.3	5.9
75th percentile	1.4	1.7	5.7	6.0	6.9	6.8	7.1	8.4	9.7	10.4	10.5

pH= measure of concentration of hydrogen ions, pCO_2= Carbon Dioxide, O_2= Oxygen, HCO_3^- & BE (B)= acid-base balance, tHb= Haemoglobin, O_2 Sat (%)= Saturation, Na^+= Sodium, K^+= Potassium, Ca^{++}= Calcium and Cl^-= Chloride. [T1=15 minutes; T2= 30 minutes; T3= 45 minutes; T4= 60 minutes; T5= 75 minutes; T6= 90 minutes; T7= 105 minutes; T8= 120 minutes; T9= 135 minutes].

Due to the limited sample size the median, 25th and 75th percentile were calculated and the median values of metabolic data were plotted to observe whether any trends could be observed in lactate <5 mmol/L and lactate > 5 mmol/L (Figure 4.12-4.14).
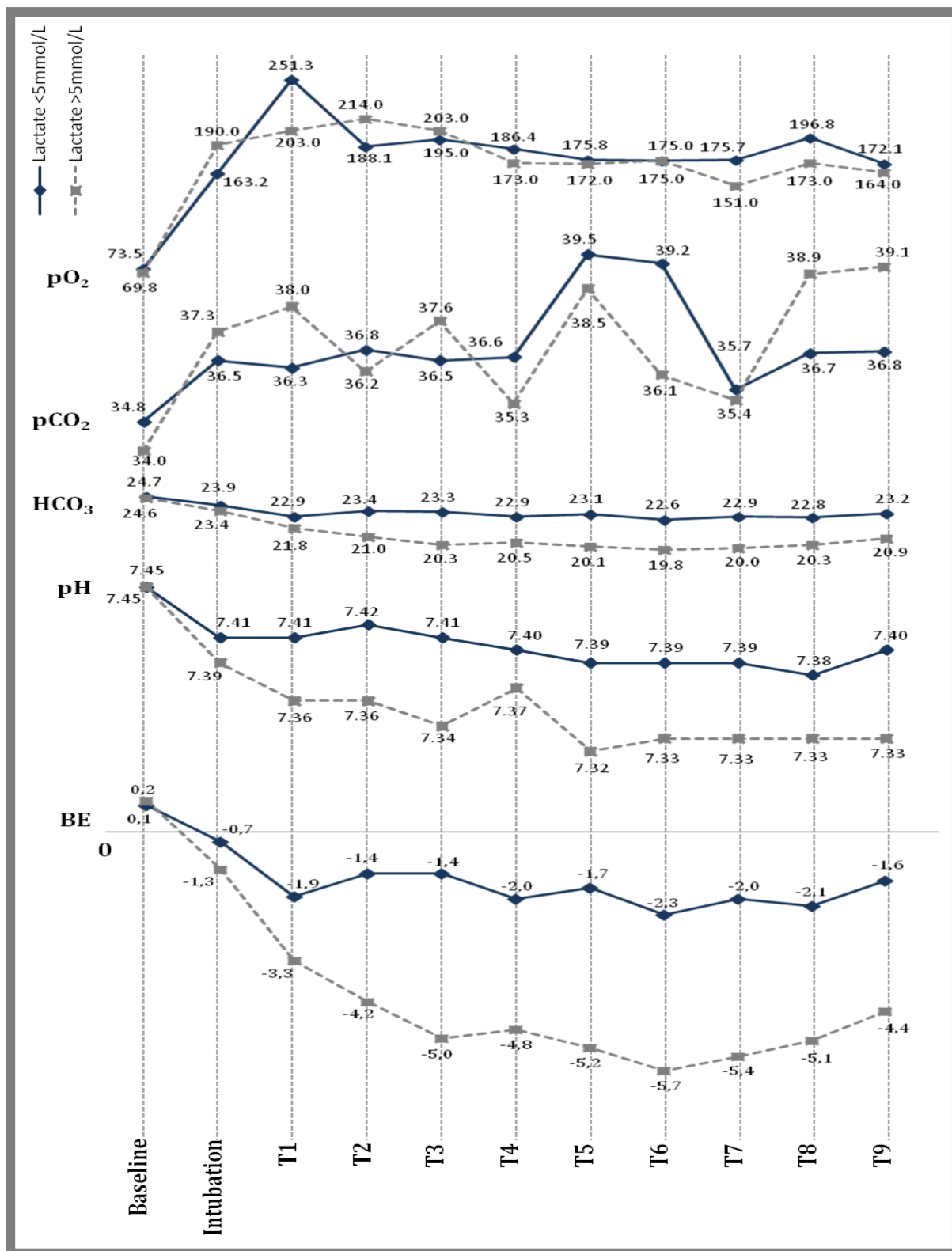
Figure 4.12   Medians for acid-base balance during the intra-operative period for lactate <5mmol/l and lactate >5mmol/L groups.

[pCO₂= Carbon Dioxide, O₂= Oxygen, pH= measure of concentration of hydrogen ions and BE (B)= acid-base balance. [T1=15 minutes; T2= 30 minutes; T3= 45 minutes; T4= 60 minutes; T5= 75 minutes; T6= 90 minutes; T7= 105 minutes; T8= 120 minutes; T9= 135 minutes].
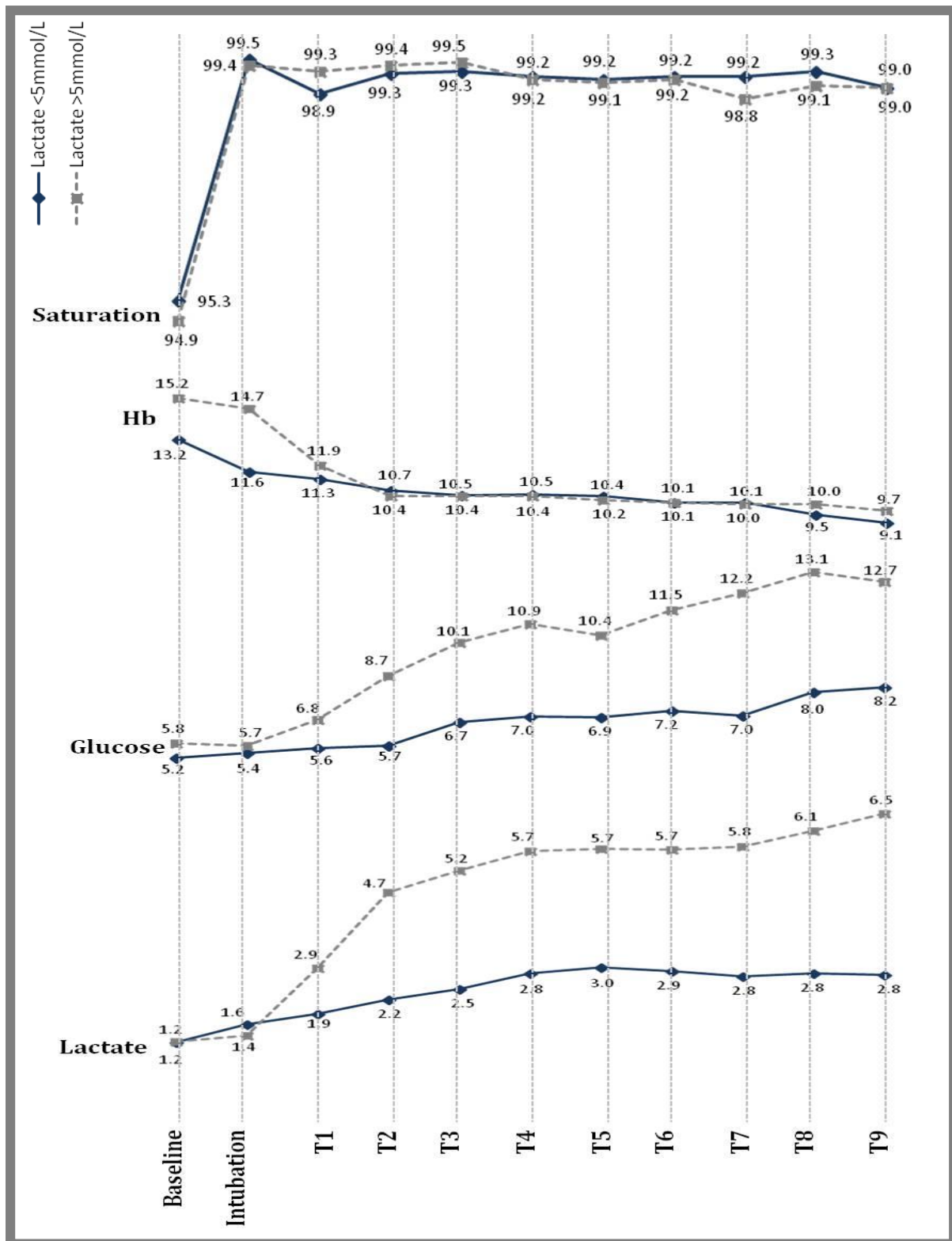
Figure 4.13   Medians for metabolites, saturation (%) and haemoglobin (tHb) during the intra-operative period for both lactate <5mmol/l and lactate >5mmol/L groups.

[T1=15 minutes; T2= 30 minutes; T3= 45 minutes; T4= 60 minutes; T5= 75 minutes; T6= 90 minutes; T7= 105 minutes; T8= 120 minutes; T9= 135 minutes].
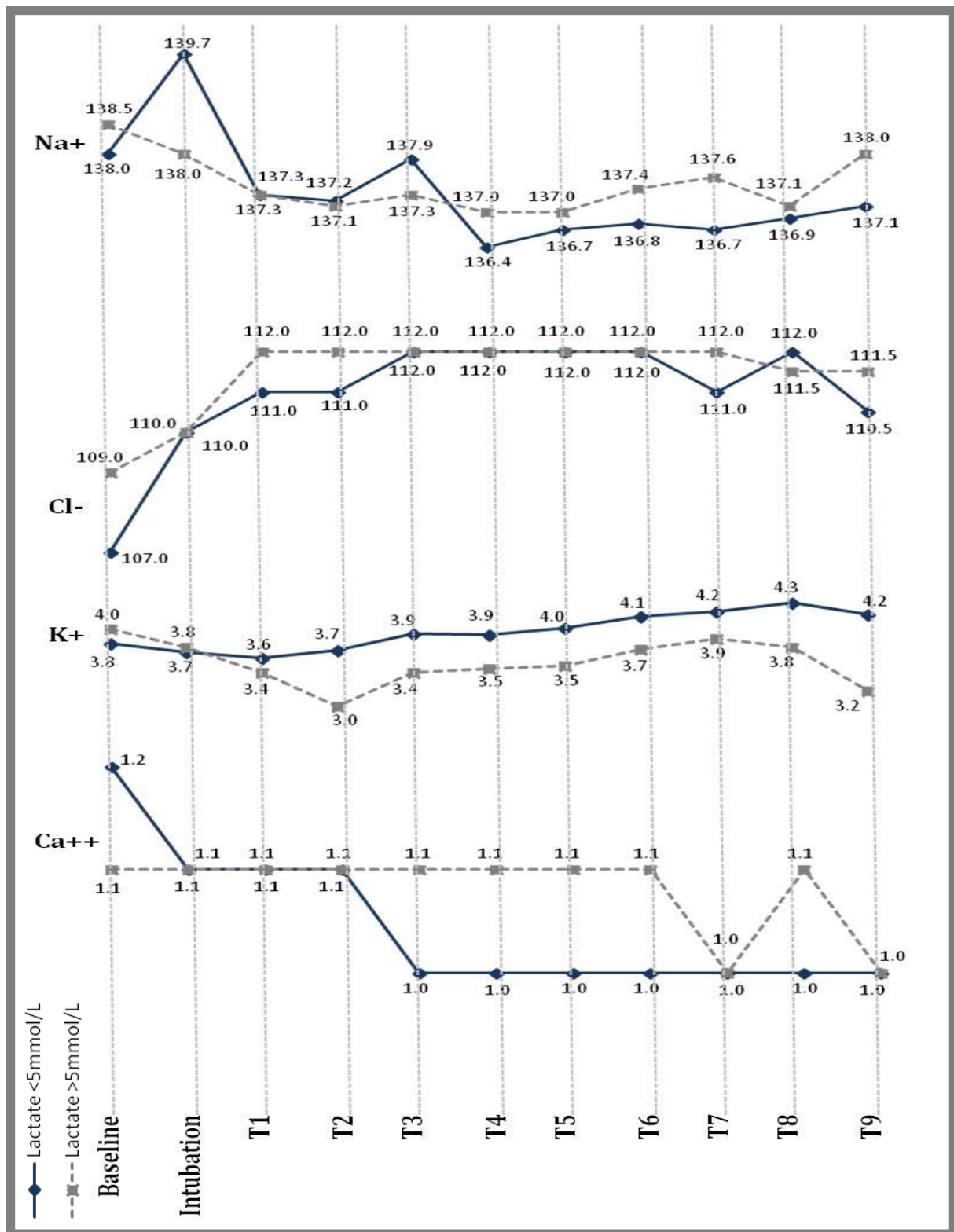
Figure 4.14   Medians for electrolytes: Sodium (Na+), Potassium (K+), Calcium (Ca++) and Chloride (Cl-) during the Intra-operative period for both lactate <5mmol/l and lactate >5mmol/L groups.

[T1=15 minutes; T2= 30 minutes; T3= 45 minutes; T4= 60 minutes; T5= 75 minutes; T6= 90 minutes; T7= 105 minutes; T8= 120 minutes; T9= 135 minutes].

4.5.5 P-values for Intra-operative Metabolic Data: Lactate <5 mmol/L vs. Lactate >5 mmol/L

At various time points during surgery, statistically significant differences ($p < 0.05$) were noted between lactate <5 mmol/L and lactate > 5 mmol/L (Table 4.19).

Variables for the acid-base balance, pO_2 and pCO_2, showed no statistically significant ($p > 0.05$) differences between the two groups (Table 4.19).

Other variables for acid-base balance, pH, HCO_3- and BE (B), showed statistically significant ($p < 0.05$) differences for most of the surgery duration.

The metabolites O_2 Sat (%) showed no statistically significant differences ($p > 0.05$), however, tHb (g/dL), glucose levels and lactate levels showed statistically significant differences ($p < 0.05$) for most of the surgery duration.

The electrolytes K^+, Ca^{++}, Na^+ and Cl^- indicated no statistically significant differences ($p > 0.05$). Groups were comparable with only a few statistically significant differences observed between the two groups.

Table 4.19   P-values for Intra-operative Metabolic Data: Lactate <5 mmol/L vs. Lactate >5 mmol/L

VARIABLE (UNIT)	BASELINE	INTUBATION	T1	T2	T3	T4	T5	T6	T7	T8	T9
pH	0.01	0.02	0.03	0.02	0.00	0.01	0.00	0.00	0.01	0.00	0.04
pCO₂ (mmHg)	0.78	0.13	0.26	0.58	0.78	0.88	0.68	0.41	0.61	0.78	0.34
pO₂ (mmHg)	0.07	0.39	0.57	0.25	0.85	0.60	0.80	0.87	0.23	0.29	0.85
HCO₃- STD (mmol/L)	0.95	0.35	0.05	0.02	0.00	0.00	0.00	0.00	0.00	0.00	0.00
BE (B) (mmol/L)	0.98	0.28	0.05	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00
tHb (g/dL)	0.01	0.00	0.32	0.36	0.88	0.71	0.26	0.33	0.95	0.30	0.86

O$_2$ SAT (%)	0.35	0.79	0.33	0.33	0.54	0.98	0.89	0.77	0.46	0.49	0.97
Na$^+$ (mmol/L)	0.87	0.45	0.96	0.52	0.74	0.64	0.63	0.99	1.0	0.71	0.21
K$^+$ (mmol/L)	1.0	0.85	0.19	0.43	1.0	0.78	0.61	0.13	0.67	0.31	0.47
Ca^{++} (mmol/L)	1.0	2.0	1.64	1.53	1.74	1.41	1.78	1.54	1.92	0.76	0.57
Cl$^-$ (mmol/L)	0.41	0.19	0.78	0.49	0.74	0.42	0.68	0.78	0.61	0.52	0.75
Glucose (mmol/L)	0.49	0.39	0.08	0.00	0.00	0.00	0.00	0.00	<0.0	0.00	0.00
Lactate (mmol/L)	0.38	0.39	0.00	<0.0	<0.0	<0.0	<0.0	<0.0	<0.0	<0.0	<0.0

pH= measure of concentration of hydrogen ions, pCO$_2$= Carbon Dioxide, O$_2$= Oxygen, HCO$_3$- & BE (B)= acid-base balance, tHb= Haemoglobin, O$_2$ Sat (%)= Saturation, Na$^+$= Sodium, K$^+$= Potassium, Ca^{++}= Calcium and Cl$^-$= Chloride. [T1=15 minutes; T2= 30 minutes; T3= 45 minutes; T4= 60 minutes; T5= 75 minutes; T6= 90 minutes; T7= 105 minutes; T8= 120 minutes; T9= 135 minutes]. The p-values were calculated using the Kruskal-Wallis test for the comparison of medians.

4.5.6 Intra-operative Hemodynamic Data and Temperature: Lactate <5mmol/L and Lactate >5mmol/L

The intra-operative hemodynamic data included systolic pressure, diastolic pressure, MAP, CVP and HR and were compared between lactate <5 mmol/L group and lactate > 5 mmol/L group to investigate the impact of the hemodynamic instability on metabolic changes.

Table 4.20 and Table 4.21 present the intra-operative hemodynamic data for the lactate <5 mmol/L group and the lactate > 5 mmol/L group, respectively. Line graphs were drawn (Figure 4.15), using the median values of the lactate groups to display possible trends observed in the two groups.

Table 4.20   Intra-operative Hemodynamic Data and Temperature: Lactate <5 mmol/L

VARIABLE (UNIT)	BASELINE	INTUBATION	T1	T2	T3	T4	T5	T6	T7	T8	T9
Systolic Pressure (mmHg)											
Median	123.0	122.0	122.0	124.0	119.0	113.0	110.0	114.0	111.0	109.0	112.0
25th percentile	67.9	77.9	87.0	77.1	99.2	81.0	73.0	71.0	83.0	69.8	74.0
75th percentile	143.0	130.0	128.0	128.0	133.0	124.0	120.0	131.0	122.0	128.0	136.0
Diastolic Pressure (mmHg)											
Median	92.7	92.3	91.3	84.3	82.4	90.3	85.5	82.9	82.6	79.6	78.0
25th percentile	82.0	77.0	68.0	67.0	80.3	64.0	62.0	71.0	75.0	62.0	59.3
75th percentile	102.6	110.0	117.0	124.00	119.7	110.0	109.7	104.2	100.0	103.8	107.2
Mean Arterial Pressure (mmHg)											
Median	92.7	92.3	91.3	84.3	82.4	90.3	85.5	82.9	78.0	75.4	78.6
25th percentile	67.8	68.5	69.2	71.5	72.6	74.0	68.7	63.8	62.1	64.9	60.7
75th percentile	98.4	97.3	99.4	100.0	101.7	103.8	109.5	95.7	97.4	91.3	90.2
HR (beats/min)											
Median	68.0	68.0	67.0	67.0	64.0	71.0	64.0	61.0	58.0	61.0	60.5
25th percentile	58.0	62.0	64.0	56.0	63.0	57.0	58.0	42.0	53.0	51.0	55.0
75th percentile	70.0	74.0	71.0	82.0	75.0	73.0	70.0	68.0	69.0	67.0	62.0
CVP (mmHg)											
Median	5.3	6.1	4.1	4.2	5.4	4.5	4.3	4.6	5.8	4.8	4.2
25th percentile	4.2	5.4	3.8	3.1	4.8	4.0	4.0	3.7	4.2	4.3	3.1
75th percentile	7.5	8.7	9.3	9.7	8.2	9.3	6.7	5.5	5.9	8.5	5.5
Temperature (°C)											
Median	36.0	36.0	35.8	33.4	32.1	32.2	32.7	32.6	32.5	33.8	34.4
25th percentile	32.2	32.0	31.8	30.3	30.4	32.0	31.6	31.6	30.3	31.1	32.0
75th percentile	36.5	36.1	36.6	36.2	36.6	36.3	36.1	36.4	36.4	36.1	36.4

CVP= central venous pressure, HR=heart rate. °C= degrees Celsius. [T1-9: time intervals of 15 minutes]

Table 4.21   Intra-operative Hemodynamic Data and Temperature: Lactate >5mmol/L

VARIABLE (UNIT)	BASELINE	INTUBATION	T1	T2	T3	T4	T5	T6	T7	T8	T9
Systolic Pressure (mmHg)											
Median	118.3	130.0	112.0	70.0	63.4	74.1	78.1	79.5	84.0	86.2	88.8
25th percentile	111.0	110.6	110.5	58.0	55.7	57.3	56.4	59.7	74.5	81.4	86.8
75th percentile	128.4	137.3	117.3	116.4	110.2	94.2	110.0	125.3	106.7	110.0	113.1
Diastolic Pressure (mmHg)											
Median	63.1	68.3	47.8	52.4	52.5	53.9	56.2	54.7	45.3	54.4	57.9
25th percentile	37.5	41.0	37.9	40.1	37.1	39.1	38.7	36.8	40.2	37.2	45.4
75th percentile	86.1	73.9	79.4	70.5	70.5	66.2	63.9	58.4	60.4	60.8	62.1
Mean Arterial Pressure (mmHg)											
Median	80.5	72.3	71.4	70.5	67.9	64.9	68.6	67.2	60.8	64.3	56.7
25th percentile	62.5	57.8	62.2	60.3	51.8	61.1	55.8	57.3	50.1	46.9	50.3
75th percentile	113.6	76.7	115.0	92.8	107.6	77.2	73.9	71.1	72.7	74.7	68.0
HR (beats/min)											
Median	67.0	66.0	74.0	73.0	69.0	75.0	69.0	67.0	62.0	64.0	64.0
25th percentile	53.0	61.0	62.0	53.0	53.0	53.0	52.0	54.0	57.0	53.0	53.0
75th percentile	83.0	82.0	80.0	78.0	77.0	76.0	84.0	80.0	81.0	84.0	77.0
Temperature (°C)											
Median	36.1	36.4	36.0	33.9	32.4	32.4	32.1	32.4	32.6	33.9	35.1
25th percentile	34.9	34.5	32.5	31.4	30.7	30.1	29.7	29.3	29.0	28.8	30.7
75th percentile	36.3	36.5	36.3	36.3	36.2	36.2	36.1	36.1	36.1	36.0	36.1
CVP (mmHg)											
Median	4.8	5.0	5.1	4.9	4.8	4.5	4.5	4.4	4.8	5.8	5.0
25th percentile	3.5	2.0	2.6	2.6	3.2	3.1	3.3	3.2	3.2	3.8	3.9
75th percentile	7.5	6.5	6.9	5.9	5.3	5.2	5.7	4.8	7.7	7.1	5.3

CVP= central venous pressure, HR=heart rate, °C= degrees Celsius. [T1-9: time intervals of 15 minutes].
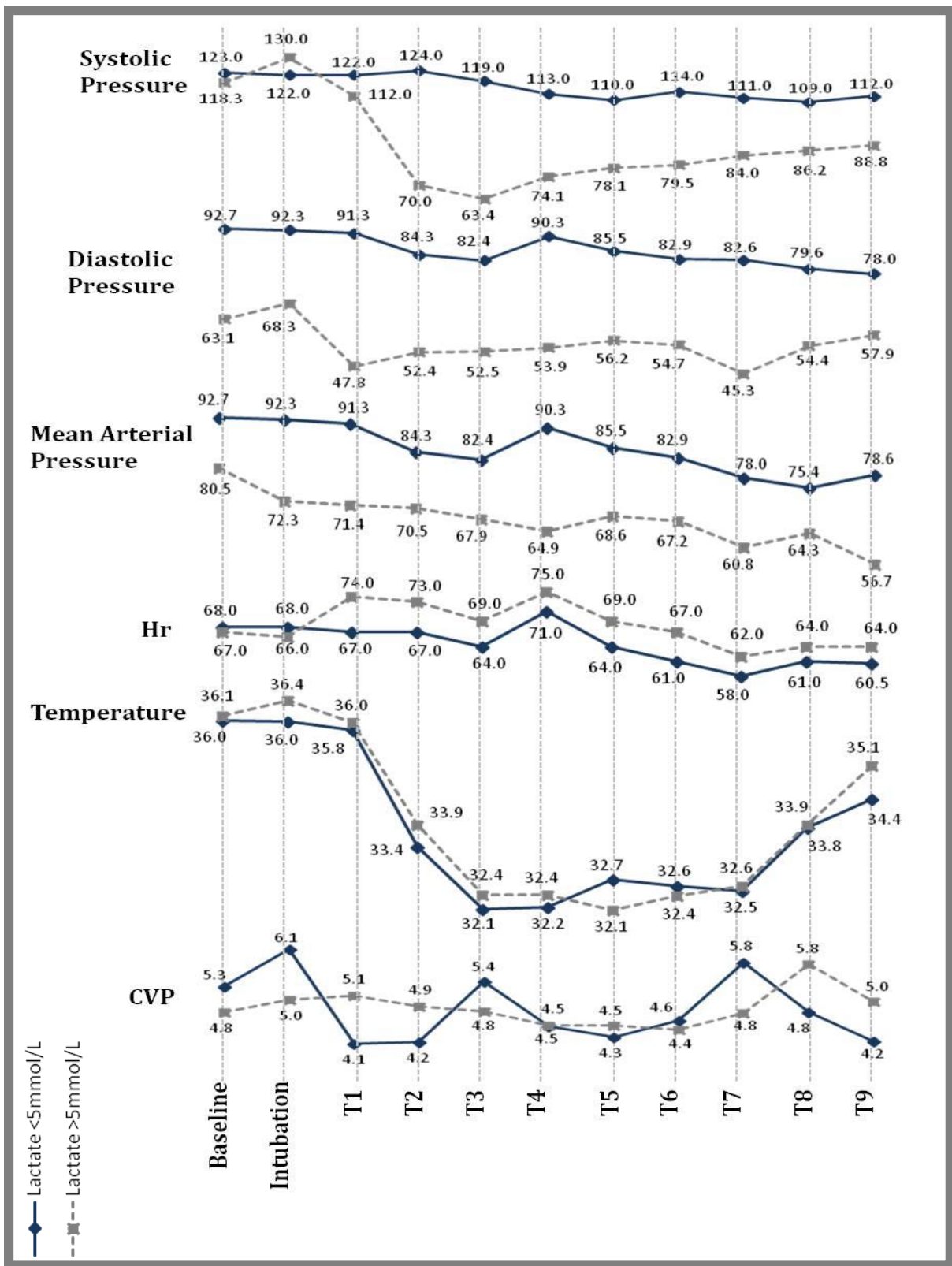
Figure 4.15 Medians for hemodynamics for both lactate <5mmol/L and lactate >5mmol/L during CABG surgery.

[CVP= central venous pressure, HR= heart rate. Temperature was measured in degrees Celsius (°C). [T1=15 minutes; T2= 30 minutes; T3= 45 minutes; T4= 60 minutes; T5= 75 minutes; T6= 90 minutes; T7= 105 minutes; T8= 120 minutes; T9= 135 minutes].

4.5.7 Intra-operative Hemodynamic Data and Temperature: Lactate <5mmol/L vs. Lactate >5mmol/L

Statistically significant differences between the lactate <5 mmol/L group and lactate > 5 mmol/L group were noted for the systolic pressures, diastolic pressures and mean arterial blood pressure data (Table 4.22) for most part of the surgery. No statistically significant differences between the two groups were noted for HR, CVP and temperature ($p > 0.05$).

Table 4.22   Intra-operative Hemodynamic Data and Temperature: Lactate < 5mmol/L vs. Lactate > 5mmol/L

VARIABLE (UNIT)	BASELINE	INTUBATION	T1	T2	T3	T4	T5	T6	T7	T8	T9
Systolic Pressure (mmHg)											
	0.32	0.70	0.93	0.03	0.00	0.05	0.00	0.01	0.01	0.27	0.31
Diastolic Pressure (mmHg)											
	0.25	0.62	0.19	0.00	0.01	0.04	0.03	0.03	0.00	0.04	0.14
Mean Arterial Pressure (mmHg)											
	0.15	0.10	0.98	0.04	0.05	0.03	0.02	0.04	0.00	0.02	0.28
HR (beats/min)											
	0.41	0.81	0.80	0.32	0.85	0.16	0.19	0.16	0.34	0.31	0.09
CVP (mmHg)											
	0.15	0.99	0.33	0.54	0.14	0.38	0.80	0.39	0.18	0.88	0.72
Temperature (°C)											
	0.69	0.95	0.18	0.70	0.27	0.35	0.72	0.64	0.68	0.78	0.61

CVP= central venous pressure, HR= heart rate. °C= Temperature was measured in degrees Celsius. [T1-9: time intervals of 15 minutes]. The p-values were calculated using the Kruskal-Wallis test for the comparison of medians.

4.5.8 Post-operative Metabolic Data: Lactate <5mmol/L and Lactate >5mmol/L

Post-operative metabolic data for the lactate <5 mmol/L group and the lactate > 5 mmol/L group were displayed in Table 4.23 and Table 4.24, respectively. The median values of the

metabolic data were plotted against each other at specific time intervals to look for trends in the 2 groups (Figure 4.16 - 4.18).

Table 4.23   Post-operative Metabolic Data: Lactate <5 mmol/L

VARIABLE (UNIT)	1HR POST OPERATIVE	2HRS POST OPERATIVE	4HRS POST OPERATIVE	8HRS POST OPERATIVE	12HRS POST OPERATIVE	24HRS POST OPERATIVE	48HRS POST OPERATIVE	72HRS POST OPERATIVE
pH								
Median	7.34	7.34	7.37	7.40	7.43	7.47	7.47	7.46
25th percentile	7.29	7.30	7.32	7.37	7.38	7.44	7.44	7.43
75th percentile	7.38	7.40	7.42	7.43	7.45	7.49	7.49	7.49
pCO$_2$ (mmHg)								
Median	43.2	41.0	35.6	33.8	34.1	33.5	34.0	35.6
25th percentile	35.9	34.3	33.4	31.0	29.6	30.9	31.0	32.0
75th percentile	43.4	43.2	40.0	37.6	35.6	36.3	36.4	40.3
pO$_2$ (mmHg)								
Median	116.5	98.5	97.6	92.5	82.9	75.7	74.7	69.4
25th percentile	94.4	82.0	85.0	78.3	71.0	63.1	64.5	60.6
75th percentile	146.0	122.6	121.2	108.5	99.2	84.5	87.0	82.5
HCO$_3$- STD (mmol/L)								
Median	21.2	20.7	21.1	21.5	23.0	24.3	25.3	25.6
25th percentile	18.8	18.7	20.0	20.4	20.7	22.6	23.7	23.7
75th percentile	22.4	22.6	23.1	23.4	24.1	26.2	26.5	26.9
BE (B) (mmol/L)								
Median	-3.4	-3.8	-3.4	-2.9	-1.8	0.6	1.0	1.7
25th percentile	-6.4	-6.6	-5.1	-4.8	-4.2	-1.7	-0.4	-0.6
75th percentile	-1.4	-1.9	-0.6	-0.7	1.1	2.4	2.5	3.0
tHb (g/dL)								
Median	12.6	14.6	15.6	13.0	11.8	9.8	7.3	7.8
25th percentile	10.6	10.9	11.1	10.2	10.7	9.0	6.5	6.0
75th percentile	12.8	15.2	15.8	14.7	12.6	12.35	12.2	12.4
O$_2$ Sat (%)								
Median	97.9	97.2	96.9	97.0	96.6	95.9	96.1	95.2
25th percentile	96.9	96.0	95.9	95.2	94.2	93.7	93.9	92.6
75th percentile	98.7	98.1	98.3	98.0	97.7	97.4	96.8	96.7
Na$^+$ (mmol/L)								
Median	138.6	138.0	137.5	137.1	136..6	136.4	135.5	135.0
25th percentile	129.3	131.9	131.0	131.8	131.6	129.3	127.1	127.2
75th percentile	149.4	147.3	148.4	148.8	147.5	144.7	141.4	141.6

VARIABLE (UNIT)	1HR POST OPERATIVE	2HRS POST OPERATIVE	4HRS POST OPERATIVE	8HRS POST OPERATIVE	12HRS POST OPERATIVE	24HRS POST OPERATIVE	48HRS POST OPERATIVE	72HRS POST OPERATIVE
K+ (mmol/L)								
Median	4.1	4.2	4.6	4.5	4.5	4.3	4.3	4.2
25th percentile	2.8	2.8	3.1	2.7	3.3	2.7	3.5	2.6
75th percentile	6.0	5.0	5.3	5.1	5.9	6.5	4.8	5.0
Ca++ (mmol/L)								
Median	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1
25th percentile	0.9	0.8	0.9	0.8	0.7	0.9	0.7	0.9
75th percentile	1.3	1.1	1.1	1.1	1.2	1.1	1.1	1.2
Cl- (mmol/L)								
Median	108.0	108.5	108.0	109.0	108.0	108.0	105.0	105.0
25th percentile	100.0	101.0	101.0	101.0	102.0	101.0	95.0	98.0
75th percentile	118.0	119.0	119.0	122.0	117.0	123.0	118.0	117.0
Glucose (mmol/L)								
Median	12.0	11.7	11.9	11.6	11.5	11.1	10.6	11.3
25th percentile	8.6	9.7	11.0	10.3	9.9	7.2	6.8	6.3
75th percentile	12.7	13.6	15.5	14.8	13.0	12.9	11.3	12.6
Lactate (mmol/L)								
Median	3.0	3.1	3.8	3.1	2.4	1.6	1.2	1.1
25th percentile	1.9	2.8	3.2	3.0	2.0	1.2	1.0	1.0
75th percentile	3.5	3.1	3.8	3.2	3.7	3.1	2.4	2.6

pH= measure of concentration of hydrogen ions, pCO_2= Carbon Dioxide, O_2= Oxygen, HCO_3- & BE (B)= acid-base balance, tHb= Haemoglobin, O_2 Sat (%)= Saturation, Na^+= Sodium, K^+= Potassium, Ca^{++}= Calcium and Cl^-= Chloride. [Data taken at specified times after admission in ICU at 1-, 2-, 4-, 8-, 12-, 24-, 48- and 72 hours during the post-operative period].

Table 4.24   Post-operative Metabolic Data: Lactate >5 mmol/L

VARIABLE (UNIT)	1HR POST OPERATIVE	2HRS POST OPERATIVE	4HRS POST OPERATIVE	8HRS POST OPERATIVE	12HRS POST OPERATIVE	24HRS POST OPERATIVE	48HRS POST OPERATIVE	72HRS POST OPERATIVE
pH								
Median	7.28	7.32	7.33	7.36	7.42	7.46	7.47	7.46
25th percentile	7.24	7.27	7.31	7.34	7.38	7.45	7.47	7.45
75th percentile	7.32	7.34	7.38	7.45	7.51	7.50	7.50	7.50
pCO$_2$ (mmHg)								
Median	40.7	37.7	35.6	34.3	33.1	33.2	33.0	36.6
25th percentile	40.4	35.7	33.9	33.5	32.5	30.5	30.4	33.1
75th percentile	46.2	43.1	38.1	37.0	36.9	37.3	40.5	42.4
pO$_2$ (mmHg)								
Median	113.8	93.8	94.4	90.7	82.9	73.5	66.2	74.7
25th percentile	95.0	88.8	84.8	74.3	73.5	67.7	54.2	50.0
75th percentile	121.7	108.5	111.3	107.3	105.5	81.5	87.0	81.2
HCO$_3$- STD (mmol/L)								
Median	19.3	19.9	19.3	20.5	22.8	25.0	25.9	26.5
25th percentile	17.9	18.4	17.8	18.8	20.9	23.1	25.2	25.3
75th percentile	20.4	21.6	21.5	21.8	24.6	26.6	27.8	28.4
BE (B) (mmol/L)								
Median	-6.3	-5.6	-6.3	-4.8	-2.1	0.5	2.2	2.8
25th percentile	-8.2	-7.3	-8.2	-6.9	-4.2	-1.6	1.2	1.1
75th percentile	-4.9	-3.4	-3.6	-3.1	0.2	2.5	3.9	4.4
tHb (g/dL)								
Median	10.5	11.9	12.9	12.7	11.4	8.5	7.7	7.1
25th percentile	10.0	11.1	11.0	10.7	11.3	8.0	6.9	6.6
75th percentile	13.0	13.2	13.0	13.6	12.7	12.0	12.0	13.0
O$_2$ Sat (%)								
Median	97.3	96.9	96.9	96.7	96.3	95.7	94.5	96.1
25th percentile	95.0	95.5	95.0	95.2	95.2	94.9	93.7	91.7
75th percentile	98.0	97.7	97.6	97.5	97.8	97.2	96.3	97.2
Na$^+$ (mmol/L)								
Median	140.0	140.3	140.7	139.8	141.1	139.8	135.5	133.3
25th percentile	131.7	131.9	133.4	131.2	134.9	135.0	134.4	130.1
75th percentile	142.4	144.9	145.0	145.4	146.0	139.8	137.6	134.0
K$^+$ (mmol/L)								
Median	3.4	3.5	3.7	4.0	4.1	4.1	4.2	4.1
25th percentile	2.6	2.7	3.4	3.0	2.9	3.7	3.5	3.9
75th percentile	4.3	4.1	4.6	4.8	4.9	4.1	4.4	4.7

VARIABLE (UNIT)	1HR POST OPERATIVE	2HRS POST OPERATIVE	4HRS POST OPERATIVE	8HRS POST OPERATIVE	12HRS POST OPERATIVE	24HRS POST OPERATIVE	48HRS POST OPERATIVE	72HRS POST OPERATIVE
Ca++ (mmol/L)								
Median	1.0	1.0	1.0	1.0	1.0	1.0	1.1	1.1
25th percentile	0.9	0.9	0.9	1.0	1.0	1.0	1.0	1.1
75th percentile	1.0	1.1	1.1	1.1	1.1	1.0	1.1	1.2
Cl- (mmol/L)								
Median	111.0	111.0	111.0	113.0	113.0	111.0	107.0	104.0
25th percentile	107.0	108.0	110.0	111.0	110.0	109.0	103.2	102.0
75th percentile	111.0	111.0	111.5	114.4	114.9	114.0	109.0	107.0
Glucose (mmol/L)								
Median	11.7	11.9	11.9	11.6	11.6	11.3	11.4	11.4
25th percentile	9.8	11.4	11.1	11.0	10.9	7.8	6.5	6.3
75th percentile	15.4	16.2	16.3	14.7	13.7	12.5	12.0	12.1
Lactate (mmol/L)								
Median	7.9	8.3	8.3	7.3	4.1	2.1	1.7	1.2
25th percentile	6.5	5.0	5.5	3.4	3.1	1.5	1.5	1.0
75th percentile	9.1	10.5	10.7	9.9	6.7	3.8	1.8	1.3

pH= measure of concentration of hydrogen ions, pCO_2= Carbon Dioxide, O_2= Oxygen, HCO_3^- & BE (B)= acid-base balance, tHb= Haemoglobin, O_2 Sat (%)= Saturation, Na^+= Sodium, K^+= Potassium, Ca^{++}= Calcium and Cl^-= Chloride. [Data taken at specified times after admission in ICU at 1-, 2-, 4-, 8-, 12-, 24-, 48- and 72 hours during the post-operative period].
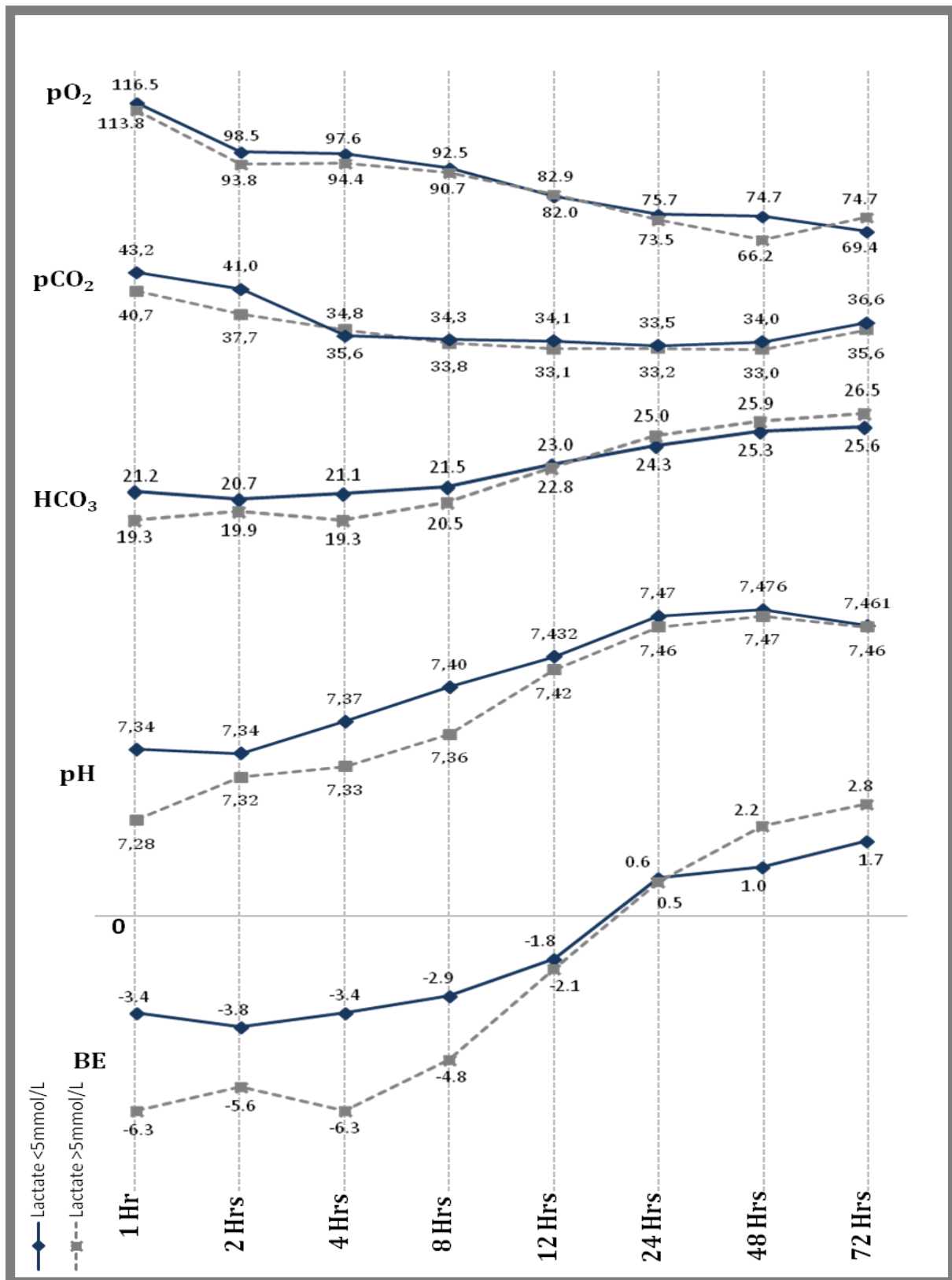
Figure 4.16 **Medians of acid-base balance during the first 72 hours post-operatively following CABG surgery for both lactate <5mmol/L and lactate >5mmol/L.**

[T1=15 minutes; T2= 30 minutes; T3= 45 minutes; T4= 60 minutes; T5= 75 minutes; T6= 90 minutes; T7= 105 minutes; T8= 120 minutes; T9= 135 minutes].
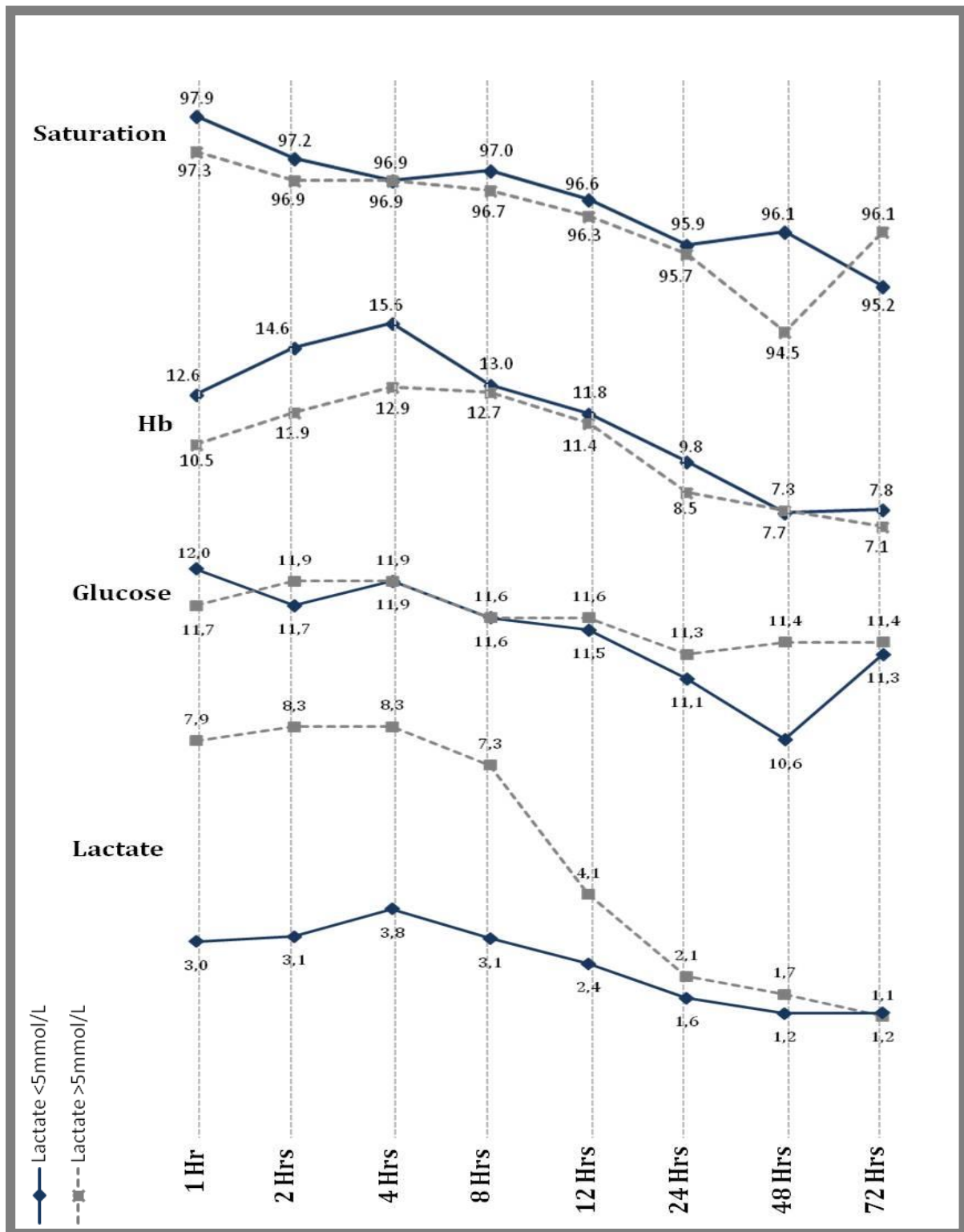
Figure 4.17   Medians for metabolites, saturation (%) and haemoglobin (Hb) the first 72hour post-operative period following CABG surgery for both lactate <5mmol/L and lactate >5mmol/L.

[T1=15 minutes; T2= 30 minutes; T3= 45 minutes; T4= 60 minutes; T5= 75 minutes; T6= 90 minutes; T7= 105 minutes; T8= 120 minutes; T9= 135 minutes].
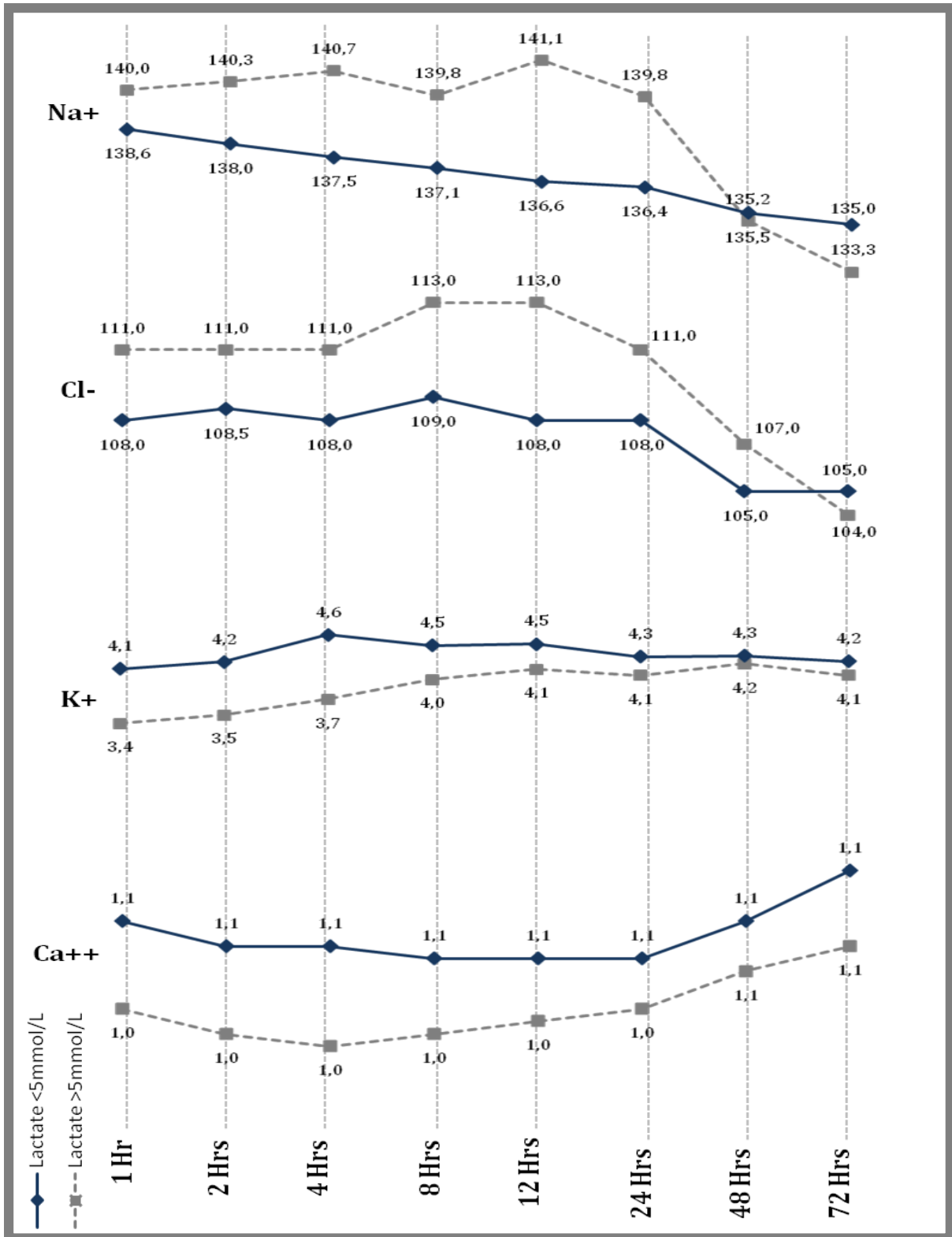
Figure 4.18   Medians for electrolytes, Sodium (Na+), Potassium (K+), Calcium (Ca++) and Chloride (Cl-) following CABG surgery for both lactate <5mmol/L and lactate >5mmol/L.

[T1=15 minutes; T2= 30 minutes; T3= 45 minutes; T4= 60 minutes; T5= 75 minutes; T6= 90 minutes; T7= 105 minutes; T8= 120 minutes; T9= 135 minutes].

4.5.9 P-values for Post-operative Metabolic Data: Lactate <5 mmol/L vs. Lactate >5 mmol/L

Variables for the acid-base balance, pO_2 and pCO_2, showed no statistically significant ($p > 0.05$) differences between the two groups (Table 4.25).

pH showed statistically significant ($p < 0.05$) differences only during the 1st hour post-operatively. HCO_3^- and BE (B) showed statistically significant ($p < 0.05$) differences only during the 1st hour and during the 4th hour post-operatively.

The metabolites O_2 SAT% and tHb (g/dL) showed no statistically significant differences ($p > 0.05$). Glucose levels showed statistically significant ($p < 0.05$) differences only during the 4th hour post-operatively. Lactate exhibited a statistically significant difference between the groups from the immediate post-operative period ($p < 0.05$) until the 12th hour post-operatively, this was expected since we stratified on this variable.

The electrolytes K^+, Ca^{++}, Na^+ and Cl^- indicated no statistically significant differences ($p > 0.05$).

Table 4.25   P-values for Post-operative Metabolic Data: Lactate <5mmol/L vs. Lactate >mmol/L

VARIABLE (UNIT)	1HR POST OPERATIVE	2HRS POST OPERATIVE	4HRS POST OPERATIVE	8HRS POST OPERATIVE	12HRS POST OPERATIVE	24HRS POST OPERATIVE	48HRS POST OPERATIVE	72HRS POST OPERATIVE
pH	0.00	0.14	0.06	0.08	0.76	0.99	0.84	0.63
pCO₂ (mmHg)	0.08	0.50	0.72	0.33	0.28	0.77	0.24	0.48
pO₂ (mmHg)	0.22	0.45	0.51	0.62	0.68	0.99	0.05	0.52
HCO₃- STD (mmol/L)	0.03	0.28	0.02	0.19	0.72	0.53	0.13	0.11
BE (B) (mmol/L)	0.01	0.13	0.01	0.08	0.72	0.93	0.10	0.13
tHb (g/dL)	0.49	0.64	0.89	0.95	0.60	0.71	0.12	0.45
O₂ Sat (%)	0.20	0.40	0.37	0.51	0.89	0.71	0.27	0.66
Na⁺ (mmol/L)	0.85	0.87	0.78	0.49	0.42	1.0	1.92	0.64

VARIABLE (UNIT)	1HR POST OPERATIVE	2HRS POST OPERATIVE	4HRS POST OPERATIVE	8HRS POST OPERATIVE	12HRS POST OPERATIVE	24HRS POST OPERATIVE	48HRS POST OPERATIVE	72HRS POST OPERATIVE
K⁺ (mmol/L)	0.52	0.19	0.31	0.47	1.41	0.76	0.61	0.45
Ca⁺⁺ (mmol/L)	0.19	1.78	1.54	0.13	0.41	0.75	0.78	1.0
Cl⁻ (mmol/L)	0.78	1.0	0.67	1.74	0.74	0.68	0.24	1.64
Glucose (mmol/L)	0.08	0.04	0.21	0.67	0.36	0.18	0.37	0.48
Lactate (mmol/L)	<0.00	0.00	0.00	0.03	0.05	0.07	0.06	0.59

pH= measure of concentration of hydrogen ions, pCO$_2$= Carbon Dioxide, O$_2$= Oxygen, HCO$_3$- & BE (B)= acid-base balance, tHb= Haemoglobin, O$_2$ Sat (%)= Saturation, Na⁺= Sodium, K⁺= Potassium, Ca⁺⁺= Calcium and Cl⁻= Chloride. The p-values were calculated using the Kruskal-Wallis test for the comparison of medians. [Data taken at specified times after admission in ICU at 1-, 2-, 4-, 8-, 12-, 24-, 48- and 72 hours during the post-operative period].

4.5.10   Clinical   Outcomes/Complications: Lactate <5mmol/L vs. Lactate >mmol/L

All 60 patients were divided into one of two groups, regardless of the type of coronary artery revascularization according to their peak lactate levels (lactate <5 mmol/L or lactate >5 mmol/L). Lactate >5 mmol/L is considered high (presents an increased risk for post-operative complications). Groups were compared according to post-operative clinical outcomes and complications Table 4.26.

Table 4.26   Clinical Outcomes/Complications between Lactate <5mmol/L vs. Lactate >5 mmol/ L

VARIABLES (UNITS)	LACTATE <5 mmol/L n (%)	LACTATE >5mmol/L n (%)	p-VALUE
Mortality			
Yes	2 (5.0%)	-	-
No	41 (95.0%)	30 (100.0%)	

VARIABLES (UNITS)	LACTATE <5 mmol/L n (%)	LACTATE >5mmol/L n (%)	p-VALUE
Return to ICU			
Yes	-	-	
No	43 (100.0%)	17 (100.0%)	
Re-intubation			
Yes	-	1 (6.0%)	-
No	43 (100.0%)	16 (94.0%)	
Re-operation			
Yes	1 (2.0%)	1 (6.0%)	-
No	42 (98.0%)	16 (94.0%)	
Post-operative MI			
Yes	-	-	-
No	43 (100.0%)	17 (100.0%)	
Pulmonary complications			
Yes	1 (2.0%)	1 (6.0%)	-
No	42 (98.0%)	16 (94.0%)	
Neurological complications			
Yes	-	-	-
No	43 (100.0%)	17 (100.0%)	
Renal complications			
Yes	1 (2.0%)	1 (6.0%)	-
No	42 (98.0%)	16 (94.0%)	
GIT complications			
Yes	-	2 (12.0%)	-
No	43 (100.0%)	15 (88.0%)	
Multi system failure			
Yes	1 (2.0%)	-	-
No	42 (98.0%)	17 (100.0%)	
Post-operative dissection of major arteries			
Yes	-	-	-
No	43 (100.0%)	17 (100.0%)	
Acute limb ischemia			
Yes	-	-	-
No	43 (100.0%)	17 (100.0%)	
Heart block			
Yes	-	-	-
No	43 (100.0%)	17 (100.0%)	
Atrial fibrillation			
Yes	-	2 (12.0%)	-
No	43 (100.0%)	15 (88.0%)	

VARIABLES (UNITS)	LACTATE <5 mmol/L n (%)	LACTATE >5mmol/L n (%)	p-VALUE
Cardiac arrest			
Yes	-	-	-
No	43 (100.0%)	17 (100.0%)	
Anticoagulant complications			
Yes	-	-	-
No	43 (100.0%)	17 (100.0%)	
Tamponade			
Yes	-	-	
No	43 (100.0%)	17 (100.0%)	
Sternal wound infection			
Yes	1 (2.0%)	-	-
No	42 (98.0%)	17 (100.0%)	
Septicaemia			
Yes	1 (2.0%)	1 (6.0%)	-
No	42 (98.0%)	16 (94.0%)	
Post-operative blood transfusions			
Yes	14 (33.0%)	9 (53.0%)	-
No	29 (67.0%)	8 (47.0%)	
Length of hospital stay (days)			
Median	8.0	7.0	
25th percentile	5.0	5.0	**0.50**
75th percentile	18.0	20.0	
Length of ICU stay (days)			
Median	3.0	3.0	
25th percentile	1.0	2.0	**0.53**
75th percentile	6.0	6.0	
Ventilation time (hours)			
Median	12.0	12.0	
25th percentile	4.0	6.0	**0.33**
75th percentile	36.0	55.0	

ICU= Intensive Care Unit; MI= Myocardial Infarction; GIT= Gastrointestinal Tract. P-value was calculated using the Kruskal-Wallis test for the comparison of medians.

Post-operative clinical outcomes and complications were summarised for the lactate <5mmol/L group and the lactate >5mmol/L group in Table 4.26.

The lactate <5mmol/L group had none of the following clinical outcomes or complications: return to ICU, re-intubation, post-operative MI, neurological complications, GIT complications,

post-operative dissection, acute limb ischemia, heart block, AF, cardiac arrest, anticoagulant complications or tamponade was noted for the on-pump group.

Clinical outcomes that were noted for the lactate <5mmol/L group were as follow: mortality 2 (5.0%), re-operation 1 (2.0%), pulmonary complications 1 (2.0%), renal complications 1 (2.0%), multi organ failure 1 (2.0%), sternal wound infection 1 (2.0%), septicaemia 1 (2.0%)

The lactate >5mmol/L group had none of the following clinical outcomes or complications: mortality, return to ICU, post-operative MI, neurological complications, multi organ failure, acute limb ischemia heart block, cardiac arrest, anticoagulant complications, tamponade or sternal wound infection.

For the lactate >5mmol/L group 1 (6.0%) patient was re-intubated, re-operation 1 (6.0%), pulmonary complication 1 (6.0%), renal complication 1 (6.0%), GIT complication 2 (12.0%), AF 2 (6.0%) and septicaemia 1 (6.0%).

Length of hospital stay length, ICU stay and ventilation time indicated non-statistically significant differences (p>0.05).

Chapter 5

Discussion

5.1 Introduction

Takala *et al.*, (1996) and Lindsay *et al.*, (2013) found increases in lactate concentrations occur frequently in cardiac surgery and reflect the changes in oxygen delivery and consumption of the patient. Previous studies (Basaran *et al.*, 2006; Munoz *et al.*, 2000 and Meyer *et al.*, 2013) have noted an association between hyperlactatemia on admission to ICU, and morbidity and mortality. This study investigated the metabolic and hemodynamic changes that occur during coronary artery bypass surgery in patients that presented with acute coronary syndrome.

Despite the fact that elevated lactate levels have been described to be associated with adverse outcomes in paediatric cardiac surgery (McLean *et al.,* 2007), as well as in general intensive care admission (e.g. sepsis), no specific lactate level has been identified as a reliable indicator of adverse outcomes in adult coronary artery bypass surgery.

Firstly, elevated lactate levels are associated with anaerobic metabolism during conditions with impaired O_2 delivery to the microcirculation, and thus elevated lactate levels could be associated with adverse outcomes. If a perfusion difference at microcirculatory level exists between on- and off-pump CABG techniques, this might be detected by elevated lactate levels in the affected group. In the debate about advantages of either technique, this might be important in selecting a specific approach for a specific individual.

Secondly, increased lactate production may be stimulated irrespective of tissue oxygenation, as a response to inflammatory mediators or through other mechanisms related to metabolic derangements.

Thirdly, when pulsatile flow is converted to laminar flow in patients during CPB, a redistribution of blood flow occurs to maintain perfusion of vital organs. Therefore, consequent mismatch of O_2 supply and demand and ineffective O_2 extraction occurs due to the alterations of blood flow.

Redistribution of blood flow can also alter regional metabolic pathways resulting in muscle tissue becoming a lactate producer. This might have an impact on patient outcomes.

After reviewing the literature, a number of assumptions were made:

1. Post-operative lactate levels and rate of clearance may be associated with morbidity and mortality as was seen by Lindsay *et al.,* (2013) and Yilmaz *et al.*, (2011).
2. Mean lactate levels during the first 6-12 hours of ICU admission may have a predictive ability as was found by Hajjar *et al.*, (2013) and McNelis *et al.*, (2001).
3. A lactate value >5 mmol/l may provide clinicians with an early indication of a patient's likelihood of experiencing various post-operative complications as was found by Munoz *et al.*, (2000) and Hajjar *et al.*, (2013).

This study was divided into two sections:

1. Is there a difference in perfusion detectable by elevated circulating lactate between on and off pump coronary artery bypass surgery in comparable groups of patients?
2. Can an intra-operative peak value of lactate (in our case >5mmol/L) predict a higher incidence of complications and adverse outcomes in CABG patients (irrespective of whether the patient was done on- or off-pump)?

5.2   On-Pump vs. Off-Pump CABG

5.2.1   Pre-operative Demographic and Clinical Data

Sixty patients (median age on-pump group 58 years and off-pump group, 61 years) met the inclusion criteria of the study and were divided into two groups (30 patients' on-pump and 30 patients' off-pump). Both groups were predominantly male [on-pump 27 (90%) and off-pump 23 (77%)] as is seen in most CAD studies (Konety, *et al.*, 2005) (Figure 4.2). The patients in the on-pump and off-pump groups were considered similar regarding risk factors and co-morbidities with EuroSCOREs of 7.1 for the on-pump group and 6.3 for the off-pump group. On-pump patients had a BMI of 31.0 kg/m² compared to the off-pump patients with a BMI of 32.8 kg/m² but this difference was not statistically significant (p>0.05) (Table 4.1).

There was a difference between the groups with respect to the number of pre-operative acute MI's (p <0.05) and last previous MI upon admission to Cardiology (p <0.05) (Table 4.2). In the

on-pump CABG group 14 (47%) of patients had a MI less than 6 hours prior to admission to Cardiology compared to the 5 (17%) in the off-pump CABG group. A large number of last previous MI was unknown and thus the difference between the groups may not be that notable. Secondly, this data was only for admission prior to cardiology and cardiac surgery was done at a later stage. Thus, pre-operative MI may have little impact on late survival.

Essentially, the study groups were considered similar in nature for the purpose of the study.

5.2.2   Intra-operative Metabolic Data: On-pump vs. Off-pump

The metabolic and clinical changes observed in the on- and off-pump CABG groups were compared by reviewing the patients' intra-operative metabolic data reflected in Table 4.3 and 4.4.

The difference noted for pO_2 and pCO_2, between the on-pump group and off-pump group, was to be expected due to the O_2 concentrations obtained with routine CPB (Figure 4.4). Compared to mechanical ventilation, at 40% O_2, during off-pump CABG surgery.

pH in the off-pump group was lower throughout a large part of surgery and correlates with HCO_3^- and BE also being lower in the off-pump group (Figure 4.4), but pH, HCO_3^- and BE did not correlate with the lactate data for the off-pump group.

Statistically significant differences between the on-pump and off-pump group for HCO_3^- and BE (B) were shown in (Table 4.5). Although values for acid-base variables were lower in the on-pump group they still remained within normal reference ranges.

Hemoglobin was lower in the on-pump group compared to the off-pump group (Figure 4.5). However, this is ascribed to the hemodilution seen during the on-pump surgical technique used.

Electrolyte data and glucose did not reveal any trends or statistically significant differences between the two groups. The electrolyte data (Table 4.5 and Figure 4.6) remained within normal reference ranges as was found by Maasoumi *et al.*, (2013).

12 patients in the on-pump group and 11 patients in the off-pump group had intra-operative lactate levels >5 mmol/L. With respect to number of patients with lactate >5mmol/L, no difference could be demonstrated between the on-pump and off-pump groups. However, the

median values of lactate between the on-pump and off-pump group did show that the lactate levels were higher in the on-pump group with a statistical significant differences ($p < 0.05$).

In order to understand the statistical differences seen for the on-pump group we need to look at the following literature:

- During on pump cardiac surgery, pulsatile flow is changed to a relative laminar pattern. This causes peripheral vasoconstriction and decreased peripheral tissue energy production (Pojar *et al.*, 2008). Further, hypoperfusion of the intestinal mucosa also stimulates divergence of oxygen away from the splanchnic vascular bed, and results in a raised hepatic lactate production (Chiolero *et al.*, 2000).
- In addition, peripheral vasoconstriction associated with CPB causes a redistribution of circulating blood volume to vital organs compromising the microcirculation. This phenomenon is associated with peripheral arteriovenous shunting (Trzeciak *et al.*, 2005), resulting in decreased perfusion to skeletal muscles, which are an important lactate oxidizer. Further, decreased perfusion of skeletal muscle might even result in lactate production (Chiolero *et al.*, 2000).
- Hemodilution during CPB reduces perfusion pressure and reduces the oxygen carrying capacity of blood. In combination with the leftward shift of oxygen hemoglobin dissociation induced by hypothermia, this might limit oxygen delivery to cells (Scaravilli *et al.,* 2012).
- Hypothermia contributes to vasoconstriction leading to further hypo-perfusion at microcirculatory level and decreased splanchnic perfusion.

All of these derangements contribute to increased lactate levels seen in the on-pump group even in the presence of normal oxygenation and circulation as seen from the data collected as was seen by Jones *et al.*, (2009).

Hypothetically, pulsatile flow, regional blood flow autoregulation and oxygen delivery remain "intact" during off-pump CABG and thus lactate levels are normal, or are at least, less affected by the surgical trauma.

5.2.3 Intra-operative Hemodynamic Data: On-pump vs. Off-pump GABG Groups

During both on-pump and off-pump CABG surgery hemodynamic changes were seen with statistically significant differences (Table 4.9) noted for systolic pressures, diastolic pressures and mean arterial pressures ($p<0.05$) for most of the surgery duration. Figure 4.7 indicates a trend where hemodynamic variables were lower in the on-pump group which would be expected considering the surgical technique used (on-pump non-pulsatile flow versus off-pump with maintained pulsatile flow).

The hemodynamic differences between the on-pump and off-pump groups merely reflect the nature of CPB flow versus pulsatile flow.

5.2.4 Post-operative Metabolic Data: On-pump vs. Off-pump CABG Groups

Post-operative metabolic data were summarized for up to 72 hrs after admission to the ICU for the on-pump and off-pump surgery groups in Table 4.10 and Table 4.11, respectively.

There were no statistically significant ($p>0.05$) differences or trends for pO_2 and pCO_2, between the two groups (Figure 4.8 and Table 4.12). pH, HCO_3- and BE (B), were lower in the on-pump group (Figure 4.8) and showed statistically significant differences ($p<0.05$) between the on-pump and off-pump CABG groups from admission to ICU until 4 hours post-operatively (Table 4.12).

O_2 Sat (%) and tHb, showed no statistically significant differences ($p>0.05$).

The median tHb was lower for the off-pump group than for the on-pump group (Figure 4.9). This could be attributed to the autotransfused blood or donor blood given to the on-pump patients after termination of CPB.

Electrolytes, K^+, Ca^{++}, Na^+ and Cl^-, indicated no statistically significant differences ($p>0.05$) nor any differing trends (Figure 4.10 and Table 4.12).

Glucose levels and lactate levels showed statistically significant differences ($p<0.05$) from admission to ICU up to 12 hours post-operatively (Table 4.12). The lactate values for the on-

pump group were significantly higher than the off-pump lactate values during the immediate post-operative period (p<0.05) (Table 4.12).

According to literature patients not recovering to a lactate level of <2mmol/L within 24 hours post-operatively are associated with increased 60-day mortality as confirmed by van Beest *et al.*, (2013). Both groups recovered to <2mmol/L by the 24th hour post-operatively. No other discrepancies were seen in the remaining metabolic data.

As is discussed in literature, pulsatile flow is converted to laminar flow during on-pump CABG. This allows for vasoconstriction and a redistribution of blood flow away from the peripheral tissue and the splanchnic circulation. Hypothermia during CPB further contributes to vasoconstriction.

We postulate that, with decreased splanchnic circulation and peripheral tissue/muscle perfusion, a buildup of lactate in the tissue occurs. During the post-operative period the on-pump group tends to have a washout of lactate. Post-operatively all of the factors contributing to decreased blood flow to non-vital organs are eliminated as the patient is returned to normo-thermic temperatures and pulsatile flow is returned, which allows for peripheral tissue and the gut mucosa to be perfused again. Therefore, a washout of lactate from previously hypo-perfused tissues is seen with the return of pulsatile flow.

As expected, increased glucose levels were evident during the post-operative period in both groups which correlates with increased lactate levels due to the metabolic response to surgery and confirmed by Burton *et al.,* (2004). Increased levels of glucose may serve as an early warning sign of metabolic imbalances that may arise due to surgery or due to post-operative complications (Anderson *et al.*, 2011).

5.2.5   Clinical Outcomes/Complications

One patient in the off-pump group presented with renal complications. Blood transfusions were more frequent in the on-pump group, as published in several studies, (El Naggar *et al.,* 2012 and Sellke *et al.,* 2005) this is ascribed to the different surgical techniques that were used.

The length of hospital stay and ventilation time were longer in the on-pump group but time spent in ICU was longer for the off-pump group (Table 4.13). The shorter mechanical ventilation in off-

pump patients was caused, at least partially, by differences in anesthetic technique as seen by van Dijk *et al.*, (2001).

Two patients from the off-pump group died and none from the on-pump group. Both patients died due to sepsis. The groups were similar with respect to pulmonary complications, atrial fibrillation and neurological complications.

The overall peri-operative complication rate as well as the number of patients, in both on-pump and off-pump groups were low for patients undergoing CABG surgery. Therefore, to make a distinct analysis, between the on-pump and off-pump groups, would be difficult. The present study did not indicate whether or not off-pump CABG surgery could be preferred to on-pump CABG surgery.

5.3   Lactate <5mmol/L vs. Lactate >5mmol/L

5.3.1   Demographic and Clinical Data

Sixty patients (median age 62 years for the lactate <5mmol/L and 57 years for the lactate >5mmol/L) were divided into two groups (lactate <5mmol/L vs. lactate >5mmol/L). The patients in the lactate <5mmol/L vs. Lactate >5mmol/L groups were considered similar with respect to risk factors and co-morbidities with a EuroSCORE of 3.95 placing both groups in a medium risk group (EuroSCORE 3-5) for early mortality.

The BMI was higher in the lactate >5mmol/L (Table 4.15) which may imply that overweight patients may have a bigger risk of hyperlactatemia. Levy *et al.* (2005) stated that coronary flow is significantly lower in obese patients, and capillary recruitment is reduced in non-diabetic obese individuals compared with lean control subjects. Obesity also appears to have an independent effect on microvascular function. Several mechanisms have been identified by which obesity could cause microvascular abnormalities. Amongst other mechanisms, deposits of fat around arterioles may be involved in local TNF-α signaling, resulting in impaired perfusion and insulin resistance. The association between the perfusion of fatty tissue during CPB and a lactate washout seen during the return of pulsatile flow suggests that it remains more difficult to perfuse fatty tissue.

Clinical data were similar and comparable for the lactate <5mmol/L group and the lactate >5mmol/L group (Table 4.16)

5.3.2 Intra-operative Metabolic Data: Lactate <5mmol/L vs. Lactate >5mmol/L

Haterill *et al.* (1997), demonstrated patients with a lactate levels >6mmol/L during cardiopulmonary bypass had a significant sensitivity (78%) and specificity (83%) for mortality within 3 days. Therefore, we decided to use a lactate value of 5mmol/L as the cut-off reference value. Group 1 consisted of patients with lactate levels <5mmol/L irrespective of surgical technique and group 2 consisted of patients whose lactate levels were raised above 5mmol/L at any time during the intra- or post-operative period, irrespective of surgical technique used.

The only statistical difference ($p<0.05$) in intra-operative metabolic data was for tHb at baseline and intubation (Table 4.19). There was no difference in for the trends of haemoglobin and O_2 Sat (%) levels between the two groups (Figure 4.13) suggesting a different mechanism to stimulate increased aerobic glucose metabolism in order to increase lactate levels in the absence of tissue hypoxia.

Studies done by Levy *et al.* (2005) have shown that the activity of the Na^+/K^+ pump system, which requires significant amounts of ATP for its function, is related to increased lactate, in the absence of tissue hypoxia. Such enhanced glycolysis can be triggered by cytokine-mediated uptake of glucose or catecholamine-stimulated increased Na-K-pump activity (Bakker *et al.*, 2013) and according to literature we know that surgical patients have increased release of cytokines and catecholamine as an early response to tissue injury (Toft *et al.*, 2008). Therefore, this phenomenon may be the trigger for increased levels of lactate, and it applies to both on and off pump surgical groups.

All patients undergoing CABG surgery showed increased levels of glucose, and they were consistently and statistically significantly higher in the lactate >5mmol/L (Figure 4.13). The difference in glucose levels for the two groups was also statistically significant ($p<0.05$) for most of the surgery (Table 4.19) and this difference correlates to the findings of a study done by Yilmaz *et al.* (2011). Hyperlactatemia invariably accompanied hyperglycaemia due to the metabolic

response to surgical trauma, where the extra glucose fails to enter the oxidative metabolic pathway and is degraded to lactate.

Data also indicated lower pH, HCO_3-STD and BE(B) levels in the lactate >5mmol/L and these levels correlate to the trends and statistical significance ($p<0.05$) seen for lactate and glucose (Figure 4.12 and Table 4.18). We postulate, that the increased lactate levels were not from respiratory acidosis, partly because metabolic data for pCO_2 and pO_2 were not only comparable for both groups but remained within normal reference ranges throughout the duration of hospital stay. Confirming, indirectly, that hyperlactatemia may be caused by the metabolic response to surgery as well as changes in whole body perfusion.

The trends for the electrolyte data were similar and the levels remained within normal reference ranges (Figure 4.14, Table 4.17 and Table 4.18), with no statistically significant differences observed ($p>0.05$) and correlates to the findings of a study done by Maasoumi *et al.*, (2013).

5.3.3 Intra-operative Hemodynamic Data: Lactate <5mmol/L vs. Lactate >5mmol/L

Although the trends for systolic pressure, diastolic pressure and MAP (Figure 4.15), in the lactate <5mmol/L and lactate >5mmol/L were similar, statistically significant differences were noted ($p<0.05$) for all these variables throughout most of the surgery duration (Table 4.22).

The statistically significant differences ($p<0.05$) in systolic pressures, diastolic pressures and MAP between the lactate <5mmol/L group and lactate >5mmol/L group could be due to the surgical technique used because a larger number patients from the on-pump group 11 (37.0%) had a lactate level of >5mmol/L vs. off-pump 6 (20.0%).

Even though generally believed to be inadequate, MAP is frequently used as an important diagnostic tool for goal oriented therapy in patients with hemodynamic instability. Low MAP leads to inadequate systemic perfusion and as a result depletion of high energy phosphates, cellular dysfunction and finally accumulation of waste products including lactate (Basaran *et al.,* 2006).

CVP, HR and temperature were comparable for the groups and showed no statistical significance ($p>0.05$).

5.3.4 Post-operative Metabolic Data: Lactate <5mmol/L vs. Lactate >5mmol/L

The metabolic data during the post-operative period (Figure 4.16) indicated a similar trends for the lactate groups with respect to all the acid-base variables and returned to normal reference ranges within the first 12 hours post-operatively and correlates to the findings of a study done by Munoz *et al.,* (2000).

Data indicated a lower HCO3-STD and BE (B) for the lactate >5mmol/L group which correlates to the increased lactate levels seen in this group. As was previously mentioned, we speculate this correlation is due to the hyperchloremic acidosis and not due to alterations of O_2 delivery and extraction at cellular level (Table 4.23 and Table 4.24).

Although, lactate was statistically significantly higher ($p<0.05$) in the lactate >5mmol/L (Table 4.25) it nonetheless returned to within normal reference values of <2mmol/L, by 24 hours post-operatively (Figure 4.17) as was seen by McNelis *et al.,* (2001).

However, dynamic indices of lactate homeostasis, which describe not only magnitude but also duration and trend over time, may be even more useful in predicting outcome.

The trends for both groups with respect to electrolytes were similar and remained within normal reference ranges (Figure 4.18), with no statistically significant differences ($p>0.05$) (Table 4.25) and correlates to the findings of a study done by Maasoumi *et al.*, (2013).

5.3.5 Clinical Outcomes / Complications: Lactate <5mmol/L vs. Lactate >5mmol/L

From clinical data that was collected (Table 4.26) it was noted that two patients died in the lactate <5mmol/L group. The proportions of other clinical outcomes such as re-operation due to post-operative bleeding and pulmonary complications were similar for both groups. None of the patients with a lactate of >5mmol/L had neurological- or renal complications. There were two patients with a lactate of >5mmol/L that presented with atrial fibrillation and GIT complications.

There were no significant differences between the two groups with respect to ventilation time, hospital stay and ICU stay; therefore lactate concentrations do not seem to be of clinical use when predicting length of stay as was found by Lindsay *et al.*, (2013)

Two patients returned to theatre, one patient from each group. Only one patient with a lactate of >5mmol/L was re-intubated. One patient from each lactate group had pulmonary complications.

In our study population, a value of >5mmol/L was not significantly related to more adverse events or complications.

6.1   General

Although the study population was relatively small, on-pump patients showed a tendency towards higher median lactate values. This is in keeping with Pojar *et al.* (2008). Lower, tHb. HCO$_3$- and BE (B) values showed statistically significant differences between the on-pump (group 1) and off-pump groups and, according to Montassier *et al.* (2012), these variables are an accurate marker for the prediction of elevated lactate levels. However, this phenomenon was not observed during this study.

The absolute values for metabolic variables generally remained within normal reference ranges during the study for all patients. Except for lactate values, which were elevated during on-pump and off-pump CABG surgery, and returned to within the normal range of <2mmol/L within 24 hours post-operatively.

A peak lactate levels >6 mmol/L is associated with mortality within 3 days with a sensitivity 78% and specificity 83% (Haterill *et al.*, 1997). Therefore, we postulate that our peak lactate value of 5mmol/L is too low to see a correlation with clinical outcomes.

Firstly, increased lactate levels could be due to type A lactic acidosis:
Type A- results from an imbalance between tissue oxygen supply and demand due to ischemia, global hypoxia, respiratory failure, regional hypoperfusion and limb/mesenteric ischemia. Lactate production results from cellular metabolism of pyruvate into lactate under anaerobic conditions.   Therefore, type A is related to total O_2 debt and the magnitude of tissue hypoperfusion.

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

Therefore, an increase or change in lactate levels during the on-pump CABG surgery may be a marker of regional hypoperfusion due to the redistribution of blood flow. This might be as a result of manipulation of the heart during off-pump surgery or due to the effect of CPB.

Secondly, increased lactate levels could be due to type B lactic acidosis

Type B lactic acidosis is due to delayed clearance of lactate, renal dysfunction, catecholamine release and accelerated aerobic glycolysis. The metabolic response to surgery itself may impair oxygen delivery and extraction at cellular level.

Assessing lactate levels at a single point in time did not correlate with clinical outcomes. A cut-off value of 5mmol/L for lactate levels is probably too low to show the association of hyperlactatemia as a predictor for clinical outcomes in this study.

The duration and the time spent with elevated lactate levels are related to both morbidity and mortality (Bakker *et al.*, 2013). In this study, the time of exposure to high lactate levels, was not sustained for an extensive period. In our practice, persistent increases in lactate levels >2.0mmol/L prompted perfusion and anaesthetic interventions. These interventions limited the time spent at an elevated lactate level and may have been a limitation of the study.

Coronary artery bypass surgery remains an established form of treatment for coronary artery disease. According to the Hawkes *et al.* (2006) the overall mortality rate of coronary artery surgery is low, at around 2%–3%, although this benefit is offset by a complication rate of 20%–30%. Data obtained from the study indicated that our results lead to similar clinical outcomes, even in the group of patients that did spent some time, however limited, with lactate levels >5mmol/L.

We conclude that the study showed a significant difference between the on-pump and off-pump group with respect to lactate levels. The cut-off peak lactate level of >5mmol/L was too low to show a positive correlation with clinical outcomes. A recovery period which describes not only magnitude but also duration and trend over time, may be even more useful in predicting outcome.

6.1.1   Limitations

1. Prospective analytical cohort study.
2. Small sample size.
3. Insufficient number of patients with extended periods of impaired flow.
4. Insufficient number of patients with complications.
5. Non- standardization of cardioplegia solutions used during surgery.

6.1.2   Recommendations

1. Randomized trial.
2. Increase study population.
3. Increase peak lactate level to >10mmol/L.
4. The evaluation and comparison of lactate levels over time by use of an "area under the curve" to summarize lactate exposure in patients.

Chapter 7

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Appendices

AN EVALUATION AND COMPARISON OF METABOLIC AND CLINICAL CHANGES IN PATIENTS WITH ACCUTE CORONARY SYNDROMES UNDERGOING ON-PUMP AND OFF-PUMP CORONARY ARTERY BYPASS SURGERY

Date: _____

CONSENT TO PARTICIPATE IN RESEARCH

You have been asked to participate in a research study.

You have been informed about the study by …………………………………… .

You received an information sheet which is a written summary of the research.

You have been informed about any available compensation or medical treatment if injury occurs as a result of study-related procedures. You may contact Prof FE Smit (082 774 1087) and Prof WMJ van Den Heever-Kriek (082 770 5356) at any time if you have questions about the research or if you are injured as a result of the research.

You may contact the Secretariat of the Ethics Committee of the Faculty of Health Sciences, UFS at telephone number (051) 4052812 if you have questions about your rights as a research subject. Your participation in this research is voluntary, and you will not be penalized or lose benefits if you refuse to participate or decide to terminate participation.

If you agree to participate, you will be given a signed copy of this document.

It has been explained to you, that by participating in this study, there is no additional medical risk to you other than those of the intervention which has been discussed with you by your Cardiologist or Cardiothoracic Surgeon.

The research study (summarised for you in the information sheet), including the above information has also been verbally described to me. I understand what my involvement in the study means and I voluntarily agree to participate.

_____   _____

Signature of Participant   **Date**

_____   _____

Signature of Witness   **Date**

(Where applicable)

_____   _____

Signature of Translator   **Date**

(Where applicable)

EVALIASIE EN VERGELYKING VAN METABOLIESE EN KLINIESE VERANDERINGE TUSSEN OP-POMP EN AF-POMP KORONêRE VAT OMLEIDINGS CHIRURGIE IN PATIENTE MET AKUTE KORONêRE SINDROOM.

Datum: _____

TOESTEMMING TOT DEELNAME AAN NAVORSING

U is versoek om aan 'n navorsingsstudie deel te neem.

U is oor die studie ingelig deur……………………………………………………................

U het 'n inligtingsdokument wat 'n geskrewe opsomming van die navorsing is ontvang.

U is ingelig oor die moontlike kompensasie en mediese behandeling wat sal intree indien komplikasies van u deelname aan die studie intree;

U kan Prof FE Smit (082 774 1087) / Prof WMJ van Den Heever-Kriek (082 770 5356) enige tyd kontak indien u vrae oor die navorsing het of as gevolg van die navorsing beseer is.

U kan die Sekretariaat van die Etiekkomitee van die Fakulteit Gesondheidswetenskappe, UV by telefoonnommer (051) 405 2812 kontak indien u enige vrae het oor u regte as 'n proefpersoon.

U deelname aan hierdie navorsing is vrywillig, en u sal nie gepenaliseer word of voordele verbeur as u weier om deel te neem of besluit om deelname te staak nie.

As u instem om deel te neem, sal 'n ondertekende kopie van hierdie dokument aan u gegee word.

Dit is aan u verduidelik dat u deelname aan hierdie studie, buite die risiko's van die chirurgiese intervensie soos bespreek met u deur u Kardioloog of Kardiotoraks-chirurg, geen addisionele mediese risiko's inhou nie.

Die navorsingstudie (opgesom in die inligtingsdokument), insluitende die bogenoemde inligting is ook verbaal aan my beskryf. Ek begryp wat my betrokkenheid by die studie beteken.

Ek verstaan ook dat my pasiënt inligting konfidensieel hanteer sal word en dat my deelname vrywillig is en ek teen enige tyd kan onttrek.

_____   _____

Handtekening van deelnemer   **Datum**

_____   _____

Getuie   **Datum**

(Indien van toepassing)

_____   _____

Hantekening van Vertaler   **Datum**

(Indien van toepassing)

TUMELLO YA HO NKA KAROLO DIPATLISISONG

O kopilwe ho nka karolo thutong ya dipatlisiso.

O ile wa tsebiswa ka thuto ena ke ………………………………………………………………..

O ka nna wa ikopanya le Prof FE Smit (082 774 1087) / Prof WMJ van Den Heever-Kriek (082 770 5356) nako e nngwe le e nngwe ebang o nale dipotso mabapi le dipatlisiso kapa ebang o ka tswa kotsi ka baka la dipatlisiso.

O ka nna wa ikopanya le Mongodi wa Ethics Committee ya Faculty of Health Sciences, UFS nomorong ya mohala ya (051) 4052812 ebang o nale dipotso ka ditokelo tsa hao jwaloka eo ho etswang dipatlisiso ka yena.

Ho nka karolo ha hao dipatlisisong tsena ke boithaopong ba hao, mme o keke wa fumantshwa kotlo kapa wa lahlehelwa ke menyetla ya hao ebang o ka hana kapa wa nka qeto ya ho kgaotsa ka ho nka karolo.

Ha o dumela ho nka karolo, o tla nehwa khopi e saennweng ya tokomane ena hammoho le leqhephe la ba nkang karolo e leng le ngotsweng kgutsufatso ya dipatlisiso.

Thuto ya dipatlisiso ho kenyellwa lesedi le ngotsweng ka hodimo, di ile tsa hlaloswa ho nna ka molomo.

Ke utlwisisa hore ho nka karolo ha ka thutong ena ho bolelang. Ke boetse ke utlwisisa hore tlhahiso leseding e mabapi le dintlha tse amang botho ba ka, e tla nkwa e le sephiri le hore ho nka karolo ha ka ke boithaopo le hore nka nna ka ikgula nako e nngwe le e nngwe.

_____   _____

Tshaeno ya motho ya   **Letsatsinkang karolo**

_____   _____

Tshaeno ya mofetoledi   **Letsats**

AN EVALUATION AND COMPARISON OF METABOLIC AND CLINICAL CHANGES IN PATIENTS WITH ACUTE CORONARY SYNDROMES UNDERGOING ON-PUMP AND OFF-PUMP CORONARY ARTERY BYPASS SURGERY. (This master's thesis was only a subsection of a research project, therefore the information leaflet contain all the information required for the parent study.)

Dear Patient

We, the department of Cardiothoracic Surgery and Cardiology, are doing research on endothelial function as a predictor of post intervention outcomes. Research is just the process to learn the answer to a question. In this study we want to learn if there is a difference in outcomes in patients presenting with acute coronary syndrome and those with worsening or chronic stable angina?

Invitation to participate

We are asking/inviting you to participate in a research study. If you grant us permission you have to sign an informed consent form so that we have evidence that you were willing to participate in the research project.

What is involved in the study?

This is an uncontrolled longitudinal study. Sixty patients with acute coronary syndrome (ACS) will be recruited from the Cardiology clinic for participation. This study will commence on the

18th of June 2007 and is expected to continue until the 31st of July 2008. Due to the fact that every test performed except the oximetry and atherosclerotic measurements is routine practice for a patient with ACS the patient won't be subjected to numerous amounts of tests.

The following tests will be performed:

A)   Physical Examination

After a confirmed diagnosis of acute coronary syndrome and granted consent a complete medical history and physical examination will be performed by a qualified medical doctor located at cardiothoracic surgery **(Routine practice for ACS).**

B)   Cardiology evaluation

The patient will be submitted for a cardiac echocardiogram and an angiogram at the catheter lab on the second floor, Universitas Hospital. **(Routine practice for ACS).**

C)   Arterial blood gas analysis

Arterial blood gas analysis will be performed by sampling whole blood in a pre-heparanized syringe from an indwelling radial artery catheter before induction of anaesthesia. **(Routine practice for ACS).**

D)   Oximetry measurements

The oximetry measurements are non-invasive measurements of regional oxygen saturation in the blood. These measurements will be taken either in the catheter lab or in theatre during the surgical procedures and the patients will therefore not experience any discomfort. SomaSensors (small round stickers) will be placed on the forehead and on the back of the patient to detect the oxygen saturation. The SomaSensors is linked to an electronic machine which will register the readings.

<u>**Risks**</u>

The research project is very safe. All the procedures are non-invasive and no adverse effects are predicted. Patients participating in this study will be well monitored and can at any time discontinue participation in the study. The study will be discontinued prematurely if the

researcher or any of the study leaders feels that a patient's confidentiality might be breached or if any unethical procedures occur.

Benefits

We know that SIRS mediators are activated in the endothelium and that this response can be abnormal in atherosclerosis. It is also known that medical treatment with statins and ACE inhibitors modifies this response and can improve or normalise endothelial function. SIRS occurs more often post –intervention in some patients (e.g. metabolic syndrome, patients with pre-op elevated TNF, microalbuminuria). Outcomes in inflammatory markers and clinical SIRS might differ between on-pump and off-pump CABG.

If we can correlate the pre-intervention endothelial function to outcomes in two different settings (stable angina and acute coronary syndrome) we might be able to develop a rational approach to intervention and choice of intervention.

Your participation will enable us to attempt to try and identify a relationship between clinical data, blood tests and endothelial function/atherosclerosis load will be made.

Participation is voluntary

Refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled; the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Confidentiality

Efforts will be made to keep personal information confidential. Absolute confidentiality cannot be guaranteed. Personal information may be disclosed if required by law. Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Ethics Committee for Medical Research and the Medicines Control Council.

If results are published, this may lead to individual/cohort identification.

Contact details of researcher(s) – for further information/reporting of study-related adverse events.

a)   **Prof FE Smit**

        Head: Department Cardiothoracic Surgery

        UFS

        Cell: 082 774 1087

b)   **Prof WMJ van den Heever-Kriek**

        Associate Professor

        CUT

        Cell: 082 770 5356

Contact details of REC Secretariat and Chair – for reporting of complaints/problems.

a)   **Prof BB Hoek**

        Chairman: Ethical Committee

        UFS

        Phone: 051 405 3177

EVALIASIE EN VERGELYKING VAN METABOLIESE EN KLINIESE VERANDERINGE TUSSEN OP-POMP EN AF-POMP KORONêRE VAT OMLEIDINGS CHIRURGIE IN PATIENTE MET AKUTE KORONêRE SINDROOM.

Beste Pasiënt

Ons, die Departement Kardiotorakschirurgie, is besig om navorsing oor endoteel funksie as 'n voorspeller van post intervensie uitkomste in koronêre siekte te doen. Navorsing is slegs die proses waardeur die antwoord op 'n vraagstuk verkry word. In hierdie studie wil ons leer of daar `n verskil is in die uitkomste van pasiënte wat presenteer met akute koronêre sindroom en die met verskwakkende of chroniese stabiele angina?

Uitnodiging om deel te neem

Ons versoek/nooi u uit om aan die navorsingstudie deel te neem. Indien u aan ons toestemming verleen moet u `n toestemmingsvorm teken sodat ons `n bewys het dat u gewillig was om aan die studie deel te neem.

Wat behels die studie

Hierdie in `n ongekontrolleerde longitudinale studie. Sestig pasiënte met akute koronêre sindroom (AKS) sal gewerf word vanaf die Kardiologie kliniek vir deelname aan die studie. Hierdie studie sal begin op die 18de Junie 2007 en word verwag om voort te gaan tot op die 31ste Julie 2008. Al die toeste wat gedoen word, behalwe vir die aterosklerotiese evaluasie en oksimetrie lesings, is roetiene toetse vir `n pasiënte met AKS. Die pasiënt sal dus nie onderworpe wees aan groot hoeveelhede toetse nie.

Die volgende toetse sal uitgevoer word:

A)   Fisiese ondersoek

Nadat `n bevestigde diagnose van akute koronêre sindroom en toestemming van die die pasiënt sal `n volledige mediese geskiedenis en fisiese ondersoek gedoen word deur `n gekwalifiseerde mediese dokter by kardiotorakschirurgie. **(Roetiene prakryk vir AKS).**

B)   Kardiologie evaluasie

`n Kardiale echokardiogram en angiogram sal van die pasiënt geneem word in die kateter lab op die tweede vloer in Universitas Hospitaal. **(Roetiene prakryk vir AKS).**

C) Arterial blood gas analysis

Arterial blood gas analysis will be performed by sampling whole blood in a pre-heparanized syringe from an indwelling radial artery catheter before induction of anaesthesia. **(Routine practice for ACS).**

D)   Oksimetrie metings

Die oksimetrie metings is nie-indringende metings van suurstof saturasie in die bloed. Hierdie meetings sal in die kateter laboratorium of in die teater gedurende die chirurgiese prosedures geneem word en die pasiënt sal dus geen ongerief/ongemak ervaar nie. SomaSensors (klein ronde plakkertjies) word of die voorkop en die rug van die pasiënt geplak om die suurstof saturasievlakke te meet. Hierdie plakkers is gekoppel aan 'n elektronies masjien wat die lesings registreer.

<u>**Risiko's**</u>

Hierdie projek is baie veilig. Al die prosedures is nie-indringend en geen nadelige gevolge word voorspel nie. Pasiënte wat aan die studie deelneem sal gemonitor word en kan enige tyd onttrek vanuit die studie. Die studie sal onmiddellik gestaak word indien die navorser of enige ander studieleier voel dat `n pasiënt se konfidensialiteit gebreek word of enige onetiese gebeurtenisse plaasvind.

Voordele

Ons weet dat SIRS middellaars geaktiveer word in die endoteel en dat hierdie respons abnormaal kan wees met aterosklerose. Dit is ook bekend dat mediese behandeling met statiene en ACE inhibitors hierdie respons verander en dat dit endoteel funksie kan verbeter of normaliseer. In sommige pasiënte vind SIRS meestal post-intervensie plaas (bv. metaboliese sindroom, pasiënte met pre-operatiewe verhoogde TNF en mikroalbumienurie waardes). Die kliniese uitkomste van SIRS gebasseer op inflammatoriese merkers mag verskil tussen KVO (met gebruik van die hart-long apparaat en daarsonder) en perkutane koronêre ingreep. Indien `n korrelasie tussen pre-intervensie endoteel funksie en uitkomste in twee verskillende gevalle (stabiele angina en akute koronêre sindroom) getref kan word, kan dit ons instaat stel om `n rasionale benadering tot intervensie en keuse van intervensie te maak.

U deelname sal ons instaat stel om te poog om die verhouding tussen kliniese data, bloedtoetse en endoteel funksie/aterosklerose lading te identifiseer.

Deelname is vrywillig

Weiering om deel te neem sal geen boete of verlies van voordele waarop die deelnemer andersins geregtig is behels nie; die proefpersoon kan te eniger tyd aan deelname onttrek sonder boete of verlies van voordele waarop die proefpersoon andersins geregtig is.

Vertroulikheid

Daar sal gepoog word om persoonlike inligting vertroulik te hou. Volkome vertroulikheid kan nie gewaarborg word nie. Persoonlike inligting kan bekend gemaak word as die wet dit vereis. Organisasies wat u navorsingsrekords mag ondersoek en/of kopieer vir kwaliteitsversekering en data-analise sluit groepe soos die Etiekkomitee vir Mediese Navorsing en die Medisynebeheerraad in. As resultate gepubliseer word kan dit lei tot individuele/groepsidentifikasie.

Kontakbesonderhede van navorser(s)

Vir verdere inligting/rapportering van studieverwante newe-effekte.

a)   **Prof FE Smit**

Hoof: Departement Kardiotorakschirurgie

UV

Sel: 082 774 1087

b)   **Prof WMJ van den Heever-Kriek**

Mede-Professor

SUT

Sel: 082 770 5356

Kontakbesonderhede van REC Voorsitter

Vir raportering van klagtes/probleme

a)   **Prof BB Hoek**

Voorsitter: Etiek komitee

UV

Telefoon: 051 405 317

	A	B	C	D	E
1		BLOOD GAS COLLECTION FORM			
		CABG OFF-PUMP			
2	DATE OF SURGERY		*INTRA-OP*		
3			*BOOK 1*		
4	UM NUMBER				
5	DOB				
6	Surgical Blood Results				
7	Events				COMMENTS
8	*Pre-operative*	TIME			
9		Acid/Base			
10			Temp		
11			pH		
12			pCO2 (mmHg)		
13			pO2 (mmHg)		
14			HCO3- act (mmol/L)		
15			HCO3- std (mmol/L)		
16			BE (B) (mmol/L)		
17			BE (ecf) (mmol/L)		
18			ctCO2 (mmol/L)		
19		Co-oximetry			
20			Hct (%)		
21			t Hb (g/dL)		
22			FO2 Hb (%)		
23			FCO Hb (%)		
24			F Met Hb (%)		
25			F HHb (%)		
26		Oxygen status			
27			Temp		
28			BO2 (mL/dL)		
29		Electrolytes			
30			Na+ (mmol/L)		
31			K+ (mmol/L)		
32			Ca++ (mmol/L)		
33			Ca++ 7.4 (mmol/L)		
34			Cl- (mmol/L)		
35		Metabolites			
36			Glu (mmol/L)		
37			Lac (mmol/L)		
38		pATM (mmHg)			
39		Insulin administration (iu/ml)			
40		Adrenaline administration (iu/ml)			
41		∂ Isoket (TNT)			
42		∂ Inotropin			
43		s Dobutrex			
44		s Phenylephrine			
45		Urine Output (ml)			
46	*Upon induction*	TIME			
47		Acid/Base			
48			Temp		
49			pH		
50			pCO2 (mmHg)		
51			pO2 (mmHg)		
52			HCO3- act (mmol/L)		
53			HCO3- std (mmol/L)		
54			BE (B) (mmol/L)		

\\ Intra-op / Post-op /

Appendix D

Adult STS Database

DEPARTMENT CARDIOTHORACIC SURGERY
SURGICAL DATABASE DATA SHEET
CARDIAC SURGERY

	Sticker

PATIENT IDENTIFICATION & DEMOGRAPHICS

First name(s)														
Surname														
Title						**Language**								
Gender	Male ○		Female ○			**ID Number**								
DOB	m m / d d / y y y y					Age							years	
Folder #	UM					**Reference**								
Practitioner						**Location**								
Category	Private ○		Academic ○											
Funder / Medical aid														
Status	Current ○	Inactive ○		Hospital ○			Deceased ○							
Address	**Home** Physical													
	Postal													
	Work Physical													
	Postal													
Phone number	Home					Work								
Fax number	Home					Work								
Cell number														
Account														
Details	Blood group					Ethnicity								
	Allergies													
	Classification													
Notes														
Admission	d d / m m / y y y y					**Discharge**		d d / m m / y y y y						
Surgery	d d / m m / y y y y					**Location**								
Surgeon						**Grade**								
Assistant						**Grade**								
Cardiologist						**Physician**								
Anesthetist						**Assistant**								
Perfusionist						**Assistant**								
Diagnosis						**Authorisation**								

Cardiac Surgery Data Sheet   1

ADULT CARDIAC - HISTORY
Cardiac History

Angina	Yes ☐		No ☐		
If YES	Stable O	Unstable O			
Angina status	*If Stable* CCS 1 O CCS 2 O CCS 3 O	**If Unstable** **CCS 4 O**	*If NO* CCS 0 O		
Dyspnoea status	NYHA I	O NYHA II	O NYHA III	O NYHA IV	O

MI	Yes ☐		No ☐		
MI type	STEMI	O non-STEMI	O Unknown	O
Previous MI's	None	O		
	One	O Two or more	O Unknown	O
Last MI	No previous	O MI < 6 hrs	O MI 6-24 hrs	O
	MI 1-30 days	O MI 31-90 days	O MI > 90 days	O

Medication	Pre-op medication	O				
	Digitalis	O	Beta-blocker	O	Ca++ antagonist	O
	ACE Inhibitor	O	Nitrates IV	O	Cordarone X	O
	Other anti-arrhythmic	O	Disprin	O	Clexan	O
	Warfarin	O	Glyco pro 3+ B Inhibitors	O	Heparin	O
	Diuretica	O	Inotropes	O	Statins	O
	Steroids	O	ADP Inhibitors	O		

Previous Cardiothoracic or Vascular Surgical Intervention

Previous surgical intervention	Yes ☐		No ☐					
If YES **Type of surgical intervention**	CABG	O	Valve	O	Congenital cardiac	O	Other cardiac	O
	Other non-cardiac	O	Other thoracic	O	Aortic – asc or arch	O	Aortic – desc or abdominal	O
	Carotid endarterectomy	O	Peripheral vascular	O				
If OTHER CARDIAC	LVA	O	VSD	O	ASD	O	Congenital	O
	Cardiac Tx	O	Pacemaker	O	AICD	O	Cardiac trauma	O
	Other	O						
If OTHER NON-CARDIAC	Aortic aneurism	O	Carotid endarterectomy	O	Other vascular	O	Other	O
Non surgical	PTCA	O	Thrombolysis	O	Stent	O	Ballon valvoplasty	O
Valve	Repair	O	Replace	O				
Operation date				d d / m m / y y y y				

Previous non-surgical intervention	Previous PCI	O	No previous PCI	O	PCI < 24 hours before surgery	O	PCI > 24 hours before surgery	O

Recent failed intervention	Yes	○ No ○										
If Yes	Intervention date		d	d	/	m	m	/	y	y	y	y

MAIN COMPLAINT AND HISTORY

RISK
Risk Factors for Coronary Disease

Diabetes	Not diabetic	O	Diet	O	Oral therapy	O	Insulin	O
Hyper-cholesterolemia	No hyper-cholesterolemia	O	Treated or > 6.5 mmol/L	O	Unknown	O		
Cholesterol								mmol/L
Hypertension	No hyper-tension	O	Treated or BP 140/90	O	Unknown	O		
Pulmonary systolic > 60 mmHg	Yes	O	No	O				
Smoking	Never	O	Ex-smoker	O	Current smoker	O		

Additional Medical History and Risk Factors for Morbidity

Renal	No renal disease	O	Functioning transplant	O	Creatinine > 200 µmol/L	O	Dialysis for acute renal failure	O
	Dialysis for chronic renal failure	O	Unknown	O				
Pulmonary	COPD / Emphysema	O	Asthma	O				
If COPD / Emphysema	COPD Grade		Mild	O	Moderate	O	Severe	O
Neurological dysfunction	Yes	O	No	O				
Neurological disease	CVA full recovery	O	CVA residual lesion	O	Rind or TIA	O	Lesion > 50 %	O
	Previous carotid surgery	O						
Peripheral vascular	Yes	O	No	O				
Carotid bruits	Yes	O	No	O				
Pre-operative heart rhythm	Sinus rhythm	O	Atrial fibrillation / flutter	O	Complete heart block / pacing	O	Ventricular fibrillation or...	O
	Other abnormal rhythm	O						

Other Risk Factors

Height		cm	BMI	
Weight		kg	Body surface area	
Weight category	Underweight	O	Normal	O	Pre-obese	O	Obese	O
	Severely obese	O						
Haemoglobin		g/dL	Creatinine (pre-op)	mmol/L

Endocarditis	Treated	○	Active	○	
Immuno-supressed					

INVESTIGATION
Catheterisation

Patient catheterised	Never	○	This admission	○	Previous admission	○		
Catheterisation date					d d / m m / y y y y			
Number of previous PCI's								
	Stented	Yes	○	No	○			
	Status	Elective	○	Urgent	○			

Haemodynamics

When	Never	○	This admission	○	Previous admission	○	Echo only	○
	Date					d d / m m / y y y y		

Thrombolysis

Thrombolysis	Yes	○	No	○			
	Agent	TPA	○	Streptokinasis	○	Urokinasis	
	Interval	< 6 hours	○	> 6 hours	○		

Coronary Anatomy

Extend of coronary vessel disease	No vessel with > 50% diameter	○	One vessel with > 50% diameter	○	Two vessels with > 50% diameter	○	Three vessels with > 50% diameter	○
	Not investigated	○						

Indices and Pressure

PA systolic	mmHg	LVEDP	cm
DPDT	Dynes/sec	Aortic valve gradient	mmHg
Mean PAWP / LAP	mmHg	Mitral valve gradient	mmHg

Ejection Fraction

Ejection fraction	%						
Category	Good (50%)	○	Fair (40 - 49%)	○	Poor (< 40%)	○	Not measured ○
Method	LV Gram	○	Radio-nucluide	○	Echo	○	Estimate ○
LVEDD	cm	LVESD				cm	

OPERATIVE
Preoperative support

Intravenous nitrates or any heparin	No	O	Until operation	O	Within one week of operation	O		
Intravenous inotropes	Yes	O	No	O				
Cardiogenic shock	Yes	O	No	O				
	If YES Type		Refractory	O	Heamo-dynamic stable	O		
Ventilated	Yes	O	No	O				

Operation

Operation date		d	d	/	m	m	/	y	y	y	y

Operative priority	Elective	O	Urgent	O	Emergency	O	Salvage	O
If Emergency	**Reason for emergency**	AMU	O	IABP	O	CCF	O
		Worsening CP	O	Anatomy	O	USA	O
		Resting angina	O	Valve dysfunction	O	Aortic dissection	O
		Cath complication	O				
If Urgency	**Reason for urgency**	Shock circ supp	O	Shock no circ supp	O	Pulmonary edema	O
		AEMI	O	Ongoing ischaemia	O	Valve dysfunction	O
		Aortic dissection	O	Cath complication	O		
Ventilated	Yes	O	No	O				

Procedures

Cardiac procedures performed	CABG	O	Valve	O	Other	O		
If Other cardiac	LV aneuris-mectomy	O	Acquired VSD	O	Atrial myxoma	O	Pulmonary embolectomy	O
	Cardiac tx	O	Pulmonary tx	O	Cardiac trauma	O	Epicardial pacemaker	O
	Peri-cardectomy	O	ASD	O	Other procedures for congenital	O	Other procedures not listed	O
	If procedure not listed		Aortic peripheral vascular	O	Carotid endarte-rectomy	O	Aortic aneurysm ascending	O
			Aortic aneurysm descending	O	Aortic aneurysm arch	O	Aortic aneurysm thoracic	O
			Aortic aneurysm abdominal	O	Other vascular	O	Other thoracic	O

Graft Procedures

No of distal coronary anastamosis			No of proximal anastamosis					
			Graft 1	Graft 2	Graft 3	Graft 4	Graft 5	Graft 6
Graft site: 1= Prox RCA　2= Mid RCA　3= Distal RCA 4= RCA-PDA　5= RCA-LV　6= LMS 7= Prox LAD　8= Mid LAD　9= Distal LAD 10= Diag 1　11= Diag 2　12= Prox Cx 13= Int　14= OM 1　15= Distal LCx 16= OM2　17= Cx-PDA								
Graft conduit: 1= Pedicle LIMA　2= Pedicle RIMA　3= Pedicle RGEA 4= Free LIMA　5= Free RIMA　6= Free RGEA 7= Radial artery　8= Long SV　9= Short SV 10= Cephalic vein　11= Other artery　12= Other								
Anastamosis: 1= End-to-side　2= Side-to-side								

VALVES
Valve Procedures

Number of valves replaced	1 ◯	2 ◯	3 ◯	4 ◯
Valve	**Aortic**	**Mitral**	**Tricuspid**	**Pulmonary**
Haemodynamic pathology	Stenosis ◯ Regurgitation ◯ Mixed ◯	Stenosis ◯ Regurgitation ◯ Mixed ◯	Stenosis ◯ Regurgitation ◯ Mixed ◯	Stenosis ◯ Regurgitation ◯ Mixed ◯
Explant type	Native valve ◯ Mechanical ◯ Biological ◯ Homograft ◯ Autograft ◯ Ring ◯	Native valve ◯ Mechanical ◯ Biological ◯ Homograft ◯ Autograft ◯ Ring ◯	Native valve ◯ Mechanical ◯ Biological ◯ Homograft ◯ Autograft ◯ Ring ◯	Native valve ◯ Mechanical ◯ Biological ◯ Homograft ◯ Autograft ◯ Ring ◯
If Native valve, pathology	Native valve not present ◯ Congenital ◯ Degenerative ◯ Active infective endocarditis ◯ Previous infective endocarditis ◯ Rheumatic ◯ Annuloaortic ectasia ◯	Native valve not present ◯ Congenital ◯ Degenerative ◯ Active infective endocarditis ◯ Previous infective endocarditis ◯ Rheumatic ◯ Annuloaortic ectasia ◯	Native valve not present ◯ Congenital ◯ Degenerative ◯ Active infective endocarditis ◯ Previous infective endocarditis ◯ Rheumatic ◯ Annuloaortic ectasia ◯	Native valve not present ◯ Congenital ◯ Degenerative ◯ Active infective endocarditis ◯ Previous infective endocarditis ◯ Rheumatic ◯ Annuloaortic ectasia ◯

Cardiac Surgery Data Sheet

7

	Calcific degeneration ○	Calcific degeneration ○	Calcific degeneration ○	Calcific degeneration ○
	Ischaemia ○	Ischaemia ○	Ischaemia ○	Ischaemia ○
	Functional regurgitation ○	Functional regurgitation ○	Functional regurgitation ○	Functional regurgitation ○
	Other native valve pathology ○	Other native valve pathology ○	Other native valve pathology ○	Other native valve pathology ○
If OTHER native valve pathology, state				
Procedure	Replace ○ Repair ○	Replace ○ Repair ○	Replace ○ Repair ○	Replace ○ Repair ○
If replacement, state reason	Thrombosis ○ Dehiscence ○ Embolism ○ Infection ○ Intrinsic valve failure ○ Haemolysis ○ Other ○	Thrombosis ○ Dehiscence ○ Embolism ○ Infection ○ Intrinsic valve failure ○ Haemolysis ○ Other ○	Thrombosis ○ Dehiscence ○ Embolism ○ Infection ○ Intrinsic valve failure ○ Haemolysis ○ Other ○	Thrombosis ○ Dehiscence ○ Embolism ○ Infection ○ Intrinsic valve failure ○ Haemolysis ○ Other ○
	If other, state	If other, state	If other, state	If other, state
Implant type	Mechanical ○ Biological ○ Homograft ○ Autograft ○	Mechanical ○ Biological ○ Homograft ○ Autograft ○	Mechanical ○ Biological ○ Homograft ○ Autograft ○	Mechanical ○ Biological ○ Homograft ○ Autograft ○
Implant type				
Implant prosthesis name				
Implant prosthesis model				
Valve / ring serial number				
Valve / ring size	mm	mm	mm	mm

Cardiac Surgery Data Sheet   8

AORTA
Aortic Procedures

Number of valves replaced	1	○	2	○	3	○	4	○
	5	○						

Aortic root								
Aortic pathology	Aneurysm	○	Syphilis	○	Dissection	○	Transection	○
Aortic procedure	Interposition tube graft							○
	Tube graft and separate AVR							○
	Root replacement with composite graft and coronary reimplantation							○
	Root replacement with preservation of native valve and coronary reimplantation							○
	Homograft root replacement							○
	Aortic patch graft							○
Ascending aorta								
Aortic pathology	Aneurysm	○	Syphilis	○	Dissection	○	Transection	○
Aortic procedure	Interposition tube graft							○
	Tube graft and separate AVR							○
	Root replacement with composite graft and coronary reimplantation							○
	Root replacement with preservation of native valve and coronary reimplantation							○
	Homograft root replacement							○
	Aortic patch graft							○
Aortic arch								
Aortic pathology	Aneurysm	○	Syphilis	○	Dissection	○	Transection	○
Aortic procedure	Interposition tube graft							○
	Tube graft and separate AVR							○
	Aortic patch graft							○
Descending aorta								
Aortic pathology	Aneurysm	○	Syphilis	○	Dissection	○	Transection	○
Aortic procedure	Interposition tube graft							○
	Aortic patch graft							○
	Thrombo-exclusion							○
Abdominal aorta								
Aortic pathology	Aneurysm	○	Syphilis	○	Dissection	○	Transection	○
Aortic procedure	Interposition tube graft							○
	Aortic patch graft							○

MYOCARDIAL
Myocardial Protection

Cardio-pulmonary bypass	Yes	○	No	○	
Method of protection	Non-cardioplegic	○	Cardioplegia	○	

Cardiac Surgery Data Sheet 9

If Cardioplegia	**Solution**	Blood	O	Crystalloid	O		
	Temperature	Cold	O	Warm	O		
	Infusion mode	Antegrade	O	Retrograde	O	Ante- and retrograde	O
If Non-cardioplegia	**Protection**	Aortic cross-clamping with fib	O	Fibrillation with perfusion	O	Cross-clamp with direct coron...	O
		Cross-clamp and beating heart	O	Beating heart without cross-clamp	O		

No cardiopulmonary bypass

Shunt	Yes	O	No	O			
Stabilizer	Compression	O	Suction	O	Snares	O	None	O
Reason off-pump	Risk factor	O	Surgeon's choice	O	Other	O	
Total OPCAB time							
Heart action	Spontaneous	O	Fibrillation	O	Block	O	A/F	O

Cardiopulmonary bypass

Cumulative bypass time		min	**Cumulative cross-clamp time**		min
Total circulatory arrest time		min	**Temperature (Lowest core)**		° C
Back on bypass	Yes O No O				

If YES	**Reason**	Low cardiac output	O	Fibrillation	O	Bleeding	O
		Technical	O	Other	O		
	Time back						min
	X-clamp time back						min
	Bypass time						min
Intra-aortic balloon pump used	No	O	Pre-operation	O	Intra-operation	O	Post-operation	O
	Reason for using balloon pump	Haemo-dynamic instability	O	Unstable angina	O	CPB wean	O
		Prophylactic	O	Low cardiac output	O	PTCA support	O
Cannulation arterial	Aorta ascending	O	Femoral	O	Axilla	O	Aorta descending	O
	Aortic arch	O						
Cannulation venous	RA	O	Femoral	O	LA	O	Pulmonary	O

INTRAOPERATIVE
Bypass

Pacing	Yes	O	No	O				
If YES	**Method**		Atrial	O	Ventricular	O	A/V sequential	O
			Permanent	O				
Haemolysis	Yes	O	No	O				
ECG normal	Yes	O	No	O				
Cell saver	Yes	O	No	O				

Inotropes & Support

Inotropes in OR	Yes	O	No	O		
Inotropes in ICU	Yes	O	No	O		
Dopamine (µg/kg)	< 5	O	5 - 10	O	> 10	O
Dobutamine (µg/kg)	< 5	O	5 - 10	O	> 10	O
Adrenaline (µg/kg)	< 0.05	O	0.06 - 0.1	O	> 0.1	O
Phenilephrine	Yes	O	No	O		
Anti-arrhythmics	Yes	O	No	O		
Cyclocapron	Yes	O	No	O		
Trasylol	Yes	O	No	O		

Blood Products

Lowest HB on bypass		mmol/L	**Volume cristalloid**			L
Vollume colloid		L				
Blood products in OR	Yes	O	No	O		
If YES	**Number**	RS	FFP	Cryo	Platelet	

OPERATIVE REPORT

Procedure

Operation report

POST-OPERATIVE
Complications

Reoperation	No re-operation required						O
	Re-operation for bleeding post-op						O
	Re-operation for valvular dysfunction						O
	Re-operation for graft procedure						O
	Re-operation for other cardiac procedure						O
	Re-operation for other non-cardiac procedure						O
	Peri-operative MI						O
	Sternum resuturing sterile						O
	Surgery for deep sternal sepsis						O
New post-operative stroke	None	O	Transient stroke	O	Permanent stroke	O	Disoriented	O
Renal complications	Dialysis	O	Renal failure	O	Creatinine / urea up	O		
Infection	Sternum superficial	O	Sternum deep	O	Leg	O	IABP	O
	Septicemia	O	Wound drainage	O	Urinary tract infection	O		

Cardiac Surgery Data Sheet   13

Intubation period									
Blood loss									ml

Valvular	Structural	O	Non-structural dysfunction	O	Thrombo-embolism	O	Valve thrombus	O
	Anti-coagulant complication	O	Prosthetic valve endo...	O				

Vascular	Limb ischemia	O	Iliac / femoral / aortic	O				

Other	Heart block	O	Cardiac arrest	O	Anti-coagulant complex	O	Tamponade	O
	Gastro-intestinal	O	Multi-organ failure	O	Other	O		
	If other, specify							

Interval	In hospital < 30 days	O	In hospital > 30 days	O	Out of hospital < 30 days	O

Follow-up

Patient status at discharge	Alive	O	Dead	O									
Date of discharge / death				d	d	/	m	m	/	y	y	y	y

Discharge destination	Home	O	Con-valescence	O	Other hospital	O

Cause of death	Cardiac	O	Infection	O	Neurological	O	Pulmonary	O
	Renal	O	Valvular	O	Vascular	O	Other	O

Interval	In hospital < 30 days	O	In hospital > 30 days	O	Out of hospital ...	O	Out of hospital	O

Days in ICU				

Blood used	RS	FFP	Cryo	Platelet

Readmission	Yes	O	No	O

If YES	**Reason**	Pulmonary	O	Cardiac	O	Shock	O
		Bleeding	O	Arrhythmia	O	Renal failure	O
		Other	O				

Reintubation	Cardiac	O	Pulmonary	O

Post-op medication	Lanoxin	O	Beta-blockers	O	Calcium antagonist	O	ACE inhibitor	O
	Diuretics	O	ADP inhibitor	O	Statins	O	Other lipid lowering	O
	Disprin	O	Glyco III Beta inhibitor	O	Cordarone X	O	Other anti-arrhythmic	O
	Warfarin	O	Onther anti-coagulant	O				

POST-OPERATIVE COURSE

Unit

Ward

Medication

FOLLOW-UP APPOINTMENTS

Removal of sutures (referring doctor/institution)
Cardiothoracic Surgery
Cardiology

EUROSORE
Patient Factors

Age				years
Gender	Male O	Female O		
Other	Chronic pulmonary disease O	Neurological dysfunction O	Serum creatinine > 200 µmol/L O	Critical pre-operative state O
	Extracardiac arteriopathy O	Previous cardiac surgery O	Active endocarditis O	

Cardiac Factors

Cardiac dysfunction	Unstable angina O	LV dysfunction poor / LVEF <30 % O	Pulmonary hypertension O	LV dysfunction moderate / LVEF30-50% O
	Recent MI O			

Operation Factors

Operation factors	Emergency O	Surgery on thoracic aorta O	Other than isolated CABG O	Post-infarct septal rupture O

EUROSCORE				%

FOLLOW-UP NOTES

Seen by doctor: _____   **Date:** ____ / ____ / _____

Clinical

Symptoms	Angina	O	Exercise inhibition	O			
	NYHA 1	O	NYHA 2	O	NYHA 3	O	NYHA 4	O
Post-operative complaints	Postoperative complaints	O	Other	O			

Complications

	Cardiac	O	Respiratory	O	GIT	O	Wound	O
	Limbs	O	Warfarin	O	Medication	O	Systemic embolism	O
	Other	O					
Complications							

Examination

	Pulse	Tempo		/min	Rhythm		
	Blood pressure	/		mmHg			
	Cardiac	O	Respiratory	O	GIT	O	Wound	O
	Limbs	O	Warfarin	O	Medication	O	Systemic embolism	O
Examination	Other						

Special investigations

	ECG	O	X-rays	O	Sonar	O	FBC	O
	SMAC	O	Digitalis	O			
Special investigations							

Cardiac Surgery Data Sheet   **17**

Medication	
1.	4.
2.	5.
3.	6.
7.	8.

Comments

NEXT APPOINTMENT WITH CARDIOTHORACIC SURGERY:

_____ / _____ / _____

THE PATIENT WAS DISCHARGED FROM DEPARTMENT CARDIOTHORACIC SURGERY AND WILL BE FOLLOWED-UP BY:

Dept of Cardiology	O	Dept of Oncology	O	Dept of Pulmonology	O
Dept of Internal Medicine	O	Dept of Surgery	O	Dept of Neurology	O
Other	O				

Appendix F

Ethical Clearance

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

Direkteur: Fakulteitsadministrasie / Director: Faculty Administration
Fakulteit Gesondheidswetenskappe / Faculty of Health Sciences

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Ms H Strauss

2007-08-14

PROF FE SMIT
DEPT OF CARDIOTHORACIC SURGERY
FACULTY OF HEALTH SCIENCES
UFS

Dear Prof Smit

FTOVS NR 51/07A
RESEARCHER: PROF FE SMIT AND OTHERS
PROJECT TITLE: EVALUATING THE RELATIONSHIP OF LACTATE AND GLUCOSE
LEVELS AND OPERATIVE SIRS IN CABG PATIENTS.

- You are hereby informed that the above mentioned study was approved by the Ethics Committee on 12 June 2007

- The following documents are used by the Ethics Committee as guidance documents: Declaration of Helsinki, ICH, GCP and MRC guidelines on bio medical research. Clinical trial guidelines 2000 Department of Health (RSA), Ethics in Health Research - Principles structure and processes Department of Health RSA 2004, the Constitution of the Ethics Committee of the Faculty of Health Sciences and the guidelines of the S.A. Medicines Control Council as well as laws and regulations with regard to the Control of Medicines.

- Any amendment, extension or other modifications to the protocol must be submitted to the Ethics Committee for approval.

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

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

- Please refer to the ETOVS reference number in correspondence to the Ethics Committee secretariat.

Yours faithfully

for   PROF BB HOEK
CHAIR: ETHICS COMMITTEE
Cc   Ms M Jansen van Vuuren, Dept of Cardiothoracic Surgery, Faculty of Health Sciences, UFS

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