EVALUATION OF NEAR-INFRARED SPECTROSCOPY IN PATIENTS WITH ACUTE CORONARY SYNDROME UNDERGOING ON- AND OFF-PUMP CORONARY ARTERY BYPASS GRAFT SURGERY

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DECLARATION OF INDEPENDENT WORK

I, LINDY LIEBENBERG, 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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ACRONYMS

↑	Increase
↓	Decrease
%	Percentage
<	Less than
>	More than
≤	Less or equal
≥	More or equal
°C	Degrees of Celsius
=	Equals
ABG	Arterial Blood Gasses
ACS	Acute Coronary Syndrome
BP	Blood Pressure
CABG	Coronary Artery Bypass Graft
CBF	Cerebrospinal Fluids
CK-MB	Creatinine Kinase, Muscle & Brain
CNS	Central Nervous System
$CMRO_2$	Cerebral Metabolic Rate of Oxygen
CO	Cardiac Output
CO_2	Carbon Dioxide
CPB	Cardiopulmonary Bypass
CVP	Central Venous Pressure
FiO_2	Fraction of Inspired Oxygen
GCP	Good Clinical Practice

Hb	Haemoglobin
Hct	Haematocrit
HR	Heart Rate
ICHT	Intracranial Hypertension
ICU	Intensive Care Unit
MAP	Mean Arterial Pressure
mmHg	Millimetres Mercury
MMSE	Mini-Mental State Examination
NIRS	Near-Infrared Spectroscopy
NIR	Near-Infrared
OPCAB	Off-Pump Coronary Artery Bypass
$PaCO_2$	Partial Pressure of Carbon Dioxide in Arterial Blood
PCI	Percutaneous Coronary Intervention
pO_2	Oxygen Partial Pressure
RBF	Renal Blood Flow
RLFP	Regional Low Flow Perfusion
rSO_2	Regional Oxygen Saturation
SIRS	Systemic Inflammatory Response Syndrome
SpO_2	Pulse Oximeter Oxygen Saturation
SVC	Superior Vena Cava
SvO_2	Mixed Venous Oxygen Saturation
U&E	Urea & Electrolytes

LIST OF DEFINITIONS

Acute Coronary Syndrome (ACS)	ACS is a series of conditions which include chest discomfort or any other symptoms caused by the decreased oxygen supply to the myocardium. Coronary artery disease caused by plaque etc. that leads to clotting in the coronary arteries and impairs the blood supply to the heart (American Heart Association, 2009).
Coronary Artery Bypass Graft Surgery (CABG; on-pump & off-pump)	Coronary artery bypass graft surgery a surgical procedure performed to relieve angina and to reduce the risk of death from coronary artery disease. Veins are harvested from the leg and grafted to the diseased coronary artery to restore coronary circulation supplying the myocardium with oxygen. This surgery is either performed with cardiopulmonary bypass (on-pump) or on a beating heart (off-pump) (Sabik and Lytle, 2008).
Cardiopulmonary bypass	A procedure to circulate and oxygenate the blood while surgery is performed on the heart. It involves the drainage of oxygen poor blood from the heart and lungs through the heart-lung machine, and then returns oxygen rich blood to the aorta (Chilton and Klein, 2009).
Cerebral Blood Flow	Indicates the amount of blood that supplies the brain with oxygen at a given time (The Free Dictionary, 2012(b)).
Complications	An adverse response to a procedure or therapy (MedicineNet.com, 2012).

Hemodynamics	Hemodynamics is the study of blood flow or the circulation – the force involved in the circulation of blood (Merriam-Webster. Online Dictionary, 2012(a); Medical-Dictionary, 2012(a)).
Hypoperfusion	Decrease blood flow through an organ, thus there is also a decrease in oxygen delivery. If hypoperfusion is prolonged it may result in cellular dysfunction and death (Merriam-Webster Online Dictionary, 2012(b)).
Mini-Mental State Examination	A brief psychological test designed to differentiate among dementia, psychosis, and affective disorders. It may include ability to count backward by 7s from 100, to identify common objects such as a pencil and a watch, to write a sentence, to spell simple words backward, and to demonstrate orientation by identifying the day, month, and year, as well as town and country (Medical-Dictionary, 2012(c)).
Near Infrared Spectroscopy	Near infrared spectroscopy (NIRS), is a non-invasive, optical method for the in vivo monitoring of tissue oxygenation (Chakravarti, Srivastava and Mittnacht, 2008).
Outcomes	The condition of a patient at the end of therapy or a disease process, including the degree of wellness and the need for continuing care, medication, support, counseling, or education (Medical-Dictionary, 2012(b)).
Oxygenation	Oxygenation is the amount of oxygen in blood, it describes the hemoglobin oxygen-carrying capacity (The Free Dictionary, 2012(a)).

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CHAPTER 4: RESULTS

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OPSOMMING

Die doel van hierdie studie was om ondersoek in te stel of die intra-operatiewe serebrale weefsel suurstof saturasie en hemodynamise monitering van pasiënte met akute koronêre sindroom tydens koronêre vat omleiding (KVO) chirurgie, kliniese uitkomste en komplikasies kan voorspel.

Data van 60 KVO pasiënte (30 met behulp van die hart-long apparaat en 30 sonder die hulp van die hart-long apparaat) is ontleed. Die plaaslike serebrale weefsel suurstof saturasie is gemonitor deur gebruik te maak van naby-infrarooi spektroskopie (NIRS). Twee Somasensors word in die middel van die pasiënt se voorkop geplaas en die kabels word dan gekonnekteer aan die sensors en aan die Somanetics INVOS 5100C® Oximeter. Volgens die NIRS waardes, is pasiënte in twee groepe verdeel. Pasiënte in Groep 1 het absolute NIRS waardes van meer as 50 of minder as 20% daling vanaf die basislyn. Pasiënte in Groep 2 het die absolute NIRS waardes van minder as 50 of 'n daling van meer as 20% van die basislyn. Die laagste waarde aangeteken tydens die prosedure is vir hierdie doel aangeteken. Die intra-operatiewe hemodinamiese monitering is opgeneem deur 'n rekenaar program (verskaffer, Datex Ohmeda, Suid Africa).

Om chirurgiese uitkomste te beoordeel is verskeie parameters ontleed en vergelyk. Dit sluit 'n pre-en post-operatiewe Mini-Mental staat toets wat uitgevoer is om neurologiese uitkomste te identifiseer. Die NIRS waardes en tendense met betrekking tot nierfunksie (U & E en kreatinien, urine, en urine elektroliete), sowel as kliniese

uitkomste is post-operatief in die verskillende groepe ontleed. Kliniese uitkomste is beskryf met behulp van die Vereniging van Thoraks Chirurge se Databank (STS databasis) data velde, en spesifiek die opname van komplikasies.

Die uitkomste tussen die pomp (met hart-long apparaat) en geen pomp (sonder hart-long apparaat) KVO groepe sowel as hul NIRS resultate is ontleed. Om die voorspellende rol van NIRS te bepaal, is die pasiënte in groepe verdeel met of verswakte / verminder NIRS waardes of aanvaarbaar NIRS waardes gebasseer op gepubliseerde resultate waar 'n vermindering van meer as 20% van die basislyn of absolute waardes van minder as 50 gepaardgaande was met slegter kliniese uitkomste.

Ten slotte is die voorspellende waarde van NIRS geëvalueer binne die pomp en dan die geen pomp KVO groepe. In hierdie analise is die uitkomste van pasiënte met verminderde NIRS waardes vergelyk met dié van pasiënte met aanvaarbare NIRS waardes.

Die studie het getoon dat die meerderheid van die pasiënte met verminderde serebrale vloei / suurstof lewering, soos weerspieël in serebrale NIRS, het pomp KVO prosedures gehad (84% het in risiko groep 2 geval). Dit het ook getoon dat NIRS vermindering van meer as 20% vanaf die basislyn en waardes van minder as 50, 'n impak het op die post-operatiewe nierfunksie.

Monitering van serebrale oximetrie intra-operatief deur van NIRS gebruik te maak tydens hartchirurgie (veral in die pomp kardiale chirurgie pasiënte) stel die perfusie

tegnoloog en narkotiseur in staat om serebrale desaturasie te noteer en daarop te reageer in 'n poging om die kliniese uitkoms te verbeter.

Dit is waarskynlik belangrik om in 'n verdere ondersoek te kyk na die tyd wat spandeer word wanneer die NIRS waarde onder 50 val of tydens 'n daling van meer as 20% van die basislyn. Dit is belangrik om vas te stel of die "area onder die kurwe" as' n spesifieke faktor vir verhoogde risiko vir post-operatiewe komplikasies betekenisvol is op 'n vergrote studiepopulasie.

Die studie ondersteun die roetine gebruik van NIRS as 'n tendens monitor van serebrale saturasie. Die gebruik daarvan het beide die perfusie tegnoloog en narkotiseer attend gemaak op serebrale perfusie, intervensie is toegepas waar nodig wat gelei het tot uitstekende kliniese uitkomste in hierdie reeks.

SUMMARY

The objective of this study was to investigate whether intra-operative regional cerebral tissue oxygen saturation (NIRS) and hemodynamic monitoring in patients with Acute Coronary syndrome (ACS) during coronary bypass graft surgery (CABG on-pump vs. off-pump) can predict clinical outcomes and complications.

Data from 60 CABG patients (30 on-pump and 30 off-pump) were analyzed. The regional cerebral tissue oxygen saturation was monitored by using near-infrared spectroscopy (NIRS). The sensors were positioned in the middle of the patient's forehead and the cables were connected to the sensors and to the INVOS 5100C® Oximeter. According to NIRS values obtained, patients were subdivided into two groups. Patients in Group 1 had absolute NIRS values more than 50 or less than a 20% drop from the baseline value. Patients in Group 2 had absolute NIRS values of less than 50 or a drop of more than 20% from the baseline value. The lowest value recorded during the procedure was recorded for this purpose, irrespective of the time this value was obtained. Intra-operative hemodynamic monitoring was captured by a computer software program (Supplier Datex Ohmeda, South Africa).

In order to describe surgical outcomes several parameters were analysed and compared. This included a Pre- and Post-operative Mini-Mental state examination that was performed to identify neurological outcomes or impairment. The NIRS

values and trends in relation to renal function (U&E and creatinine, urine output, and urine electrolytes), as well as clinical outcomes were analyzed post-operatively for the different groups. Clinical outcomes were described using the Society of Thoracic Surgeons Database (STS database) data fields, and specifically the recording of complications.

The overall clinical outcomes were analysed between the on-pump and off-pump groups as well as the NIRS results between the two groups.

In order to elucidate the predictive role of NIRS the patients were divided into groups with either impaired /reduced NIRS values or acceptable NIRS values according to published results where a reduction of more than 20% from baseline or absolute values of less than 50 were associated with inferior outcomes.

Finally, the predictive value of NIRS was evaluated within the on- and then the off-pump groups. In this analysis the outcomes of patients with reduced NIRS values was compared to those of patients with acceptable NIRS values.

The study demonstrated that by far the majority of patients with reduced cerebral flow/oxygen delivery as reflected in cerebral NIRS, had on-pump CABG procedures (84% fell in risk group 2). It also showed that a NIRS reduction of more than 20 % from baseline and values of less than 50, has an impact on post–operative renal function.

Monitoring of cerebral oximetry intra-operatively by using near-infrared spectroscopy during cardiac surgery (especially in on-pump cardiac surgery patients) allows the perfusionist and anaesthesiologist to detect cerebral desaturation and to intervene

as necessary. This study also showed a tendency towards less renal function impairment in patients with absolute NIRS values > 50 or where there was < 20% drop from baseline.

It is probably important to consider studying the time spend below 50 or a drop of more than 20% from baseline NIRS values, or the "area under the curve" as a specific factor contributing to the increased risk for post-operative complications applied on an increased study population.

The study supports the routine use of NIRS as a non-invasive trend monitor of cerebral saturation and certainly initiated interventions by both anaesthetic and perfusion staff which contributed to excellent clinical outcomes in this research study.

Chapter 1

INTRODUCTION

Acute Coronary Syndrome (ACS) refers to a range of acute myocardial ischemic states that occurs after the sudden blockage of a coronary artery. This may cause a reduction in blood supply to certain areas of the myocardium and results in ischemia (Warnica, 2008). 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).

Cardiac surgery and anaesthetic techniques have improved over the years, but Central Nervous System (CNS) dysfunction continues to be a major cause of morbidity after cardiac surgery (Fun-Sun, Chia-Chih, Chee-Yueh, Serle and Powel, 2004). Cerebral micro-embolism and hypoperfusion have been proposed to be major mechanisms of dysfunction, where low perfusion pressure and re-warming during CPB may cause an imbalance between oxygen supply and demand. In both mechanisms, tissue hypoxia is the common pathway causing cerebral dysfunction (Fun-Sun *et al*., 2004).

Performing CABG without cardiopulmonary bypass (off-pump CAB) has shown to reduce the risk of peri-operative stroke. Whether off-pump CAB (OPCAB) reduces the incidence of less severe neurocognitive impairment has not yet been clearly established (Scarborough, White, Derilus, Mathew, Newman and Landolfo, 2003).

Heart manipulation during OPCAB can impair cardiac output and induce hypotension, which can result in significant brain hypoperfusion (Berry, McGarvey, Zeng and Woo, 2005).

Greater focus is being put on neuro-protective strategies to improve quality of life. Various neurological complications remain prevalent, but regional ischemia leading to adverse outcomes is detectable and correctable and a variety of parameters have been used traditionally to guide the question of whether oxygen supply is meeting oxygen demand at tissue level. Blood pressure, pulse oximetry (SpO_2) central venous oximetry (SvO_2), arterial blood gasses and serial lactates are a few examples of these parameters.

The Somanetics® INVOS® Cerebral Oximeter (Covidien) augments these existing strategies by providing a new "vital sign" called regional saturation of oxygen (rSO_2). The system alerts clinicians of cerebral ischemia and proved an early warning for regional oxygen imbalances that may be encountered in surgery or in the cardiac laboratory.

The aim of this study is to predict the incidences of complications and clinical outcomes in patients with acute coronary syndrome related to reduced cerebral perfusion. Observations with near-infrared spectroscopy will be done during on-pump and off-pump CABG to measure cerebral oxygenation, and will be related to hemodynamic changes and intra−operative manipulation.

Chapter 2
LITERATURE REVIEW

2.1 ACUTE CORONARY SYNDROME (ACS)

2.1.1 Definition

The term Acute Coronary Syndrome (ACS) refers to a range of acute myocardial ischemic states after the sudden blockage of a coronary artery. This may cause a reduction in blood supply to certain areas of the myocardium resulting in ischemia. ACS encompasses unstable angina, non-ST segment elevation myocardial infarction (ST segment elevation generally absent), and ST segment elevation infarction [persistent ST segment elevation usually present, (Warnica, 2008)].

2.1.2 Treatment

Therapy for acute coronary syndrome includes medical treatment (e.g. Aspirin, Clopidogril, Nitoglycerin and ACE Inhibitors), Percutaneous Coronary Intervention (PCI, which is a revascularization therapy that avoids the need for bypass), and Coronary Artery Bypass Grafts (CABG) with or without the use of cardiopulmonary bypass [Figure 2.1; (Warnica, 2008)].

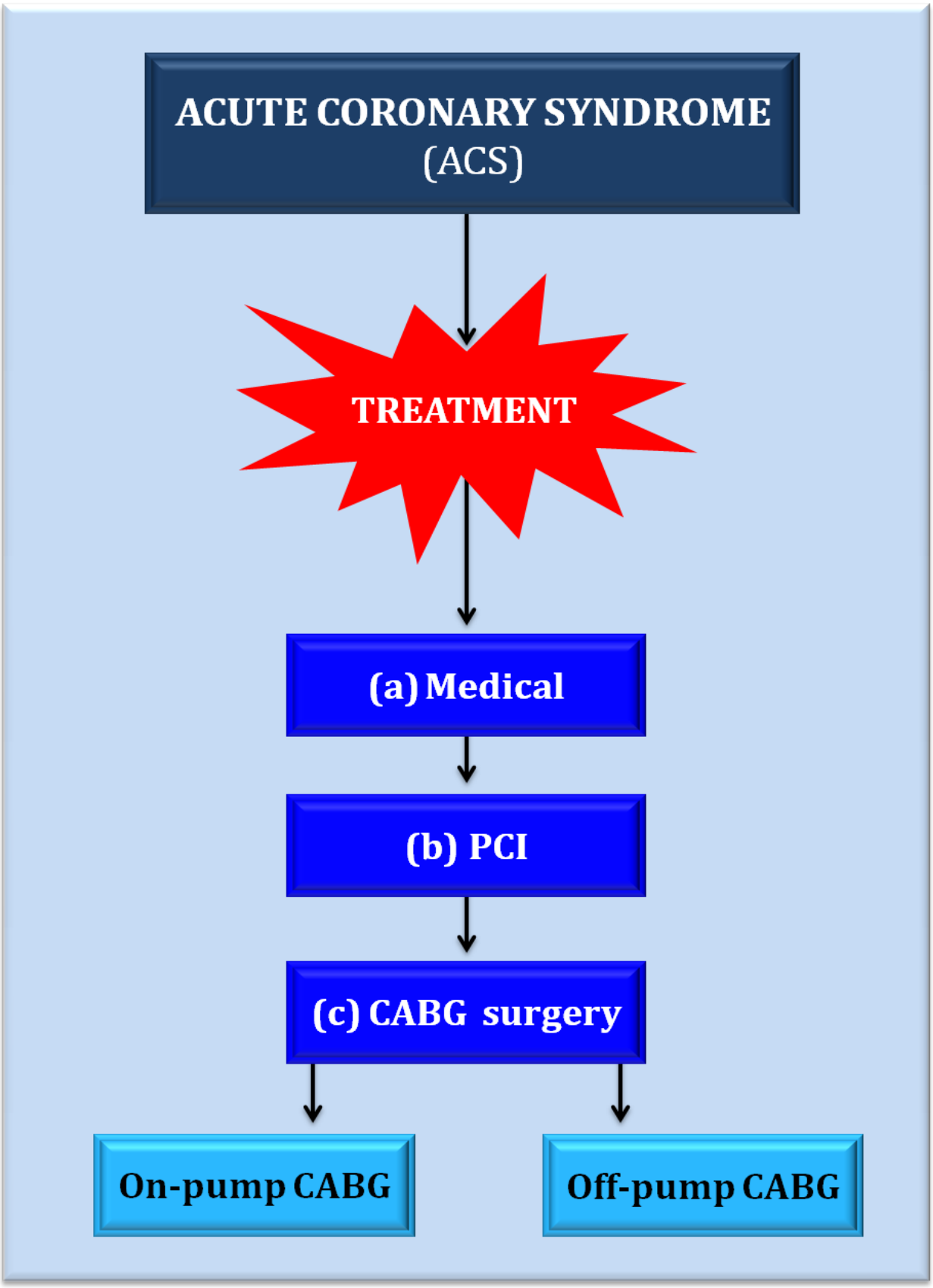


Figure 2.1 **Summary of the Treatment options available for Acute Coronary Syndrome (ACS)**

[PCI = Percutaneous Coronary Intervention; CABG = Coronary Artery Bypass Grafting]

2.1.2.1 Medical Treatment

The treatment for ACS can be achieved through the administration of pharmacological drugs (Table 2.1) thus without the use of interventions such as PCI or CABG.

Table 2.1 Pharmacological drugs used in the treatment of ACS (adapted from: Heart and Stroke Information point, 2010).

DRUG	MODE OF ACTION
Aspirin	An antiplatelet drug used in all patients with coronary artery disease.
Clopidogrel	Is also an antiplatelet drug that is used with aspirin or in patients who cannot tolerate aspirin alone.
Calcium channel blockers	Relaxes the arteries and lowers blood pressure, resulting in a decrease in workload of the heart.
ACE inhibitors	Also reduces workload of the heart by relaxing the arteries and lowering blood pressure. This drug also reduces the risk of a heart attack and stroke.
Angiotensin Receptor blockers	This drug is an effective alternative for patients who cannot tolerate ACE inhibitors.
Statins	A cholesterol lowering drug that is given to the patient, even if the patient's cholesterol levels are normal, to reduce the risk of a heart attack.
Beta-Blockers	Is a drug for long-term use, and is prescribed for patients with unstable angina or patients with any sign of heart muscle damage.
Eplereone	This drug is an aldosterone receptor antagonist and is prescribed to patients who had a heart attack and have diabetes.
Nitrates	It dilates the blood vessels, resulting in a decrease in the workload of the heart.
Anticoagulants	For long-term use in patients with ACS to reduce the risk of systemic emboli.

2.1.2.2 Percutaneous Coronary Intervention (PCI)

Percutaneous Coronary Intervention (PCI) is a non-invasive way to treat diseased arteries. The procedure is performed by inserting a balloon catheter into the femoral artery in the groin area, through the blood vessels, and then to the blocked artery of the heart. The balloon is then dilated to open the vessel, which sometimes may include a metal tube called a stent. Although PCI is non-invasive there is always 'n risk of needing another intervention later on in life (Torpy, Lynm and Glass, 2004).

2.1.2.3 Coronary Artery Bypass Graft (CABG) Surgery

Coronary Artery Bypass Grafting (CABG) was introduced in the 1960s and is effectively used for the relief of angina and the stabilization of ventricular function. Since then CABG was established as a safe and effective operation worldwide (Livesey, 2006). Just as a detour on the highway in case of a roadblock, CABG involves the strategic placement of bypass grafts that will act as an alternative route for blood flow to bypass blockage (Shekar, 2006).

For the purpose of this study emphasis will be place on CABG surgery as the treatment method of choice for patients diagnosed with ACS.

Currently, there are two different ways in which surgeons perform CABG surgery, the traditional way with the use of cardiopulmonary bypass (CPB) which is called on-

pump CABG and the latest approach which is without the use of CPB which is called off-pump CABG.

2.1.2.3.1 On-pump Cardiopulmonary Artery Bypass Graft (CABG) Surgery

Cardiopulmonary bypass (CPB) is a technique that temporarily takes over the function of the heart and lungs during surgery via a heart-lung machine, to maintain the circulation of blood and the oxygen content of the body.

In short, during on-pump CABG, saphenous veins are harvested from the patient's leg, and if need be the radial artery is dissected from the forearm. These veins are grafted to the coronary arteries to bypass atherosclerotic narrowing. The chest is opened via a median sternotomy and a cannula is placed in the right atrium to withdraw blood from the body into an oxygenator where gas exchange takes place. The cannula that is used to return oxygenated blood is inserted into the upper ascending aorta. The patient is then taken onto bypass, cooled down and cardioplegia is administered to stop the heart (Livesey, 2006).

2.1.2.3.2 Off-pump Cardiopulmonary Artery Bypass Graft (CABG) surgery

Off-pump CABG, also known as OPCAB, is very similar to the conventional on-pump CABG procedure. OPCAB still utilizes a medial sternotomy, however the important difference is that the cardiopulmonary bypass pump is not used, and the surgery takes place on a beating heart. With the heart still beating, there is a greater difficulty in performing a bypass on the posterior and lateral walls of the heart. The surgeon manipulates the heart to the necessary position and uses a stabilizer to expose the site where the anastomoses must be performed (Livesey, 2006).

2.2 COMPLICATIONS ASSOCIATED WITH CORONARY ARTERY BYPASS GRAFT (CABG) SURGERY

CABG is considered as one of the landmark operations in the history of cardiac surgery that rescued millions of people diagnosed with coronary artery disease (Shekar, 2006). However, this breakthrough operation was not without complications and adverse events. Some of the complications associated with CABG was systemic inflammatory response, cerebral dysfunction, myocardial depression and hemodynamic instability (Shroyer, Grover, Hattler, Collins, McDonald, Kozora, Lucke, Baltz and Novitzky, 2009). CABG may be successful in the revascularization of the heart but the surgical procedure may have adverse effects on the brain (Zangrillo, Crescenzi, Landoni, Leoni, Marino, Calabrò, Corno, Pappalardo and Alfieri, 2005).

Neurological abnormalities surpassed mortality as the primary distinguishing feature of cardiac surgery. Nearly half a million adult patients worldwide are annually affected by neurologic disability related to CABG. The mechanisms of injury implicated include reperfusion, inflammatory, excitotoxic, compromised cerebral blood flow, ischemic and embolic events (Hoffman, 2006).

The frequent occurrence of ischemic episodes during CABG has been linked to transient and permanent neurocognitive impairment, brain abnormalities, and bio-chemical and histopathologic signs of injury (Hoffman, 2006). Age also contributes to the incidence of cerebral complications after cardiac surgery. For instance the incidence of stroke after CABG is less than 1% in patients under the age of 64 years but 5% in patients aged 65 to 75 years and 7-9% in patients older than 75 years (Tan, 2008).

The neurological damage encountered after cardiac surgery is divided in type I (focal injury, stupor, or coma at discharge) and type II [deterioration in intellectual function, memory deficit, or seizures; (Zangrillo *et al*., 2005)]. Neurocognitive decline (intelligence, problem solving, concentration, learning, memory, error free performance and dexterity) occurs more frequently than stoke with 60% at 1 week after surgery, and 25 to 30% between 2 months and 1 year (Tan, 2008).

2.2.1 Neurological dysfunction and Cardiopulmonary Artery Bypass Graft (CABG) surgery

The incidence of neurocognitive disorders increase with the use of total circulatory arrest and hypothermia (Tabaee, Rostami, Arefi and Sadeghi, 2009). However, brain injury following CABG is usually attributed to two main causes: embolization (macro/micro) and compromised cerebral blood flow (Tan, 2008).

2.2.1.1 Compromised Cerebral Blood Flow (on-pump and off-pump)

The brain is the most vulnerable organ that can be affected by a complete lack of blood supply. However, should the blood flow through the brain be compromised, it may be tolerated briefly by an increase in oxygen extraction from available blood flow. The amount of cerebral blood flow depends mainly on carbon dioxide (CO_2) tension in the cerebral tissue. The cerebral vessels will dilate due to a decrease in oxygen tension. Administration of anaesthetics may reduce brain metabolism as much as 40%, which will cause a partial decrease in cerebral blood flow (Reed and Anderson, 1986).

Under conditions that often pertain in adults undergoing cardiac operations, cerebral blood flow is about 25 $ml.min^{-1}.m^{-2}$ (normal cerebral blood flow range from 45–50 $mL.min^{-1}.100g^{-1}$) brain tissue with some variability depending on $PaCO_2$ (Govier, Reeves, McKay, Karp, Zorn, Morawetz, Smith, Adams and Freeman,1984).

During normothermic and moderately hypothermic CPB in adults, cerebral blood flow is not significantly altered with variations of mean arterial blood pressure (Brusino, Reves, Smith, Prough, Stump and McIntyre, 1989). This is similar to situations in a normal awake human adult, in whom cerebral blood flow does not vary significantly with variations of mean arterial blood pressure (from about 60 to 150 mmHg). When arterial blood pressure during CPB falls below 40 mmHg, cerebral blood flow may decline appreciably, with a decrease in oxygen consumption (Feddersen, Aren, Nilsson and Radegran, 1986).

Therefore, a decrease in CPB flow rate has an effect on cerebral blood flow, because there is a direct correlation between CPB flow rate and cerebral blood flow, despite the poor correlation between arterial blood pressure and cerebral blood flow. Soma and co-workers (1989) performed a study on two groups; one was a hypotensive group and the other group "normal". They concluded that mean arterial pressure had no significant influence on cerebral blood flow during CPB, in other words cerebral blood flow is CPB flow rate dependant (Soma, Hirotani, Yozu, Onoguchi, Misumi, Kawada and Inoue, 1989).

Cerebral blood flow during CPB is also affected by $PaCO_2$. Hypercarbia increase cerebral blood flow, whereas hypocarbia decrease cerebral blood flow (Govier, 1984). Under usual conditions of CPB, the metabolic needs of the brain are met with a $PaCO_2$ of 33 mmHg (Kern, Ungerleider, Quill, Baldwin, White, Greeley and Reves, 1991).

Cerebral blood flow during CPB may at times be excessive in relation to cerebral oxygen consumption. During CPB, the patient's body temperature is reduced from 37°C to 28°C; in which cerebral blood flow decrease less than cerebral oxygen consumption (Croughwell, Newmann, Blumenthal, White, Lewis, Frasco, Smith, Thyrum, Herwits and Leone, 1994).

A major complication following cardiac surgery is cerebral injury. Off-pump CABG (OPCAB) has become popular over the years since CPB is associated with neurologic dysfunction. Although, there are several reports in favour of OPCAB, beneficial effects of OPCAB on cerebral function are still controversial (Kim, Kwak, Oh, Kim, Yoo and Hong, 2005). Manipulation of the heart during OPCAB to expose the graft site induces hemodynamic instability, and could compromise cerebral perfusion (Murkin, Kaplan, Reich, Konstadt and Saunders, 2000). The effect of hemodynamic derangement occurring during positioning of the heart on cerebral perfusion is however, not known, for example:

- Steep Trendelenburg position to the expose posterior side of the heart elevates the jugular venous pressure, compromising cerebrospinal fluid (CBF) independent of an acceptable mean arterial pressure [MAP; (Kim, Kwak, Oh, Kim, Yoo and Hong 2005)].
- Decrease in cardiac output [CO; (due to arrhythmias, dislocation of the heart, ischemia etc.) may compromise blood flow to the brain (Kim *et al.*, 2005).

- Positioning the heart for anastomoses of the circumflex and posterior descending artery is a risk for inducing hypotension, impaired cardiac index and generalized hemodynamic instability with risk of cerebral compromise (Murkin *et al*., 2000).

- Compromised right ventricular diastolic filling as a result of direct ventricular compression may be the primary mechanism for producing hemodynamic instability during OPCAB surgery (Murkin *et al.,* 2000).

- Embolic events may also occur due to the placement of the partial occlusion aortic clamp to perform proximal graft anastomoses, because arteriosclerotic plaque may detach and end up in the systemic circulation (Nierich, Diephuis, Jansen, Borst and Knape, 2000).

(a) Microcirculation

The microcirculation is the part of the systemic and pulmonary circulation responsible for the exchange of water, gases, nutrients and waste material. The microcirculation includes arterioles, capillaries, venules, and terminal lymphatic vessels (De Backer, 2005).

Features of the microcirculation differ from that of the systemic circulation:

- Capillary PO_2 is much lower than arterial PO_2.
- Local hematocrit differs from systemic hematocrit.
- Microcirculatory blood flow control is complex and depends on both local metabolic control and systemic humoral control.
- Microvessels differ among organs, for that reason some organs may be more vulnerable to a decrease in global blood flow (De Backer, 2005).

Keeping this in mind CPB affects the microcirculation of a patient in the following ways:

- The tone of the arterioles and capillary walls are affected – regulation of vascular resistance change with alterations in temperature.
- Leucocytes were activated and adhere to vascular endothelium under conditions of cardiopulmonary bypass (Wagner, Schiller, Dilg, Depner, Welz and Lacour-Gayet, 2001).

Comparing exposure to normothermic and hypothermic CPB, it was found that the temperature of perfusion has no effect on microcirculation during non-pulsatile CPB (Wagner *et al.*, 2001).

However, de Jaegere and Suyer (2002) stated that non-pulsatile flow produced by CPB have an adverse effect on the microcirculation, resulting in arteriolar shunting and post-operative organ dysfunction/failure.

(b) Brain Temperature and regional Oxygen Saturation (rSO_2)

Temperature has an important effect on tissue oxygenation. Standard temperature monitoring during CPB may not accurately characterize the efficacy of cerebral cooling (Hogue, Sundt, Goldberg, Barner and Davila-Roman, 1999).

Hypothermia reduces the solubility of gases, such as CO_2, in blood. Thus, at lower systemic temperatures, the $PaCO_2$ is relatively low, resulting in an elevated pH with alkalosis. The higher pH causes the oxyhemoglobin dissociation curve to shift to the left, which result in:

- Decrease oxygen availability to the brain tissue and
- Cerebral vasoconstriction – leading to a reduced cerebral blood flow (Hogue *et al.*, 1999).

There are two acid-base strategies during hypothermic CPB:

i) pH stat

- Which restore $PaCO_2$ and pH to normal non-hypothermic levels.
- In pH stat CBF is relatively high, but pressure-flow auto regulation is lost.

ii) Alpha stat

- $PaCO_2$ is allowed to be relatively low and the pH is allowed to remain high.
- CBF is reduced but pressure-flow auto regulation is still maintained so that the reduced CBF is met with a decrease in cerebral metabolic rate (Hogue *et al.,* 1999).

Although there is a lack of evidence to support the option to use alpha-stat or pH-stat management, as to which is more beneficial to brain protection, temperature reduction by means of extracorporeal circulation with alpha-stat acid-base management result in a decrease in cerebral blood flow and a decline in metabolic rate (Greeley *et al*., 1989). Predicted flow should ensure adequate cerebral oxygenation during cooling. However, other variables are also involved in the maintenance of adequate tissue oxygenation, for instance rSO_2 varied inversely with cooling rate (Daubeney, Pilkington, Janke, Charlton, Smith and Webber, 1996).

Hypothermia (33-35°C) during cardiopulmonary bypass definitely has neuroprotective benefits and evidence suggest that hypothermic improves neurologic outcome even when induced after a cerebral ischemic event (Nussmeier, 2005).

However, the rate and extend of re-warming from hypothermic CPB can promote neurologic injury. Several studies have shown that rapid rates of re-warming after hypothermic CPB resulted in reduced jugular venous oxygen saturation, presumably a result of increased cerebral metabolism and elevated oxygen extraction levels within the cerebral circulation (Cook, Oliver, Orszulak and Daly, 1994). Grigore and co-workers (2002) have linked rapid re-warming rates and cerebral hyperthermia to post-operative neurocognitive decline (Grigore, Grocott, Mathew, Philip-Bute, Stanley, Butler, Landolfo, Reves, Blumenthal and Newman, 2002).

In summary a reduced arterial blood pressure during CPB contributes to post-operative neurological dysfunction, because hypotension resulted in reduced cerebral blood flow (Branthwaite, 1974). When cerebral blood flow was measured during operations involving hypothermia, it was observed that patients with an increased oxygen extraction before hypothermia may be more vulnerable to cerebral injury. During cooling a reduction in cerebral oxygen consumption and cerebral blood flow occurred. Other studies have confirmed the observation that cerebral blood flow generally decrease with temperature during cooling, and that the link with cerebral metabolism is maintained even with low temperatures when

ventilation is managed according to the alpha-stat strategy (Greeley, Kern, Underleider, Boyed, Quill, Smith, Baldwin and Reves, 1991).

In a healthy normothermic brain, cerebral blood flow and metabolism is tightly linked. Vital neuronal function may be maintained during flow reduction of up to 50% by increasing oxygen extraction. During re-warming there is often a result of desaturation, as the temperature induced an increase in cerebral metabolism, which is usually not linked to augmentation of brain perfusion. Daubeney *et al*., (1996) again described a relationship between rSO_2 and nasopharyngeal temperature during re-warming.

2.2.1.2 Embolization (on-pump and off-pump CABG)

As previously stated one of the main causes for neurocognitive impairment during CPB is embolization. This includes both macromolecules (macroembolization) and microparticles (microembolization). Macroemboli occludes vessels larger than 200 µm and are possibly related to massive air embolisms, usually due to human error or set-up defaults in the CPB circuit (Baufreton, 2010). Embolisms of particles or thrombi that become detached from aortic plaques during aortic operative manipulation can also cause these occlusions (Scarborough *et al*., 2003).

On the other hand microemboli occludes small vessels, arterioles and capillaries (10 to 70 µm) with neurological manifestations that are usually only detected by

specialized neuropsychological tests to confirm neurocognitive decline (Scarborough *et al*., 2003). Microembolization (50% of patients when detected systematically) occur much more frequent than macroembolization [about 10 times fewer; (Roach, Kanchuger, Magano, Newman, Nussmeier, Wolman, Aggarwal, Marschall, Graham, Ley, Ozanne and Mangano, 1996)]. Microemboli can also result from cardiac activities such as de-airing, circulating lipid particles or platelet aggregates to numerous particles associated with surgery itself like glove talcum powder or it can originate from the CPB circuit (Baufreton, 2010).

Microemboli are also distributed in proportion to blood flow. Alpha-stat acid-base management and phenylephrine during CPB reduce cerebral injury by causing cerebral vasoconstriction and reducing the number of microemboli. Also, major changes in CBF occur with changes from pulsatile to non-pulsatile flow with the initiation of cardiopulmonary bypass (Edmonds *et al*., 2004). However, low perfusion pressure and related changes in cerebral blood flow during CPB affect the clearance and destination of embolic particles. The clearance of microemboli from the brain is probably impeded by a decreased flow in patients with a lower mean arterial pressure (MAP) which leads to lower cerebral perfusion and ultimately cerebral injury (Tan, 2008). Anaemia and elevated cerebral temperatures increase cerebral blood flow but may cause inadequate oxygen delivery to the brain (Edmonds *et al*., 2004).

Cerebral blood flow increases with temperature: brain injury associated with normothermic and hyperthermic CPB are more likely due to increase cerebral microemboli, which produce large lesions at higher cerebral temperatures.

- **Brain temperature = important neuroprotective strategy that is protective against neural cell necrosis** (Edmonds *et al*., 2004).

Murkin and co-workers (2002) has demonstrated that although higher MAP is a requirement for cerebral well-being during CPB, cerebral venous hypertension might be a potential contributor to cerebral dysfunction. They described that dislocation of the heart in the presence of a single, two-stage venous cannula during CPB, may occlude the superior vena cava and result in jugular venous hypertension. This give rise to inadequate cerebral perfusion pressure, despite "normal" MAP, resulting in cerebral venous hypertension and decrease cerebral blood flow (Murkin, Boyd, Ganapathy, Adams, Peterson, Morgan and Lok, 2002).

Keeping the complications associated with CPB (intense systemic response, systemic and pulmonary capillary leak and pulmonary, renal and neurocognitive dysfunction) in mind CABG is now possible without the use of CPB (Ascione, Lloyd, Underwood, Lotto, Pitsis and Angelini, 2000).

It is believed that off-pump surgery reduce postoperative morbidity, including reduced myocardial injury, renal dysfunction, neurocognitive deficit, and SIRS. However, off-pump cardiac surgery still results in tissue trauma, cardiac manipulation, pericardial suctioning and the administration of exogenous drugs such

as heparin, protamine and many anaesthetic agents. Therefore, a physiological stress response with resulting increases in pro-inflammatory markers still exist. The magnitude of the response, however, is significantly less than that observed when using CPB (Ascione *et al*., 2000).

Research shows that OPCAB should improve neurologic outcome due to both a reduction in cerebral emboli generation as well as avoidance of prolonged periods of cerebral hypoperfusion. However, several investigators have failed to demonstrate an improvement in cognitive function following CABG (Hernandez, Cohn, Baribeau, Tryzelaar, Charlesworth, Clough, Klemperer, Morton, Westbrook, Olmstead, O'Conner, Mack, Grover and Hasan, 2001). Some found no difference in cognitive function in patients after OPCAB or CABG with CPB. Hernandez and colleagues (2001) have found that the post−operative stroke rate after OPCAB (1.33%) was not significantly different from that after CABG with CPB (1.82%). Thus, although off-pump CABG is associated with a reduction in the number of intra−operative cerebral microemboli, a clear relationship between the reduction in microemboli and improvement in neurocognitive function remains inconclusive.

Technical advances may further improve the neurological outcomes after OPCAB. Cardiac displacement to gain access to the posterior wall during OPCAB causes transient elevation in central venous pressure and simultaneously decrease systolic blood pressure thus producing hemodynamic instability (Nierich *et al*., 2000). Even without CPB, periods of cerebral hypoperfusion are possible during OPCAB. Embolic events may occur due to the placement of the partial occlusion aortic clamp to

perform proximal graft anastomoses. OPCAB does not entirely eliminate the possibility of either cerebral microembolism or cerebral hypoperfusion.

Moritz, Arlt, Voelkel, Hilker and Hobbhahn (2007) has shown in a randomize study that positioning of the heart during OPCAB, provoke changes in cerebral oxygen saturation. They concluded that an alteration in $PaCO_2$, decrease cardiac output and systemic oxygen delivery, which has an effect on cerebral oxygen saturation, but not with changes in MAP. This means that when $PaCO_2$ remains constant, changes in cerebral oxygen saturation are most likely to reflect a decrease in cardiac output or systemic oxygen delivery. Displacement of the heart may lead to systemic hypoperfusion and cerebral venous hypertension.

2.3 METHODS TO ASSESS COGNITIVE DECLINE AFTER CABG SURGERY

Cognitive assessment is regarded as a valuable clinical skill. Cognitive assessment is commonly used for the following reasons (a) screening for cognitive impairment, (b) differential diagnoses of cause and (c) rating the severity of the disorder or monitoring the disease progression(Woodford and George, 2007).

Over the years a wide range of tools have been developed and used by clinicians to assess cognitive function. These include screening tools that takes less than 1 minute to complete to formal neurophsycological assessments that lasts for several

hours. However, the choice of the appropriate tool depends on both the time available and the purpose of the assessment (Woodford and George, 2007).

Some of the assessment tools that can be used includes the Abbreviated Mental Test (AMT), Six-Item Screener (SIS), Six-Item Cognitive Impairment Test (6CIT), Clock Drawing Test (CDT), Mini-Cog and the Mini Mental State Examination (MMSE). The psycho-geriatricians in the United States of America, Canada and the United Kingdom regard MMSE as the most commonly used cognitive screening tool (Woodford and George, 2007). The test generally correlates well with other cognitive screening test scores and reasonably well with a number of neuropsychological tests (Woodford and George, 2007). Many studies used the MMSE as one the tests to assess neurocognitive outcome in patients undergoing cardiac surgery (Nussmeier, Miao, Roach, Wolman, Mora-Mangano, Fox, Szekely, Tommasino, Schwann, Mangano, 2010).

2.3.1 The Mini Mental State Examination (MMSE)

Originally used to screen for Alzheimer's disease, MMSE is a brief, standardized and validated instrument to screen for dementia (Table 2.2). It is used in the clinical and research setting and measure cognitive impairment in various disease states, document intellectual changes over time and assess the effects of potential therapeutic agents on cognitive function (Nussmeier *et al*., 2010).

The MMSE is a brief 30-point questionnaire (Figure 2.2) grouped into 7 cognitive domains (Lopez, Charter, Mostafavi, Nibut and Smith, 2005). It is commonly used in medicine to screen for dementia. In a time span of about 10 minutes, it samples various brain functions, including arithmetic, memory and orientation (Folstein, Folstein and McHugh, 1973).

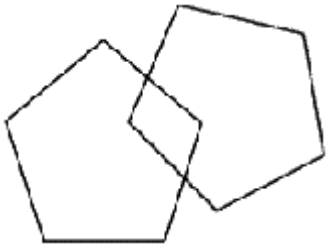
MAXIMUM SCORE	SCORE	
		ORIENTATION
5	( )	What is the: (year) (season) (date) (day) (month)
5	( )	Where are we: (state) (county) (town) (facility) (floor)
		REGISTRATION
3	( )	Name three objects and have person repeat them back. Give one point for each correct answer on the first trial. 1. _____ 2. _____ 3. _____ Then repeat them (up to 6x) until all three are learned. [Number of trials ___]
		ATTENTION AND CALCULATION
5	( )	Serial 7's. Count backwards from 100 by serial 7's. One point for each correct answer. Stop after 5 answers. [93 86 79 72 65] Alternatively spell "world" backwards. [D - L - R - O - W]
		RECALL
3	( )	Ask for the names of the three objects learned above. Give one point for each correct answer.
		LANGUAGE
9	( )	Name: a pen (1 point) and a watch (1 point) Repeat the following: "No ifs, ands, or buts" (1 point) Follow a three-stage command: "Take this paper in your [non-dominant] hand, fold it in half and put it on the floor". (3 points) [1 point for each part correctly performed] Read to self and then do: "Close your eyes" (1 point) Write a sentence [subject, verb and makes sense] (1 point) Copy design [5 sided geometric figure; 2 points must intersect] (1 point)
Score: ___/30__		Alert Overtly Anxious Concentration Difficulty Drowsy
		CLOSE YOUR EYES
		
		SENTENCE

Figure 2.2 Mini-Mental State Examination (adapted from Folstein *et al.*, 1975)

The MMSE is performed prior to surgery to obtain a baseline value of the patient's current cognitive status. The test is then repeated after the procedure and the results are compared with the pre-operative MMSE see whether cognitive decline can be confirmed. Patients exposed to transient ischemic attacks, hypertension, agina and stroke which is often the case with CABG patients usually show deficits in short-term memory first. They are more prone to have changes in speech and language function, such as naming objects and following the three-step command (Vertesi, Lever, Molloy, Sanderson, Tuttle, Pokoradi and Principi, 2001)

Table 2.2 **Deficits that can be addressed with MMSE** (adapted from Vertesi *et al*., 2001).

MMSE Components		Alzheimer's Disease	Vascular dementia	Dementia with LEWY bodies
1-5	Orientation on time	**X**		
6-10	Orientation to place	**X**		
11	Repeat three objects			
12	Spelling WORLD backward			**X**
13	Recall Three Objects	**X**	**X**	**X**
14, 15	Recognize objects		**X**	
16	Recognize idiom			
17	Close your eyes		**X**	
18	Copy a design		**X**	**X**
19	Write a sentence		**X**	
20	Three-step Command		**X**	

2.3.1.1 Interpretation of MMSE scores

Lopez *et al.,* (2005) recommended the following cut-off values to assess cognitive ability:

- ≥ 27 = normal
- 21-26 =mild
- 11-20 = moderate
- ≤ 10 = severe.

Dementia and other neurological complications can be closely correlated with low to very low MMSE scores. Scores can be influenced by educational level, language and cultural barriers, meaning that patients with a low educational level can be wrongly classified as being demented and those with higher levels may be missed. A decline in MMSE scores are also seen in patients with advance age. However, the raw score can be corrected for educational level and age (Woodford and George, 2007).

The MMSE alone cannot be used for accurate diagnosis, but data on its sensitivity and specificity shows the usefulness of the test as a screening instrument (Vertesi *et al*., 2001). However, "prevention is better than cure". Due to the importance and frequency of cognitive decline during CABG surgery, emphasis was placed on the development and application of monitors to aid clinicians to enhance detection

and improve treatment of conditions associated with brain injury. Oxygen is essential to the survival of any human being. If we can accurately assess the adequacy of oxygen delivery to key organs it can have a major impact on pre- and post-operative complications and outcomes.

This led to the development of various brain oxygen monitoring systems in the form of intracranial oxygen electrodes, jugular venous saturation monitoring and various forms of transcranial oximetry via near-infrared spectroscopy (Hoffman, 2006).

2.4 METHODS TO ASSESS CEREBRAL OXYGEN SATURATION DURING CABG SURGERY

German physiologist Karl von Vierordt was the first person to monitor human blood oxygenation in 1874. In 1930 another German Karl Metthes first used variable transmission of red and infrared light through the human ear to access oxygenation. But it was only in 1942 that American Glenn Milliken coined the term oximeter. This was followed by the development of pulse oximetry by a Japanese bioengineer Takuo Aoyagi in 1972 and was later modified by William New an anaesthesiologist for use in anaesthesia and critical care (Cohn, 2007).

Greater focus is being turned to neuro-protective strategies to improve quality of life. Various neurological complications remain prevalent, but regional ischemia leading to adverse outcomes is detectable and correctable and a variety of parameters have been used traditionally to guide the question to whether oxygen supply is

meeting oxygen demand at tissue level. Blood pressure, pulse oximetry (SpO_2) central venous oximetry (SvO_2), arterial blood gasses and serial lactate levels are a few examples of these parameters (Somanetics®, 2005 (a)).

Non-invasive infrared monitoring of cerebral oxygenation was first demonstrated by Jobsis in 1977. He showed that the absorption of infrared light by the human body tissue was negligible and can be used to evaluate cerebral oxygenation (Zaslin and Chistyakov, 2006). To date there is several near-infrared spectroscopy (NIRS) techniques that have been developed to investigate tissue hemodynamics, and the majority of these techniques are based on Beer's law which was modified to be apply on live tissue (Maikala, 2010). However, for this study emphasis will be placed on near-infrared spectroscopy (NIRS).

2.4.1 NEAR-INFRARED SPECTROSCOPY (NIRS)

Near-infrared spectroscopy is based on the Beer-Lambert Law which states that when light is transmitted through a solution containing a coloured compound a potion will be absorbed by the compound resulting in a reduced intensity of the emerging light [(Cohn, 2007); Figure 2.3].

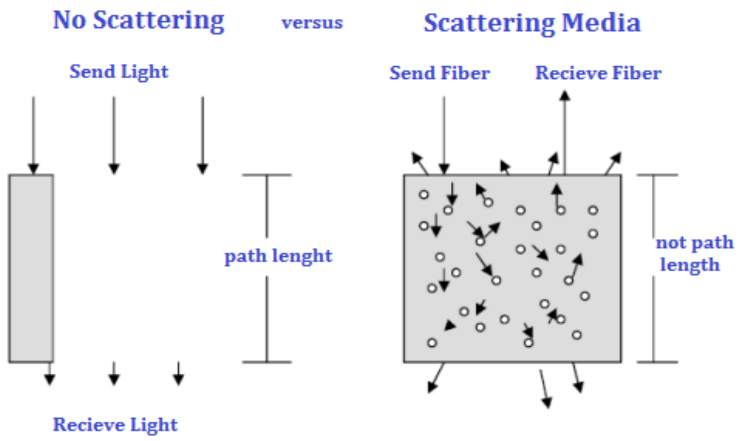


Figure 2.3 **The Beer Lambert Law** (a portion of the light is transmitted through a solution containing a coloured compound is absorbed by the compound, with the result that the intensity of the emerging light is reduced (adapted from Cohn, 2007).

In tissue, light scatters and in the microcirculation oxygenated and deoxygenated haemoglobin is absorbed differently (Figure 2.4). The amount of light that returns to the sensor will provide a ratio of oxygenated haemoglobin to total haemoglobin and it will be expressed as a percentage. When Jobsis developed non-invasive NIRS he observed that deoxygenated haemoglobin exhibits a weak absorption peak at 760 nm, and oxygenated haemoglobin does not. Based on these findings he was the first to suggest that NIRS might have value as a monitor of oxygen sufficiency (Cohn, 2007; Murkin and Arango, 2009).

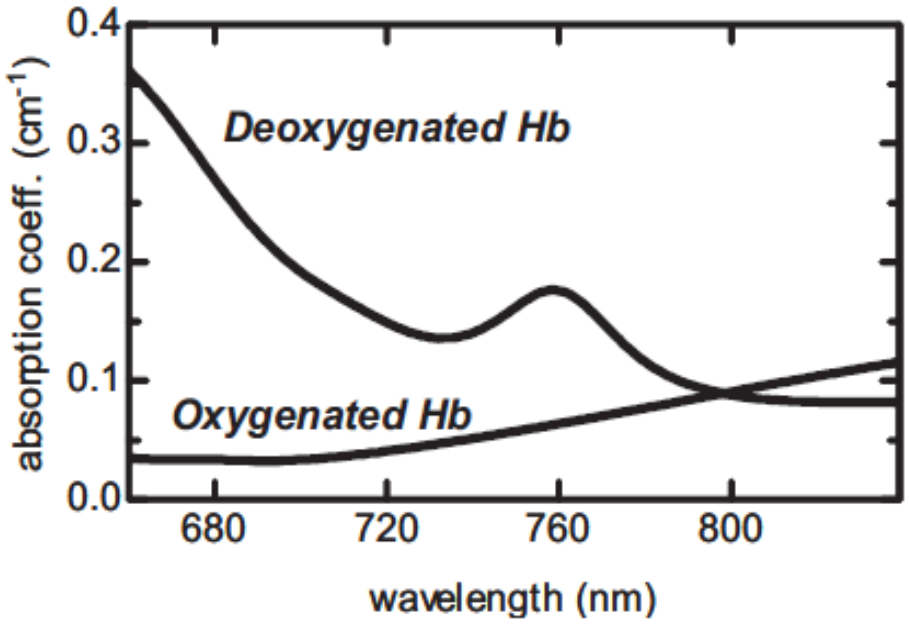


Figure 2.4 **Light absorption of haemoglobin related to its state of oxygenation**. (In the near-infrared range, absorption of light is different in deoxygenated haemoglobin when compared with oxygenated haemoglobin. These differences can be measured and used to differentiate the adequacy of haemoglobin oxygenation in blood adapted from Cohn, 2007).

Another important fact to remember is that NIRS primarily assesses the haemoglobin saturation of venous blood, and with capillary blood, composes approximately 90% of the blood volume in tissues. On the other hand pulse oximetry, uses fewer and different wavelengths of light, requires pulsatile flow, and targets only small additional arterial blood volume produced at the measurement site during systole. Due to these differences it is believed that NIRS reflect the oxygen saturation of haemoglobin in the post-extraction compartment of tissue (Cohn, 2007; Tan, 2008).

2.4.1.1 Somanetics® INVOS® Cerebral Oximeter

The Somanetics® INVOS® Cerebral Oximeter augments these existing strategies by providing a new "vital sign" called regional saturation of oxygen (rSO_2). The system alerts clinicians of cerebral ischemia and proved an early warning of regional oxygen imbalances that may be encountered during surgery or in the cardiac laboratory (Somanetics®, 2005 (a)).

The principal of auto regulation states that over a wide mean arterial pressure range, 50 mmHg to 150 mmHg, cerebral blood flow remains independent of perfusion pressure. Numerous studies have concluded that cerebral auto regulation remains intact during cardiac operations, both before and during CPB bypass. This conclusion may be correct for large groups of patients, but it does not apply to each individual patient (Edmonds *et al*., 2004). Cerebral oximetry provides a method to identify lower limits of auto regulation; this is the point where cerebral blood flow and cerebral oxygenation becomes pressure dependant. The independence of mean arterial pressure (MAP) and rSO_2 establishes the correct auto regulation during surgery for each individual patient (Figure 2.5).

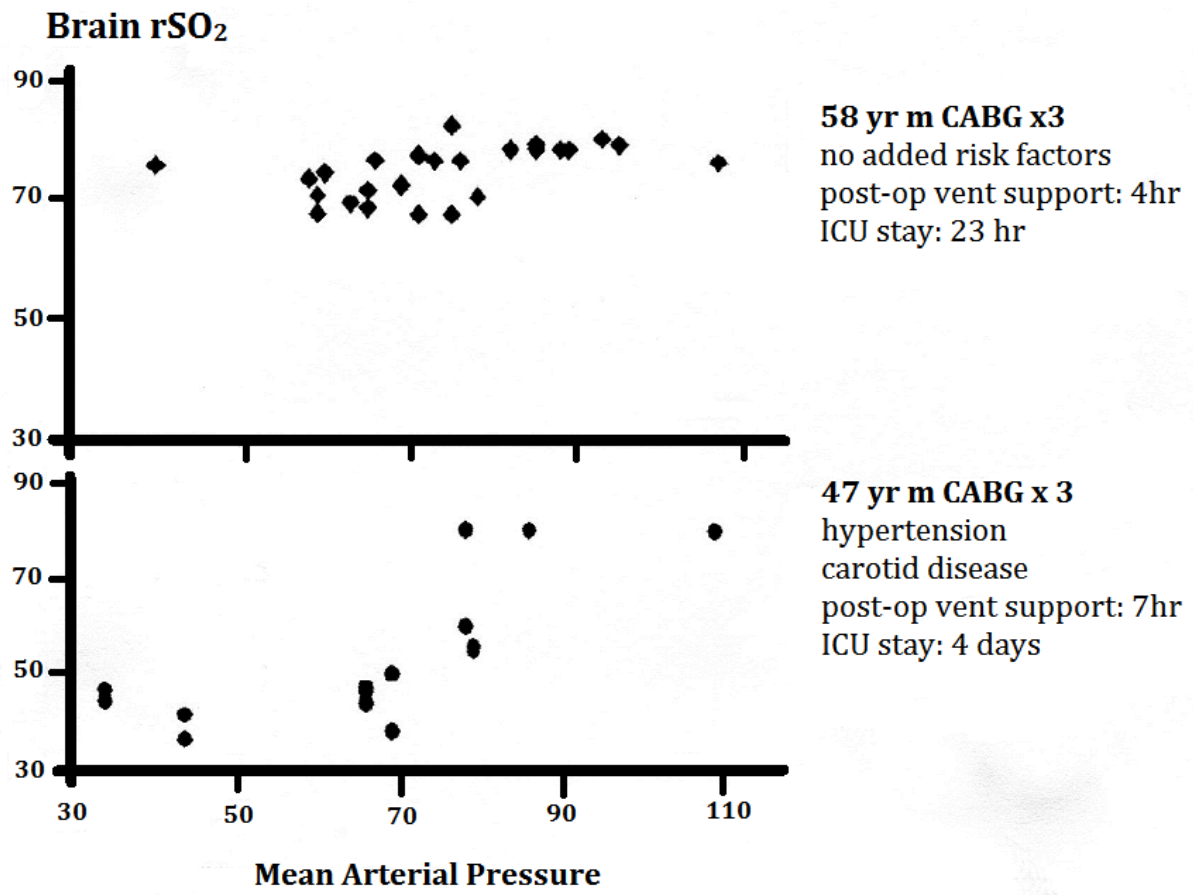


Figure 2.5 Oximetry Defines Lower Limit of Auto regulation (Adapted from Edmonds *et al.*, 2004). The relationship between rSO_2 and mean arterial pressure (MAP) during CPB is depicted. Each symbol represents a single-point paired measurement obtained at 5 minute intervals. The upper Figure illustrates intact cerebral auto regulation with clear independence of rSO_2 and MAP over a wide pressure range. The patient's outcome was uneventful. In contrast, the lower Figure depicts de-auto-regulation with classic appearance of a vascular waterfall. Each time the MAP fell below 80 mm Hg, a marked rSO_2 decrease occurred, indicating that cerebral perfusion pressure had fallen below the lower limit of auto regulation. Presumably as a result of suboptimal cerebral perfusion, the patient experienced a prolonged recovery complicated by delirium.

Two conclusions are reached:

(i) Lower limit of auto regulation varies widely among patients – from MAP <40 mmHg to >100 mmHg.

(ii) Large portion of patients do not maintain auto regulation throughout operation due to a decrease in temperature.

These findings emphasize the importance of cerebral perfusion monitoring during cardiovascular surgery (Edmonds *et al*., 2004).

The driving force for haemoglobin through the gas exchanging microvasculature is not arterial pressure but pressure differential between arterial and venous. Factors that increase cerebral venous pressure will compromise oxygen delivery, even if MAP is in normal range. It is useful to monitor the relationship between rSO_2 and cerebral perfusion pressure (Edmonds *et al*., 2004).

Cerebral Perfusion Pressure = **Mean Arterial Pressure** - **Central Venous Pressure**

Cerebral oximetry is also a useful guide for the management of regional low flow perfusion (RLFP). NIRS has been used to guide bypass flow during RLFP with the intention to match cerebral blood volume during RLFP to baseline blood volume on full bypass flow to the whole body. Monitoring rSO_2 will individualize titration of pump flow to prevent both cerebral hypoperfusion and hyperperfusion. In agreement with these observations, Hofer, Haizinger and Geiselseder (2002), found a linear

relationship between rSO_2 and antegrade supplemental cerebral perfusion pump flow (Edmonds *et al*., 2004).

Deeb and co-workers (1995) demonstrated that NIRS-guided retrograde cerebral perfusion extended the "safe time" for hypothermic circulatory arrest during aortic arch reconstruction. Superior vena cava cannula malpositioning is also detectable by cerebral oximetry during retrograde cerebral perfusion (Edmonds *et al*., 2004).

As previously stated, renal dysfunction is a complication of cardiac surgery. A reduction in MAP and blood flow can result in renal hypoperfusion leading to ischemic injury. Andersson and co-workers (1994) showed that auto regulation of renal blood flow (RBF) is not operational during hypothermic CPB due to the fact that RBF was largely proportional to systemic blood pressure. According to the statistical analysis the pump flow rate was the primary determinant of RBF and that systemic blood pressure was of secondary importance (Andersson, Bratteby, Ekroth, Hallhagen, Joachimsson, Van Der Linden and Wesslen, 1994).

(a) Technical Overview Somanetics® INVOS® Cerebral Oximeter

The INVOS® System consists of disposable, single-patient use SomaSensors, an INVOS monitor display and associated accessories. The system's light-emitting diodes generate near-infrared (NIR) wavelengths (730 – 810nm) that when applied to the frontal lobe of the brain for example, pass through the scalp and bone tissue

beneath the sensor. Once *in vivo* they are either absorbed or scattered back up to the sensors' shallow and deep detectors. Red-coloured haemoglobin molecules within red blood cells have the highest light absorption of the wavelengths used, and the exact shade of red of each haemoglobin molecule indicates the amount of oxygen it is carrying. The absorption data returned to the detectors reflects deoxy-haemoglobin and total haemoglobin from which regional saturation of oxygen (rSO_2) is calculated. Application of the NIR light-emitting sensors to the brain thus allows for direct measurement of changes in oxygen saturation in the blood capillary bed below the sensor through non-invasive measurements. Since the vascular bed is predominantly venous, the INVOS® System reflects the balance of oxygen delivery and consumption [the surplus of oxygen remaining after the tissues have taken what they require; (Somanetics®, 2005 (a)].

(b) Interpretation of Results

A decline in rSO_2 below 50, or a decline of more than 20 percent from baseline is cause for concern and warrants the initiation of intervention. Absolute values below 40 and a drop of more than 25 percent from baseline, is associated with neurological dysfunction and other adverse outcomes (Edmonds *et al*., 2004).

(c) sRO2 Desaturation Risk Score

rSO_2 is at the core of "risk score" calculation to determine cognitive decline (Slater, Stack, Vinod, Guarino and Bustami, 2007). The rSO_2 desaturation risk score is calculated by multiplying the number of points below 50% rSO_2 by the time in seconds. Patients with any combination where the rSO_2 value and time resulted in >6000% seconds are found to be at increased risk for post-operative cognitive decline.

For example,

- an rSO_2 of 48 (2 points below 50) could remain there for 3000 seconds before reaching the 6000% seconds threshold (2 x 3000 seconds, or 50 minutes, = 6000).

Applying this calculation helps clinicians to track the risk for post-operative cognitive decline when either the rSO_2 value or time is increased (Slater, Guarino, Stack, Vinod, Bustami, Brown, Rodriguez, Magovern, Zaubler, Freundlich Parr, 2009).

For example,

- 45 rSO_2 (5 x 1200 seconds, or 20 minutes, = 6000% seconds)
- 40 rSO_2 (10 x 600 seconds, or 10 minutes, = 6000% seconds)
- 35 rSO_2 (15 x 400 seconds, or 6.6 minutes, = 6000% seconds)

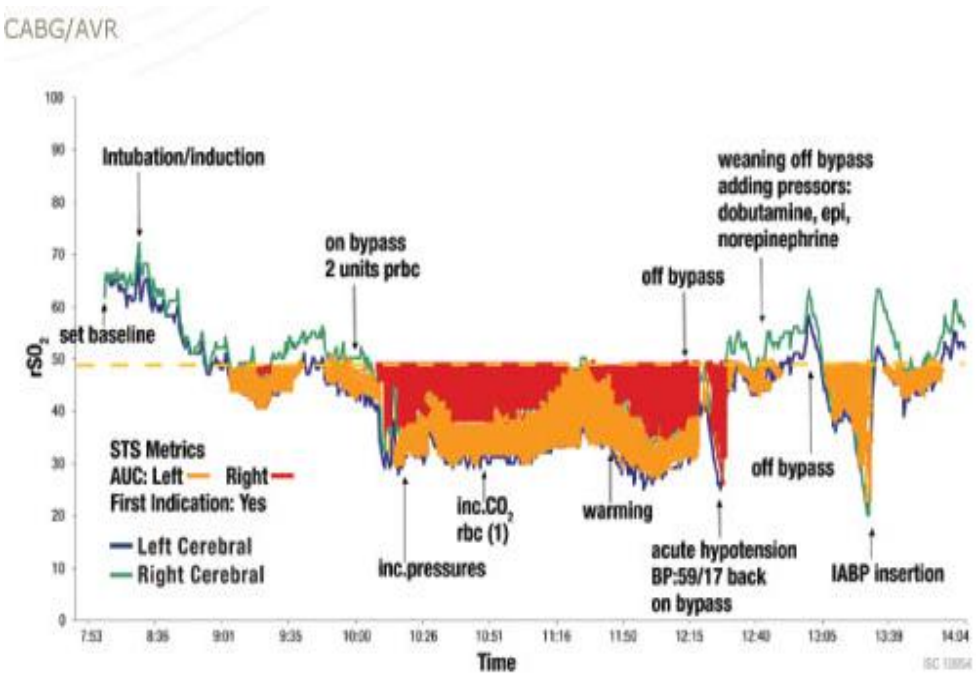


Figure 2.6 Common Times for rSO_2 reactions (adapted from Somanetics®, 2005 (b)).

2.4.1.2 Traditional Parameters versus rSO_2

Traditionally a variety of parameters are used to establish whether or not oxygen supply is meeting oxygen demand (Murkin, 2004):

- Heart rate (HR)
- Blood pressure (BP)
- Pulse oximetry (SpO_2)
- Central venous oximetry (SvO_2)
- Arterial blood gasses (ABG) and
- Serial Lactate Levels

However, the most important ones are SpO_2, SvO_2 and lactate and these parameters will be compared to rSO_2 in the section below.

(a) rSO_2 versus Pulse Oximetry (SpO_2)

A comparison between cerebral oximetry (NIRS) and pulse oximetry is displayed in Table 2.3. The major differences between the two are summarized as:

- rSO_2 reflects predominately venous blood and it evaluates the balance between oxygen delivery and oxygen consumption, where as pulse oximetry only measures arterial blood oxygenation.
- rSO_2 measure oxygenation specific to the brain (end-organ perfusion). SpO_2 is a global measure of oxygenation in the periphery.
- rSO_2 eliminates the need for pulsatility and flow, as are required for SpO_2 (Somanetics®, 2005 (a)).

Table 2.3 Comparison between Pulse Oximetry and Cerebral Oximetry (adapted from Tan, 2008)

	PULSE OXIMETRY	CEREBRAL OXIMETRY
Light transmission	Transmission (usually)	Reflectance
Wavelength	660/940 nm	730/810 nm
Arterial Component	Mainly arterial	25% arterial: 75% venous
Oxygen saturation	Hb (arterial)	Cerebral venous saturation
LED	1 Emitter / 1 sensor	1 Emitter / 2 sensors
Validation	In volunteers	In volunteers
Limitation	Diathermy	Diathermy
Pulsatility	Pulsatile	Non-pulsatile

(b) rSO_2 versus mixed Venous Oxygen Saturation (SvO_2)

- rSO_2 is non-invasive in nature which avoid added stress on critical ill patients.
- rSO_2 (**regional balance** between oxygen supply and demand) correlates well with invasive measured SvO_2 (**global indicator** of balance between oxygen supply and demand).
- Alerts against regional hypoperfusion which can occur even when SvO_2 values are within normal range due to alterations in regional vascular resistance.
- Indwelling catheters are associated with infection, thrombosis, and bleeding upon removal, therefore rSO_2 eliminates those risk factors (Somanetics®, 2005 (a)).

(c) rSO_2 versus Lactates

- Regional organ-specific information versus lactate's global reflection of cellular metabolism without oxygen occurring somewhere in the body.
- rSO_2 values will change immediately if tissue oxygen supply is not meeting tissue oxygen demand. Lactate is a later indicator of anaerobic metabolism and accumulates by-products (lactate), which means ischemic injury has already occurred (Somanetics®, 2005 (a)).

2.5 HEMODYNAMIC MONITORING DURING CABG SURGERY

Ischemic episodes may be associated with frank hemodynamic disturbances like the presence of tachycardia and systolic hypotension but usually these episodes are associated with little hemodynamic change. The absence of hemodynamic change during ischemic episodes of CABG suggests that regional rather than global factors are responsible for the genesis of ischemia (Tupper-Carey, Newman, Price, Walesby, Ridout, Feneck, 2000). NIRS might be a much more sensitive tool to detect episodes of ischemia in these CABG patients.

2.5.1 HEART RATE

An electrocardiogram (ECG) gives information regarding ischemia, arrhythmias, electrolyte imbalances and drug toxicity (Webster, 1999).

Decrease cardiac performance result in an increase in brain oxygen extraction which will lower oximetry values (Daubeney, Pilkington, Janke, Charlton, Smith, Webber, 1996).

2.5.2 MEAN ARTERIAL PRESSURE (MAP)

When peripheral vascular resistance (PVR) is constant, arterial blood pressure is proportional to cardiac output. The arterial pressure is usually affected by any changes in volume status of the patient, vasomotor tone and cardiac output. Blood flow to the tissues is dependent on the mean arterial pressure (Webster, 1999). Edmonds and co-workers (2004) stated that the lower limit of auto-regulation varies widely among patients, from MAP < 40 mmHg to > 100 mmHg.

2.5.3 CENTRAL VENOUS PRESSURE (CVP)

Central venous pressure (CVP) has been used to assess the volume status of the patient. An increase in CVP may be the result of the manipulation of the heart or even of the Superior Vena Cava (SVC) cannula (Urdaneta and Gravenstein, 1999).

Normal values for CVP

- Pre-CPB - < 10 mmHg
- During CPB - 0 mmHg (increased with obstruction to venous flow)
- Coming off CPB - <10 mmHg (Evans, Dunningham and Wallwork, 2009; Magder, 2007).

CVP values themselves do not provide clinical data that is useful; it must be interpreted keeping the patient's condition and if possible the cardiac output in mind (Madger, 2006).

2.5.4 TEMPERATURE

Temperature has an important effect on tissue oxygenation; even mild hypothermia will diminish the severity of ischemia. Hypothermia causes the oxygen dissociation curve to shift to the left, resulting in a possible decrease in tissue oxygenation (Nollert, Möhnle, Tassani-Prell and Reichart, 1995). Mora, Henson and Weintraub, 1996 have shown that cardiac patients undergoing normothermic CPB is at increased risk of cerebral desaturation.

In a randomized trial by Regragui and co-workers (1995), three groups of patients were evaluated at different temperatures, 28°C, 32°C and 37°C. The minimum post-operative dysfunctions were recorded in the 28°C group, but they suggested that perfusion temperature has no effect on renal function (Regragui, Izzat, Birdi, Lapsley, Bryan, and Angelini, 1995).

Re-warming, on the other hand, can be a cause of neurological dysfunction after cardiopulmonary bypass, and full re-warming to 37°C should be avoided. Hyperthermia increases the oxygen demand of the body (Cook, Orszulak, Daly, and Buda, 1996).

2.5.5 URINE OUTPUT

In the event of cardiopulmonary bypass, low perfusion flow, hypotension, vasoconstriction and microembolism may occur resulting in reduced renal blood flow. The best way to measure adequate kidney perfusion is to monitor urine output and the best way to keep optimal kidney perfusion intra-operatively is to limit CPB time and to keep MAP > 60 mmHg (Pramodh, Vani, and Muralidhar, 2003). Urine output should be a minimum of 0.5 to 1.0 ml/kg/hr, and any decrease below these values should be investigated (Salenger, Gammie and Vander Salm, 2003).

2.5.6 THE EFFECT OF HEART MANIPULATION / STABILIZATION ON HEMODYNAMIC DATA

During OPCAB, hemodynamic changes often occurs during surgical displacement of the heart which mainly involves changes in arterial and venous pressures, intraventricular volumes, cardiac output and mixed venous oxygen saturation. Manipulation resulting in hypotension is associated with an increase in filling pressure (Couture, Denault, Limoqes, Sheridan, Babin, and Cartier, 2002).

Stabilization technique can be the cause of hemodynamic changes. Dislocation of the heart causes a 26% decrease in MAP and a 37% decrease in cardiac output (Couture *et al.*, 2002).

2.6 POST-OPREATIVE OUTCOMES / COMPLICATIONS

2.6.1 CLINICAL OUTCOMES

One of the most controversial debated issues in cardiothoracic surgery is whether CABG without the use of CPB and cardioplegia is superior to CABG with CPB and a chemically arrested heart (Sellke, DiMaio, Caplan, Ferguson, Gardner, Hiratzka , Isselbacher, Lytle, Mack, Murkin and Robbins, 2005). However, controversy exits regarding the selection of patients, who are likely to benefit from the procedure and on the claims of improved outcome. Initially OPCAB revealed excellent results in regard to the amount of resources needed, decreased blood loss, decreased morbidity and a shortened hospital stay, however the majority of these studies were non-randomized clinical reports rather than controlled clinical studies (Sellke *et al*., 2005). Whether OPCAB is associated with a distinct advantage in comparisons to CABG with CPB (the golden standard) remains debatable.

Sellke *et al*. (2005) reviewed various research studies conducted on this topic and the pro's and con's of the two procedures are summarized in Table 2.4. Ultimately they concluded that whether a patient benefit from the golden standard on-pump CABG or the OPCAB technique depend more on familiarity, comfort, and the skill of the surgeon rather than on an intrinsic benefit. Both of these procedures usually result in excellent outcomes but neither should be judge to be inferior to the other (Sellke *et al*., 2005).

Table 2.4 Findings favouring on-pump CABG and OPCAB (adapted from Sellke *et al*., 2005)

Findings favouring OPCAB
(a) Probably less bleeding
(b) Probably less renal dysfunction
(c) Probably less short-term neurocognitive dysfunction, especially if the aorta is calcified
(d) Possibly shorter overall length of hospital stay
Findings favouring on-pump CABG
(a) Less Technically demanding
(b) Shorter "learning curve"
(c) Possibly better long-term graft patency
(d) Easier to graft posterior (circumflex) bypass targets
(e) Probably more bypass grafts constructed

2.6.2 POST-OPERATIVE COMPLICATION ANALYSIS

The Society of Thoracic Surgeons Adult Cardiac Database were used as a measure to assess surgical outcomes and is represented in Figure 2.7.

Figure 2.7 **STS Adult Cardiac Surgery 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 13/05/2008]).

2.7 RELAVANCE OF THE STUDY

Intra-operative cerebral oxygen desaturation is associated with early postoperative neuropsychological dysfunction in patients undergoing cardiac surgery with CPB. Microembolism and hypoperfusion is suggested to be the major cause of dysfunction. Another potential complication after CPB is renal dysfunction. Again hypoperfusion, systemic inflammatory response, and non-pulsatile flow are among the causes of dysfunction.

Due to the fact that cognitive deficits is reported for both on-pump and off-pump CABG patients efforts are made to improve neuromonitoring during cardiac surgery. Literature provide evidence that intra-operative neuromonitoring helps to prevent the occurrence of postoperative cognitive dysfunction, decreases hospital stay and minimize the adverse effects on vital organs (de Tournay-Jetté, Dupuis, Bherer, Deschamps, Cartier and Denault, 2011). Oximetry monitoring, via Near-Infrared Spectroscopy (NIRS), measure regional oxygen saturation (rSO_2), and any changes in rSO_2 reflects changes in the balance between oxygen delivery and consumption. The use of NIRS have shown a significant relationship between low rSO_2 values and neurologic complication, cognitive dysfunction and a prolonged hospital stay in CABG patients (de Tournay-Jetté *et al*., 2011).

Therefore, in this study the value of intra-operative NIRS monitoring will be assessed by evaluating the oximetry values and hemodynamic changes in patients presenting with acute coronary syndrome as a predictor of clinical

outcome/complication in patients that either received coronary bypass graft surgery (CABG) on-pump or off-pump.

2.7.1 Aim

The aim of this study is to predict the incidences of complications and clinical outcomes in patients with acute coronary syndrome related to reduced cerebral perfusion.

- Evaluation of the correlation between cerebral oximetry values and hemodynamic changes during CABG (on-pump and off-pump), and its impact on post-operative clinical outcomes and complications.

2.7.1.1 Objectives

i. Cognitive assessment, in both on-pump and off-pump CABG patients, by performing Mini-Mental State Examination (MMSE) both pre-operatively and post-operatively.

ii. Pre-operative measurement of cerebral oxygen saturation (rSO_2) to identify baseline.

iii. Intra-operative measurement of cerebral rSO_2 to assess blood flow.

iv. Comparison of rSO_2 values between on-pump and off-pump CABG surgery.

v. The relationship between hemodynamic change (blood pressure, heart rate, central venous pressure, temperature, and blood gasses) and NIRS in on-pump and off-pump CABG patients.

vi. Observation of post−operative clinical outcomes and complications of CABG patients.

vii. Post−operative hemodynamic monitoring (heart rate, blood pressure, central venous pressure, temperature, urine output, and blood gasses).

viii. Identifying intra-operative cerebral risk groups (in both on-pump and off-pump groups):

- **Group 1**

Satisfactory Cerebral Blood Flow - rSO_2 > 50 or < 20% drop from baseline.

- **Group 2**

Average/Compromised Cerebral Blood Flow = rSO_2 < 50 or > 20% drop from baseline.

Chapter 3
METHODOLOGY

3.1 STUDY LOCATION

The research study was conducted at Universitas Hospital involving the departments of Cardiology, Cardiothoracic Surgery, Anaesthesiology and Chemical Pathology (NHLS). Universitas is a State/Private hospital located in Bloemfontein, capital city of the Free State, South Africa.

3.2 STUDY DESIGN

The study design was an observational cross-sectional analytical study that involved 60 patients (volunteers) with Acute Coronary Syndrome (ACS). In light of the study design it is important to remember that nothing more than associations can be proofed from the research study. The 60 patients were recruited from Universitas hospital, Bloemfontein and were assigned to take part in the study only when informed consent was granted.

3.3 STUDY LAYOUT

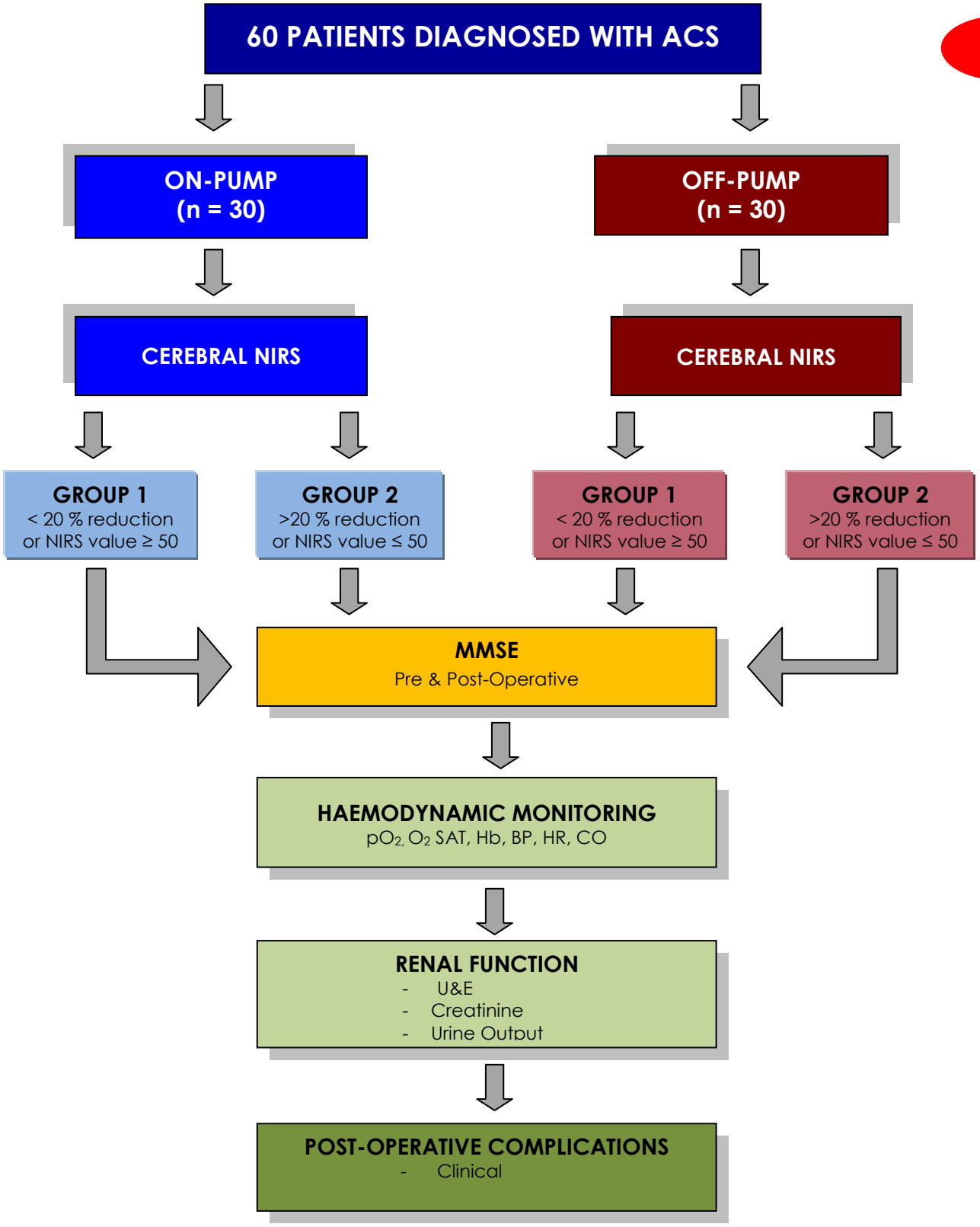


Figure 3.1 **Schematic presentation of Study Layout** [Acute Coronary Syndrome (ACS); Near-Infrared Spectroscopy (NIRS); Less-than (<); Greater-than (>); Greater-than or Equal to (≥); Less-than or Equal to (≤); Mini-Mental State Examination (MMSE); Partial Pressure of Oxygen in the Blood (PO_2); Arterial Blood Oxygen Saturation (O_2 SAT); Haemoglobin (Hb); Arterial Blood Pressure (BP); Heart Rate (HR); Cardiac Output (CO); Urea and Electrolytes (U&E)].

The study involved 60 patients diagnosed with ACS. The group was divided into two subgroups which included 30 on-pump Coronary Artery Bypass Graft (CABG) patients and 30 off-pump CABG patients (Figure 3.1).

Pre-operative clinical examination for all volunteers included a Mini-Mental State Examination, which was done a day before the operation, to evaluate neurological dysfunction. A U&E and creatinine blood test was also done pre-operatively and the results were used as a baseline value for post-operative assessment.

On the day of surgery all intra-operative hemodynamic data of the patient were recorded via the Datex-Ohmeda S/5™ Collect Program. This data included arterial blood pressure, central venous pressure and arterial cannula pressure (systolic, diastolic and mean), heart rate and nasopharyngeal and esopharyngeal temperature. The total volume of urine excreted was also documented during the surgery, to exactly calculate the amount of urine output (ml/kg/h).

Arterial blood gasses were done routinely at 15 minute intervals. The haemoglobin (Hb), pO_2, and O_2 SAT values were used to assess the oxygen transfer.

Cerebral oximetry values were captured by the INVOS 5100C® Oximeter to assess regional oxygen saturation during cardiac surgery. These values were recorded every 30 seconds, and were saved then exported after the case to an Excel spreadsheet.

Post-operatively, the Mini-Mental State Examination was repeated when the patients arrived at the ward after being discharged from the ICU. This examination was compared with the pre-operative examination to identify possible neurological dysfunctions that could be attributed to the CABG surgery.

Hemodynamic data (arterial blood pressure, central venous pressure, core temperature, and urine output) were charted on the ICU chart, and data points at 6 hour intervals (for up to 84 hours post-operatively) were statistically analyzed. The U&E and creatinine results were recorded up to 72 h post - operatively.

Any complications and all outcomes were documented on the Universitas Cardiothoracic Database. Complications were recorded according to the STS database format (Appendix D). This information was also used to note outcomes in the different groups.

3.4 STUDY POPULATION

3.4.1 Number of Subjects

The study involved 60 patients diagnosed with ACS referred by the department of Cardiology, Universitas Hospital. After a thorough physical examination the ACS patients (n = 60 patients) were divided into two groups according to the specific intervention method, CABG on-pump (n = 30 patients) and off-pump (n = 30

patients). It remained the surgeon's decision whether he/she wants to operate the patient on-pump or off-pump and in no way did the study interfere with this decision.

A patient was considered for the clinical study if informed consent (Appendix A) was granted by the patient and if the patient met the inclusion criteria set for the study. Every patient participating in the study received an information leaflet to inform him/her about the project details (Appendix B).

3.4.2 Subject Identification

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

3.4.3 In- and Exclusion Criteria

3.4.3.1 Inclusion Criteria

- Patients with acute coronary syndrome
- Patients must be available for pre- and post surgery interviews.
- The patient must be able to give informed consent.

3.4.3.2 Exclusion Criteria

- Patients with existing organ failures other than congestive heart failure

3.5 ASSESSMENT FOR NEUROLOGICAL DYSFUNCTION

3.5.1 Mini-Mental State Examination

Pre-operative neurological testing (the day before surgery, before the patient was administered his/her premedication), the Mini-Mental State Examination (MMSE) or Folstein test was done, and the same test was done post-operatively after extubation (when transferred to the ward) to determine whether or not neurological dysfunction occurred in the patients undergoing cardiac surgery (Figure 3.4). Note, if the patient already had his/her premedication the MMSE test was not done but the patient was not excluded from the study.

- Examinations have been done, pre- (day before operation) and post-operatively (when transferred to the ward), by the same person and were explained to each patient in the same way.
- Each patient received a score out of thirty.
- Post-operatively, the same examination was done with each patient when transferred to the ward.
- Again a score was given out of thirty.

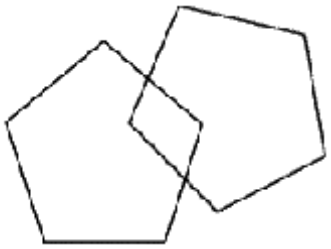
3.5.1.1 Interpretation of Data

- Normal = ≥ 27 out of 30.
- Mild impairment = a score between 21 and 26 out of 30.
- Moderate impairment - a score between 11 and 20.
- Severe impairment = a score ≤ 10 out of 30 (Folstein *et al*., 2001; Lopez *et al*., 2005).

MAXIMUM SCORE	SCORE	
		ORIENTATION
5	( )	What is the: (year) (season) (date) (day) (month)
5	( )	Where are we: (state) (county) (town) (facility) (floor)
		REGISTRATION
3	( )	Name three objects and have person repeat them back. Give one point for each correct answer on the first trial. 1. _____ 2. _____ 3. _____ Then repeat them (up to 6x) until all three are learned. [Number of trials ___]
		ATTENTION AND CALCULATION
5	( )	Serial 7's. Count backwards from 100 by serial 7's. One point for each correct answer. Stop after 5 answers. [93 86 79 72 65] Alternatively spell "world" backwards. [D - L - R - O - W]
		RECALL
3	( )	Ask for the names of the three objects learned above. Give one point for each correct answer.
		LANGUAGE
9	( )	Name: a pen (1 point) and a watch (1 point) Repeat the following: "No ifs, ands, or buts" (1 point) Follow a three-stage command: "Take this paper in your [non-dominant] hand, fold it in half and put it on the floor". (3 points) [1 point for each part correctly performed] Read to self and then do: "Close your eyes" (1 point) Write a sentence [subject, verb and makes sense] (1 point) Copy design [5 sided geometric figure; 2 points must intersect] (1 point)

Score: ___/30__ Alert Overtly Anxious Concentration Difficulty Drowsy

CLOSE YOUR EYES



SENTENCE

Figure 3.2 **Mini-Mental State Examination** (adapted from Folstein *et al.*, 1975).

3.6 TREATMENT PROCEDURES FOR ACS

After thorough collaboration between the Cardiologists and Cardiothoracic Surgeons a decision was made regarding optimal treatment as standard practice for patients with ACS. The patient could have received one of the following treatments:

- Medical treatment
- PCI
- CABG

The study did not influence the surgeon's decision whether to operate the patient on-pump or off-pump. Taking all factors into consideration it was the surgeon's decision whether on-pump or off-pump surgery will yield the best possible outcome for the patient

3.6.1 Surgical Techniques

3.6.1.1 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).

(B) Prior to CPB the circuit was de-aired using the following prime:

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

(C) Transducer prepared for measurement of arterial cannula pressure:

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

(D) Cardioplegia

Two cardioplegia solutions are used in this centre, 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).
- 50 ml, 4% Albusol (Human Plasma Albumin, Ref: T/30.3/738, National Bioproducts Institute, Pinetown, RSA).
- 30 ml, 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).
- 200 mg Lignocaine (Lignocaine HCl-Fresenius, Ref: M/4/254, Fresenius Kabi for Bodene Limited trading as Intramed, Port Elizabeth, RSA).
- 4 g 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).
- 30 mmol/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) Pre operative management of the patient prior to surgery:

- Somasensors were placed on forehead of the patient.
- Three point ECG was connected to the patient's back.
- Peripheral lines and arterial blood pressure lines were inserted.

- Anaesthesia is commenced.
- Central venous line was inserted.
- Median sternotomy is performed by the surgeon and saphenous vein grafts were harvested from patient's legs by the assistant. Internal Mammary Artery may also be 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 were done.
- The ascending aorta was cannulated and as soon as an ACT of 480 seconds is achieved, bypass was commenced.
- Access to the right atrium and venous blood is obtained through cannulation with a two-stage venous cannula via the right atrial appendage.
- Systemic hypothermia of between 28 to 30 ^{0}C was achieved and the alpha-stat principle is 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 were repeated every 20 min.
- Topical ice slush was applied onto heart.
- Distal venous anastomoses were performed on the coronary artery.
- When last distal anastomosis was preformed, rewarming was 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 is reached.
- Oxygenated blood was flowed into the bypassed vessels using a manifold.
- Proximal anasotomosis 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.

3.6.1.2 Off-pump CABG Surgery

- Somasensors were placed on the forehead of the patient.
- Three point ECG was connected to the patient's back.
- Peripheral lines and arterial blood pressure lines were inserted.
- Anaesthesia was commenced.
- The central venous line was inserted.
- Patient was draped and autologous cell salvage suction/aspiration line was given of.

- Surgeon performed median sternotomy and the assistant harvested saphenous veins from the patient's legs. Internal Mammary Artery may also be harvested by surgeon.
- 1 mg/kg Heparin were 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 can be 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 obtained, mediastinal and pericardial underwater drains are inserted.
- Sternum were wired and the sternotomy was closed.

3.7 CEREBRAL rSO_2 MEASUREMENTS

Non-invasive measurement was performed using two sensors, called Somasensors. Harmless near-infrared light passed through the patient's forehead and into the brain. With the two detectors at different distances from the light source, two depths of penetration were measured. The difference in these measurements eliminates signals common to both, minimizing changes occurring in the extra-cranial tissues.

3.7.1 Procedure

- The patient's head (for cerebral blood flow) was cleaned with Hibitane to avoid any interference with the sensors and for accurate readings. The skin was dried before the sensors were applied.
- The sensors were applied in the middle of the forehead (Figure 3.2), the cables were connected to the sensors and to INVOS 5100C® Oximeter (Figure 3.3) (Manufacturer: Somanetics, Serial no: 07-10224, Model: 5100C, License no: 432/12008).
- After connecting the cables the baseline was set on the INVOS Cerebral Oximeter by pressing the "SET BASELINE" button.
- Following the baseline setting, every 30 seconds readings were monitored and recorded on the INVOS Cerebral Oximeter throughout the procedures.
- Post-operatively, the data were downloaded via a memory stick and were then exported to an Excel spreadsheet on a computer.

3.7.2 *Interpretation of Cerebral Data*

- With every event values were recorded.
- Patients were divided into 2 groups:
  - Group 1: Satisfactory cerebral blood flow (NIRS values > 50 or < 20% drop from baseline).
  - Group 2: Compromised cerebral blood flow (NIRS values ≤ 50 or ≥ 20% drop from baseline).

Figure 3.3 **SomaSensors placed on patient's forehead** (Adapted from Piacentini, 2000).

Figure 3.4 **INVOS 5100C® Machine and SomaSensors** (Adapted from: Somanetics®, 2005(c). Available from: http://www.somanetics.com/invos-system. [Accessed 13/05/2008].)

3.8 HEMODYNAMIC MONITORING

3.8.1 Datex-Ohmeda S/5™

The hemodynamic data was captured electronically via the Datex-Ohmeda S/5 ™ monitors in theatre (Datex-Ohmeda S/5 ™ Cardiovascular Anaesthetic monitor Serial no: 90027365 and 4416799) onto a computer throughout surgery. The data was

captured every 10 seconds on the Datex-Ohmeda S/5™ Collect Program, which was then converted by the Datex-Ohmeda software into an Excel spreadsheet (Datex-Ohmeda S/5™ Collect, GE Healthcare software, Ref: L-COLLECT4-01-EN, SN: 6521804, GE Healthcare, Finland). This information is then processed, and every 5 minutes values were used to determine the average values in each group.

- Heart rate - recorded via 3 lead ECG.
- Arterial Blood Pressure – placement in Radial artery.
- Central Venous Pressure (CVP) – placement in Internal Jugular Vein.
- Temperature – temperature probe was placed Nasopharyngeal and Esopharyngeal.
- Urine output – urine catheter through the urethra up to the bladder.
- Event marking was done intra-operatively. This was done electronically on the INVOS and manually on paper. The INVOS machine has a function that by pressing the "EVENT" button on the screen, a list of all possible events appears, and the suitable events can be marked by pressing the "SELECT" button on the screen.

Table 3.1 **Listed events for on-pump CABG Surgery** (Adapted from: Somanetics®, 2005(c). Available from: http://www.somanetics.com/invos-system. [Accessed 13/05/2008]).

ON-PUMP CABG EVENTS		
▸ Baseline	▸ Intubation	▸ Incision
▸ Tachycardia	▸ Bradycardia	▸ Blood drained
▸ Cannulate	▸ On CPB	▸ Increase MAP
▸ Decreased CO_2	▸ Pump flow decrease	▸ Pump flow increase
▸ Stop flow	▸ Hemoconcentrate	▸ Cardioplegia
▸ Cross clamp on	▸ Cross clamp off	▸ Side clamp on
▸ Side clamp off	▸ Blood transfusion	▸ CPB terminated
▸ Reposition heart	▸ Manipulate heart	▸ Reposition clamp
▸ Paced	▸ Defibrillated	▸ Bleeding
▸ IABP on	▸ Chest closed	▸ Atrial Fibrillation
▸ Reposition head		▸ Heparin administered

Table 3.2 **Listed events for off-pump CABG Surgery** (Adapted from: Somanetics®, 2005(c). Available from: http://www.somanetics.com/invos-system. [Accessed 13/05/2008]).

OFF PUMP CABG EVENTS		
▸ Baseline	▸ Intubation	▸ Incision
▸ Tachycardia	▸ Bradycardia	▸ Blood drained
▸ Decreased CO_2	▸ Blood transfusion	▸ Increase MAP
▸ Side clamp off	▸ Manipulate heart	▸ Side clamp on
▸ Reposition heart	▸ Stabilizer off	▸ Reposition clamp
▸ Stabilizer on	▸ Defibrillated	▸ Bleeding
▸ Paced	▸ Chest closed	▸ Atrial Fibrillation
▸ IABP on	▸ Heparin administered	

3.9 LABORATORY ANALYSIS

3.9.1 U&E and Creatinine

The U&E and Creatinine were done routinely as requested by the medical practitioner overseeing the patient. All these tests were performed in accordance with the standard operating procedures as accredited by the National Health Laboratory Service (NHLS).

3.10 POST-OPERATIVE COMPLICATIONS

The Society of Thoracic Surgeons Adult Cardiac Database (Figure 3.4) was used as a measure to assess surgical outcome (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 13/05/2008]).

Figure 3.5 **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 13/05/2008]).

3.11 STATISTICAL ANALYSIS

Data was captured using a Microsoft Excel spreadsheet. The statistical analysis was done by a qualified statistician using SAS Version 9.1.3. The data was summarized using descriptive statistics, namely frequencies and percentages for categorical data. Means and standard deviations or medians and percentiles were used to summarize numerical data. Analytical statistics compared the frequencies and percentages in different groups by using the Chi-square statistic to calculate p-values. Means or medians of different groups were compared using the T-test or Kruskal-Wallis test to calculate p-values. Significant differences were noted at $p < 0.05$.

Firstly, the on-pump and off-pump groups were compared to assess whether the two groups of patients were comparable regarding demographic, risk profiles and intra-operative data. Thereafter the following analyses were conducted:

3.11.1 Analysis 1: Cerebral NIRS performed on on-pump and off-pump CABG groups

In order to assess the impact of surgical techniques on cerebral blood flow, using NIRS as a monitoring instrument. Outcomes were compared between patients undergoing on-pump versus off-pump CABG procedures.

3.11.2 Analysis 2: Comparison of cerebral NIRS values between Group 1 (rSO_2= ≥ 50, < 20% drop from baseline value) and Group 2 (rSO_2 < 50, > 20% drop from baseline value) irrespective of Surgical Technique

Published data on neurological outcomes were used to divide all patients into two groups, irrespective of bypass technique, in order to determine the predictive value of impaired cerebral flow on patient outcomes.

Group 1 had NIRS values of more than 50 or a less than 20 % drop from the baseline value. Group 2 had NIRS values of less than 50 or a drop of more than 20% from the baseline value. The lowest value recorded during the procedure was captured and used irrespective of the amount of time that value was sustained. Patient outcomes were then analyzed in accordance.

The Mini-mental State Examination, renal function (U&E and creatinine, urine output, and urine electrolytes), and clinical outcomes were analyzed to evaluate the relationship between NIRS values or trends and outcomes, irrespective of surgical technique used.

In order to assess the intra- group predictive value of cerebral NIRS measurements, each surgical group was then analyzed separately.

3.11.3 Analysis 3: Comparison of Cerebral NIRS values between Group 1 *(rSO2 > 50; < 20% drop from baseline value)* & Group 2 *(rSO2 ≤ 50; > 20% drop from baseline value)* in patients receiving On-Pump CABG surgery

On-pump CABG patients were divided into two groups, Group 1 had NIRS values more than 50 or less than 20% drop from the baseline value and Group 2 had NIRS values of less than 50 or a drop of more than 20% from the baseline value.

Patient outcomes were analyzed. Mini-mental State Examination, renal function (U&E and creatinine, urine output, and urine electrolytes), and clinical outcomes were analyzed to evaluate the relationship of NIRS values or trends and outcomes in patients that received on-pump CABG surgery.

3.11.4 Analysis 4: Comparison of Cerebral NIRS values between Group 1 *(rSO2 > 50; < 20% drop from baseline value)* & Group 2 *(rSO2 ≤ 50; > 20% drop from baseline value)* in patients receiving Off-Pump CABG surgery

During this analysis, all off-pump CABG patients were divided into two groups (Group 1 had NIRS values more than 50 or a less than 20% drop from the baseline value and Group 2 had NIRS values of less than 50 or a drop of more than 20% from the baseline value).

Patient outcomes were analyzed. Mini-mental State Examination, renal function (U&E and creatinine, urine output, and urine electrolytes), and clinical outcomes were analyzed to evaluate the relationship between NIRS values/trends and outcomes in patients that received off-pump CABG surgery.

3.12 ETHICAL ASPECTS AND GOOD CLINICAL PRACTISE

3.12.1 Ethical Clearance

The study was ethically approved by the Ethics Committee, University of the Free State, Bloemfontein (ETOVS No. 51/07B). The study strictly adheres to all the ethical guidelines outlined by the Ethics Committee of the University of the Free State (Appendix E).

3.12.2 Safety Variables

3.12.2.1 Patient Safety

Patients participating in this study were well monitored and could at any time discontinue their participation without influencing their quality of care.

3.12.2.2 Good Clinical Practice (GCP) / Quality Assurance

All clinical work conducted under this protocol is subjected to the GCP guidelines (The Principles of the Declaration of Helsinki, 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).

3.12.2.3 Financial Implications to the Patient

No financial constraint was inflicted on the patient if he/she participated in the study and no financial remuneration was given if a patient decided to participate in the study.

3.12.2.4 Withdrawal Criteria

Participation was completely voluntarily. Patients had the right to withdraw from this particular study at any time, irrespective the reason(s), without detriment to their medical care at present or in future. The elimination of a patient from this particular study, did not involve any penalties.

3.12.2.5 Subject Information and Informed Consent

All the patients were informed about the purpose and necessity of the research project, the financial implications and the consequences as well as the adverse effects and their right to withdrawal without any effects on them or their doctor-patient relationship. They signed an informed consent form (Appendix A) and received an information sheet (Appendix B).

3.12.2.6 Confidentiality

The personal details of every patient that participated in this the study were kept confidential, as far as possible. At no time during the research have any of the patients' identification details been made known to any other people other as to whom the patient gave his/her consent to.

Chapter 4

RESULTS

4.1 INTRODUCTION

Sixty patients that presented with Acute Coronary Syndrome (ACS) who received Coronary Artery Bypass Graft Surgery (CABG) were observed during this study. Thirty patients underwent on-pump CABG and 30 patients received off-pump CABG surgery.

4.1.1 Statistical Analysis

Data was captured using a Microsoft Excel spreadsheet. The statistical analysis was done by a qualified statistician using SAS Version 9.1.3. The data was summarised using descriptive statistics, namely frequencies and percentages for categorical data. Means and standard deviations or medians and percentiles were used to summarize numerical data. Analytical statistics compared the frequencies and percentages in different groups by using the Chi-square statistic to calculate p-values. Means or medians of different groups were compared using the t-test or Kruskal-Wallis test to calculate p-values. Significant differences were noted at $p < 0.05$.

Four different analyses were performed to compare the two groups (on-pump versus off-pump) and the risk groups identified (adequate cerebral perfusion versus

inadequate cerebral perfusion). A short description of each of the four analyses is illustrated in Figure 4.1.

Figure 4.1 Schematic description of Data Analysis 1-4

4.2 DEMOGRAPHIC AND CLINICAL DATA, ON-PUMP AND OFF-PUMP CABG PATIENTS

4.2.1 Pre-operative demographic and clinical data (on-pump and off-pump)

The demographic data and pre-operative clinical characteristics for both on-pump and off-pump CABG patients are displayed in Table 4.1. Although the groups were limited in numbers they revealed similar and comparable data. The data for both the on-pump and off-pump CABG groups revealed no statistical significant differences (Table 4.1) for the EuroSCORE, age, gender, weight, height, Body Mass Index (BMI) and Body Surface Area (BSA). In both groups more males presented with Acute Coronary Syndrome [on-pump, n=27 (90%) versus (off pump, n=23 (76.67%)].

Pre-operatively, Acute Coronary Syndrome was classified as unstable angina, STEMI, and NONSTEMI. No differences were found between the two groups. In the on-pump CABG group, 83% (n=25) of the patients presented with unstable angina, 26% (n=8) with STEMI and 73% (n=22) with NONSTEMI. In the patients receiving off-pump CABG surgery, 73% (n=22) patients presented with unstable angina, 10% (n=3) with STEMI and 90% (n=27) with NONSTEMI (Table 4.1).

The only statistical significant difference between the on-pump and off-pump CABG groups were the last myocardial infarctions noted at admission to Cardiology (p=0.0326). A total of 14 patients in the on-pump group had a myocardial infarction less than 6 hours prior to admission compared to 5 in the off-pump group (Table 4.1).

Pre-operative risk factors such as diabetes, smoking, renal insufficiency, neurological complication, hypertension, and peripheral vascular disease did not reveal any statistical significant differences between the two groups. Only one patient in the off-pump CABG group had a previous stroke (3.33%), but fully recovered. In both groups, 20% (n=6) of patients had mild pre-operative Coronary Obstructive Pulmonary Disease (COPD). In the on-pump CABG group 3.33% (n=1) of patients presented with moderate COPD and in the off-pump CABG group 3.33% (n=1) had severe COPD and 10% (n=3) had mild COPD with asthma (Table 4.1).

The pre-operative MMSE showed no difference in the two groups and no cognitive impairment could be demonstrated. However, this data could be compromised due to patients refusing to take the test, educational level, and pre-operative medication.

Table 4.1 Demographic and Pre-operative Clinical Data for on-pump and off-pump CABG patients

DEMOGRAPHIC DATA	ON-PUMP (n=30)	OFF-PUMP (n=30)	p-value
EuroSCORE %			
Median	4.03	3.33	0.3867
25th percentile	2.64	1.83	-
75th percentile	7.12	6.32	-
Age (years)			
Mean	59.13	61.20	0.3679
Std Dev	8.58	9.05	-
Height (cm)			
Mean	177.03	176.50	0.8383
Std Dev	10.54	9.58	-
Weight (kg)			
Mean	87.13	91.47	0.4129
Std Dev	19.45	21.21	-
BSA (m^2)			
Mean	1.99	2.01	0.8199
Std Dev	0.25	0.36	-
BMI (kg/m^2)			
Mean	27.99	29.42	0.3412
Std Dev	5.89	5.46	-
Gender			
Male	n = 27 (90%)	n = 23 (76.67%)	0.1659
Female	n = 3 (10%)	n = 7 (23.3%)	
PRE-OPERATIVE CLINICAL DATA			
LVEF %			
Mean	51.32	55.68	0.2258
Std Dev	15.19	12.17	-
MMSE	**n = 24**	**n = 23**	
Median	28.50	28.00	0.6109
25th percentile	24.50	25.00	-
75th percentile	29.00	29.00	-
Haemoglobin (kPa)			
Median	14.20	13.60	0.1254
25th percentile	13.30	12.20	-
75th percentile	15.10	15.00	-
Minimum	8.60	9.80	-
Smoking			
Ex-smoker	6 (20.00%)	12 (40.00%)	
Never	6 (20.00%)	4 (13.33%)	0.2345
Current	18 (60.00%)	14 (46.67%)	
Renal Insufficiency			
None	-	-	-
Neurological dysfunction			
None	-	-	-
Neurological disease			
CVA with full recovery	-	1 (3.33%)	-
Pulmonary Disease			
Mild COPD	6 (20.00%)	6 (20.00%)	
Moderate COPD	1 (3.33%)	-	0.2992
Severe COPD	-	1 (3.33%)	
Asthma + mild COPD	-	3 (10.00%)	

Peripheral Vascular Disease			
None	-	-	-
Carotid Bruits			
None	-	-	-
Creatinine (mEq/L)			
Median	94.50	96.00	0.7844
25th percentile	86.00	80.00	-
75th percentile	105.00	107.00	-
Urea (mEq/L)			
Median	4.70	4.50	0.5441
25th percentile	3.70	3.60	-
75th percentile	5.70	5.20	-
Sodium (mEq/L)			
Median	140.00	139.00	0.3244
25th percentile	138.00	137.00	-
75th percentile	141.00	140.00	-
Potassium (mEq/L)			
Median	4.15	4.05	0.8936
25th percentile	3.90	3.70	-
75th percentile	4.40	4.40	-
Chloride (mEq/L)			
Median	107.00	107.00	0.5123
25th percentile	105.00	105.00	-
75th percentile	109.00	109.00	-
Acute Coronary Syndrome			
Unstable Angina	n = 25 (83.33%)	n = 22 (73.33%)	0.0835
STEMI	n = 8 (26.67%)	n = 3 (10.00%)	0.0953
NONSTEMI	n = 22 (73.33%)	n = 27 (90.00%)	0.0953
Previous MI			
One	n = 8 (26.67%)	n = 3 (10.00%)	0.1024
Two or more	n = 14 (46.67%)	n = 12 (40.00%)	
Last previous MI upon admission to Cardiology			
Unknown	n = 10 (33.337%)	n = 18 (60%)	
< 6hrs	n = 14 (46.67%)	n = 5 (16.67%)	
6 – 24hrs	n = 1 (3.33%)	n = 1 (3.33%)	
1 – 30 days	n = 5 (16.67%)	n = 4 (13.33%)	**0.0326**
31 – 90 days	-	-	
> 90 days	-	n = 2 (6.67%)	
Previous non-surgical intervention			
Previous PCI	n = 3 (10.00%)	n = 2 (6.67%)	0.6707
Dyspnoea			
NYHA I	n = 8 (26.67%)	n = 3 (10.00%)	0.2564
NYHA II	n = 18 (60.00%)	n = 23 (76.67%)	
NYHA III	n = 4 (13.33%)	n = 3 (10.00%)	
NYHA IV	-	n = 1 (3.33%)	
Diabetes			
Diet	n = 1 (3.33%)	n = 5 (16.67%)	
Oral therapy	n = 3 (10.00%)	n = 4 (13.33%)	0.3489
Insulin	n = 2 (6.67%)	n = 2 (6.67%)	
Hypertension			
Treated	n = 19 (63.33%)	n = 20 (66.67%)	0.1674

The data is given as mean with standard deviation (Std Dev) or median with 25th and 75th percentile. The p-values were calculated with t-test and the Kruskal-Wallis-Test. Categorical variables are demonstrated with an n-value and percentages. The p-values were calculated with Chi-square test. A $p < 0.05$ indicates statistical significance. [BSA: Body Surface Area; BMI: Body Mass Index; LVEF: Left Ventricular Ejection Fraction; MMSE: Mini-Mental State Examination; 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].

Essentially the patients in the on- and off-pump groups were considered to be similar regarding risk factors and co-morbidities.

4.3 ANALYSES 1-4

4.3.1 Cerebral NIRS performed on on-pump and off-pump CABG patients (Analysis 1)

In order to assess the impact of surgical techniques on cerebral blood flow, using NIRS as a monitoring instrument, outcomes were compared between patients undergoing on-pump versus off-pump CABG procedures. The intra-operative data between the on-pump and off-pump CABG groups were relatively comparable with limited statistical significant differences between the two groups (Table 4.2). The number of grafts in the on-pump CABG group ranged from 1 to 5, and in the off-pump CABG group from 1 to 3, but no statistical significant difference ($p = 0.0814$) was shown between the two groups.

The most important and statistical significant difference ($p < 0.0001$) was demonstrated for cerebral NIRS values. Twenty six (86.67%) of the on-pump CABG patients fell in group 2 (average or compromised cerebral blood flow = <50; ≥ 20% drop from baseline) and only five (16.67%) of the off-pump CABG patients fell in group 2 (Table 4.2).

Table 4.2 Intra-operative data for on-pump and off-pump CABG groups

INTRA-OPERATIVE DATA	ON-PUMP (n=30)	OFF-PUMP (n=30)	p-value
Number of grafts			
1 graft	1 (3.33%)	6 (20.00%)	
2 grafts	12 (40.00%)	14 (46.67%)	
3 grafts	14 (46.67%)	10 (33.33%)	
4 grafts	2 (6.67%)	-	0.0814
5 grafts	1 (3.33%)	-	
Median	3.00	2.00	
25th percentile	2.00	2.00	
75th percentile	3.00	3.00	
Haemoglobin (kPa)			
Median	14.45	13.20	**0.0162**
25th percentile	13.80	12.30	-
75th percentile	15.40	14.90	-
PO2 (kPa)			
Median	71.15	71.65	0.4246
25th percentile	66.80	66.10	-
75th percentile	84.90	126.10	-
O2SAT (%)			
Median	95.40	95.05	0.8024
25th percentile	94.20	93.30	-
75th percentile	96.10	96.60	-
Cerebral NIRS risk groups			
Group 1	4 (13.33%)	25 (83.33%)	**<0.0001**
Group 2	26 (86.67%)	5 (16.67%)	
Cerebral NIRS			
Median	69.00	65.50	0.3398
25th percentile	59.00	59.00	-
75th percentile	74.00	70.00	-
Heart Rate (beats/min)			
Median	67.00	68.00	0.8605
25th percentile	62.00	61.00	-
75th percentile	85.00	75.00	-
Mean Arterial Pressure (mmHg)			
Median	78.68	116.74	0.4341
25th percentile	71.27	64.25	-
75th percentile	92.74	133.87	-
Systolic Pressure (mmHg)			
Median	115.65	171.45	0.1928
25th percentile	98.50	97.57	-
75th percentile	130.29	179.71	-
Urine output (ml/kg/hr)			
Median	3.38	1.90	**0.0030**
25th percentile	2.07	1.29	-
75th percentile	5.09	2.89	-

The continuous variables are given as mean with standard deviation (Std Dev) or median with 25th and 75th percentile. The p-values were calculated with t-test and the Kruskal-Wallis-Test. Categorical variables are demonstrated with an n-value and percentages. The p-values were calculated with Chi-square test. A $p < 0.05$ indicates statistical significance. [CPB: Cardiopulmonary Bypass; PO_2: Partial Pressure of Oxygen; O_2SAT: Oxygen Saturation; NIRS: Near Infrared Spectroscopy; min: minute; °C: Degrees Celsius; kPa: kilopascal; %: percentage; mmHg: millimetres mercury; ml/kg/hr: millilitre per kilogram per hour].

Statistical significant differences were also found in intra-operative haemoglobin values (p = 0.0162) and urine output (p = 0.0030) although these values were still within the normal range. Three patients in the off-pump group were converted to on-pump CABG surgery due to hemodynamic instability or aortic dissection.

4.3.1.1 On-pump and Off-pump Cerebral NIRS linked to Pre-determined Intra-operative Events

During this analysis the cerebral NIRS values of the on-pump and off-pump CABG groups were linked to pre-determined intra operative events in order to reflect the hemodynamic impact of events during these procedures on oxygen delivery (as reflected by NIRS values). The results are displayed in Table 4.3. for the on-pump and Table 4.4 for the off-pump CABG groups.

Table 4.3 On-pump CABG Cerebral NIRS linked to Intra-operative Events

CEREBRAL NIRS	n	ON-PUMP CABG GROUP		
		25th percentile	75th percentile	Median
EVENTS				
Baseline	30	58.25	70.75	66.50
Intubation	30	71.00	81.25	77.00
Incision	30	66.00	75.75	69.50
Tachycardia	2	75.50	78.50	77.00
Bradycardia	1	56.00	56.00	56.00
Cannulate	19	65.00	74.00	72.00
On CPB	30	62.25	73.75	69.50
Cooling	18	53.75	72.00	58.50
↑MAP	3	63.00	69.00	66.00
↓MAP	5	56.00	73.00	65.00
Cardioplegia	30	52.25	62.75	58.50
Clamp on	30	54.00	66.50	60.50
Clamp off	30	49.25	54.75	51.50
Side clamp on	30	47.00	57.00	51.00
Side clamp off	30	51.50	58.25	51.50
Warming	28	47.75	57.75	54.00
Off CPB	30	52.00	61.00	58.00
Chest closed	26	55.25	64.00	59.50

The continuous variables are given as median with 25th and 75th percentile. [NIRS: Near Infrared Spectroscopy; MAP: Mean Arterial Pressure; CPB: Cardiopulmonary bypass].

Table 4.4 Off-pump CABG Cerebral NIRS linked to Intra-operative Events

EVENTS	n	OFF-PUMP CABG GROUP		
		25th percentile	75th percentile	Median
Cerebral NIRS				
Baseline	30	58.00	68.00	64.50
Intubation	30	72.00	78.00	75.00
Incision	29	63.00	74.00	70.00
Tachycardia	4	62.50	77.50	69.50
Reposition heart	28	61.75	74.25	67.00
Manipulate heart	3	48.00	63.50	54.00
Side clamp on	26	60.00	72.00	66.50
Side clamp off	26	62.00	73.00	68.00
↑MAP	13	58.00	75.00	68.00
↓MAP	16	60.50	75.25	66.50
Stabiliser on	24	60.00	74.00	63.50
Stabiliser off	21	56.00	71.00	63.00
Chest closed	27	59.50	68.00	63.00
Cannulate	2	68.25	70.75	69.50
On CPB	3	62.00	69.00	65.00
Cooling	2	61.50	66.50	64.00
Cardioplegia	3	42.00	61.00	57.00
Warming	3	47.00	57.50	54.00
Clamp on	3	39.50	58.50	52.00
Clamp off	3	43.50	58.00	56.00
Off CPB	3	61.50	65.50	63.00

The continuous variables are given as median with 25th and 75th percentile. [NIRS: Near Infrared Spectroscopy; MAP: Mean Arterial Pressure; CPB: Cardiopulmonary bypass].

As events are non-comparable between the two surgical groups, time lines were used and median values were compared between on-pump and off-pump groups (Table 4.5).

Table 4.5 Comparison between on-pump and off-pump CABG in regards to Cerebral NIRS using time lines

VARIABLES	n	ON-PUMP		OFF-PUMP		p-value
		Mean	Std Dev	Mean	Std Dev	
Cerebral NIRS						
Baseline	30	67.76	10.83	65.20	9.20	0.3268
T5	30	68.53	10.95	66.53	8.71	0.4371
T10	30	69.26	11.19	67.96	8.49	0.6144
T15	30	71.53	9.98	69.70	9.49	0.4690
T20	30	72.63	8.85	71.23	10.38	0.5764
T25	30	74.03	7.71	72.66	10.66	0.5690

The continuous variables are given as mean with standard deviation (Std Dev). The p-values were calculated with t-test and the Kruskal-Wallis-Test. A $p < 0.05$ indicates statistical significance. T = 5 minute intervals [NIRS: Near Infrared Spectroscopy; Std Dev: Standard Deviation; T: Time].

Comparing cerebral NIRS vales according to time lines in on-pump (n = 30) and off-pump (n = 30) CABG patients revealed no statistical significant differences.

4.3.2 *Comparison of cerebral NIRS values between Group 1 ($rSO_2 \geq 50$, < 20% drop from baseline value) and Group 2 ($rSO_2 < 50$, > 20% drop from baseline value) irrespective of Surgical Technique (Analysis 2)*

In Analysis 2 all 60 CABG patients, irrespective whether they had on-pump or off-pump CABG surgery were divided into cerebral NIRS groups 1 and 2. Group 1 consisted of patients considered to have satisfactory cerebral blood flow ($rSO_2 \geq 50$;< 20% drop from baseline value) and group 2 had average/or compromised cerebral blood flow ($rSO_2 < 50$, > 20% drop from baseline value).

4.3.2.1 Near Infrared Spectroscopy (NIRS): Group 1 vs. Group 2 irrespective of Surgical Technique

Of the 60 patients 48.33 % (n = 29) fell in group 1 and 51.67 % (n = 31) in group 2 (Table 4.6). The median value for group 1 was 68.68 and differs significantly from group 2 with a median value of 63.40 (Table 4.6).

In group 1, only 14% (n=4) of the patients had on-pump CABG surgery whereas 86% (n=25) received off-pump CABG surgery. In group 2, 84% (n=26) of the patients had on-pump CABG surgery and only 16% (n=5) of the patients received off-pump CABG surgery. Therefore it is important to note that the majority of patients with reduced cerebral flow/oxygen delivery as reflected by cerebral NIRS, received on-pump CABG surgery (84% fell in group 2).

Table 4.6 NIRS: Group 1 vs. Group 2 irrespective of surgical technique

NIRS	GROUP 1 (n=29)	GROUP 2 (n=31)	p-value
Median	68.68	63.40	**0.0004**
25th percentile	64.07	57.21	-
75th percentile	71.47	65.53	-

The continuous variables are given as median with 25th and 75th percentile. The p-values were calculated with t-test and the Kruskal-Wallis-Test. A $p < 0.05$ indicates statistical significance.

4.3.2.2 Mini-mental State Examination (MMSE): Group 1 vs. Group 2 irrespective of Surgical Technique

No significant differences between the two groups were found in regard to pre- and post-operative MMSE. Pre-operatively Group 2 showed a lower 25th percentile of

24.00 in comparison to Group 1's 27. However, post-operatively the 25th percentile for Group 2 were 23 versus the 25 in Group 1 (Table 4.7). Due to pre-operative sedation medication and refusal of the patients to take the test, not all of the patients that participated in the study have a pre- and post-operative MMSE. The patients that did not participate in the MMSE was not excluded from the study.

Table 4.7 MMSE: Group 1 vs. Group 2 irrespective of surgical technique

	GROUP 1				GROUP 2				p-VALUE
	N	Median	25TH percentile	75TH percentile	n	Median	25TH percentile	75TH percentile	
Pre	21	28.00	27.00	29.00	26	28.00	24.00	29.00	0.6320
Post	19	28.00	25.00	30.00	25	26.00	23.00	28.00	0.1505
Diff	19	0	-1.00	2.00	25	1.00	0	1.00	0.3207

Interpretation of data (Normal – any score above 27 out of 30; Some cognitive impairment – a score between 20 and 26 out of 30 and Moderate to severe cognitive impairment – a score between 10 and 19). The continuous variables are given as median with 25th and 75th percentile. The p-values were calculated with t-test and the Kruskal-Wallis-Test. A $p < 0.05$ indicates statistical significance. [Pre: pre-operative MMSE; Post: post-operative MMSE; Diff: difference between pre-operative MMSE and post-operative MMSE].

4.3.2.3 Renal Function: Group 1 and Group 2 irrespective of Surgical Technique

Figure 4.2 - 4.13 illustrates the renal function reflected by the U&E, creatinine and urine output for the patients that fell in group 1 and the patients that fell in group 2 irrespective of surgical technique.

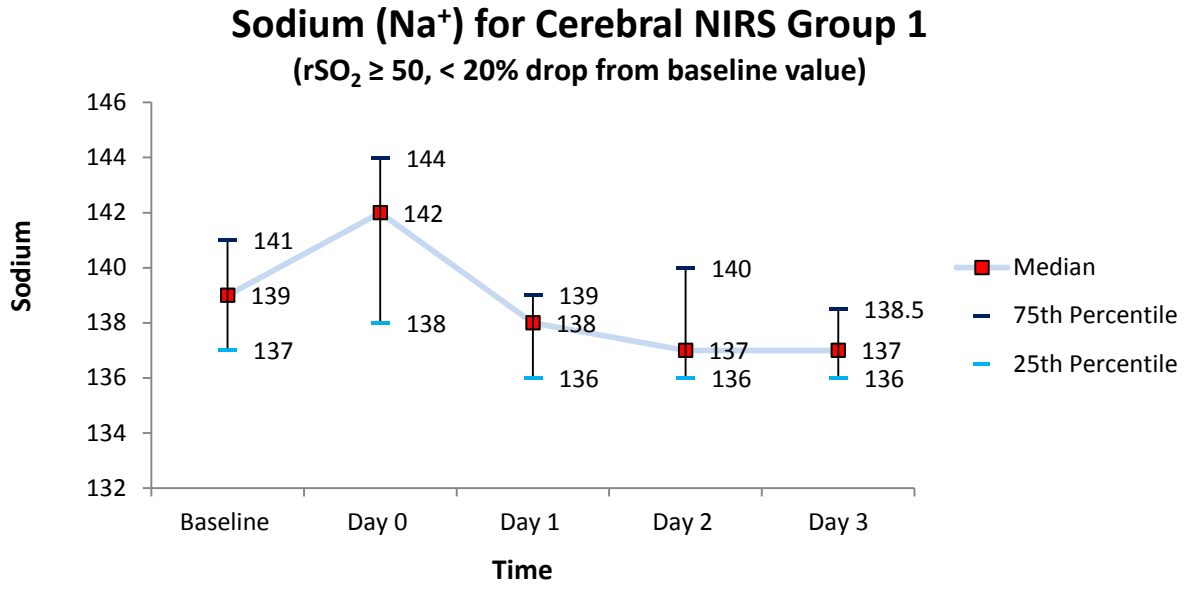


Figure 4.2 Sodium for Cerebral NIRS Group 1 irrespective of surgical technique

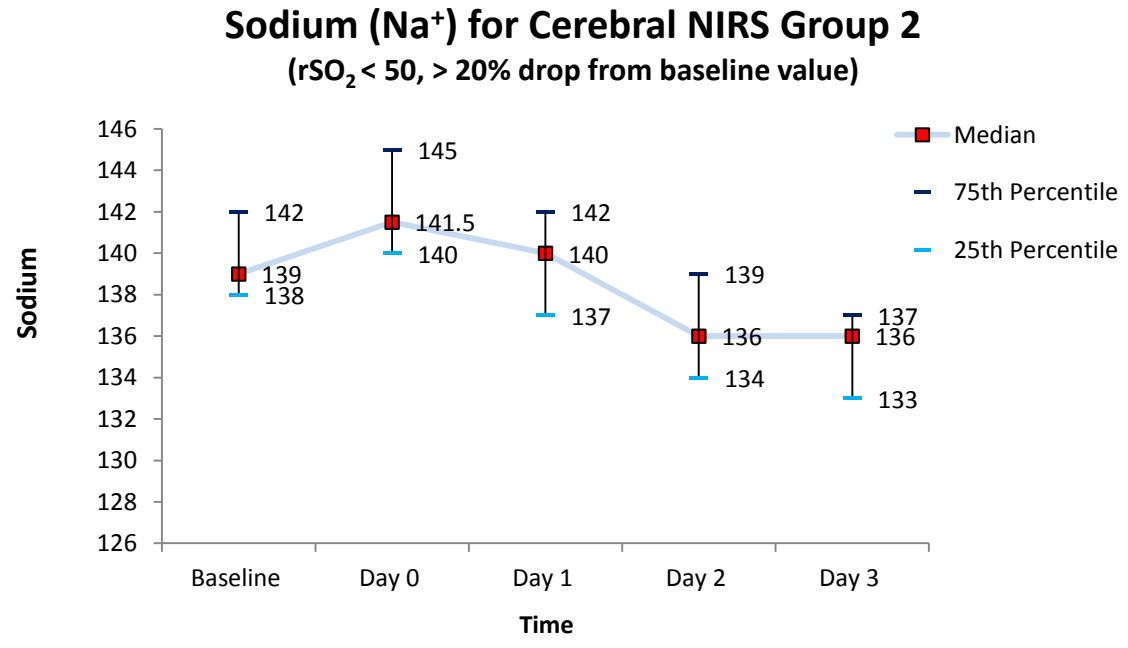


Figure 4.3 Sodium for Cerebral NIRS Group 2 irrespective of surgical technique

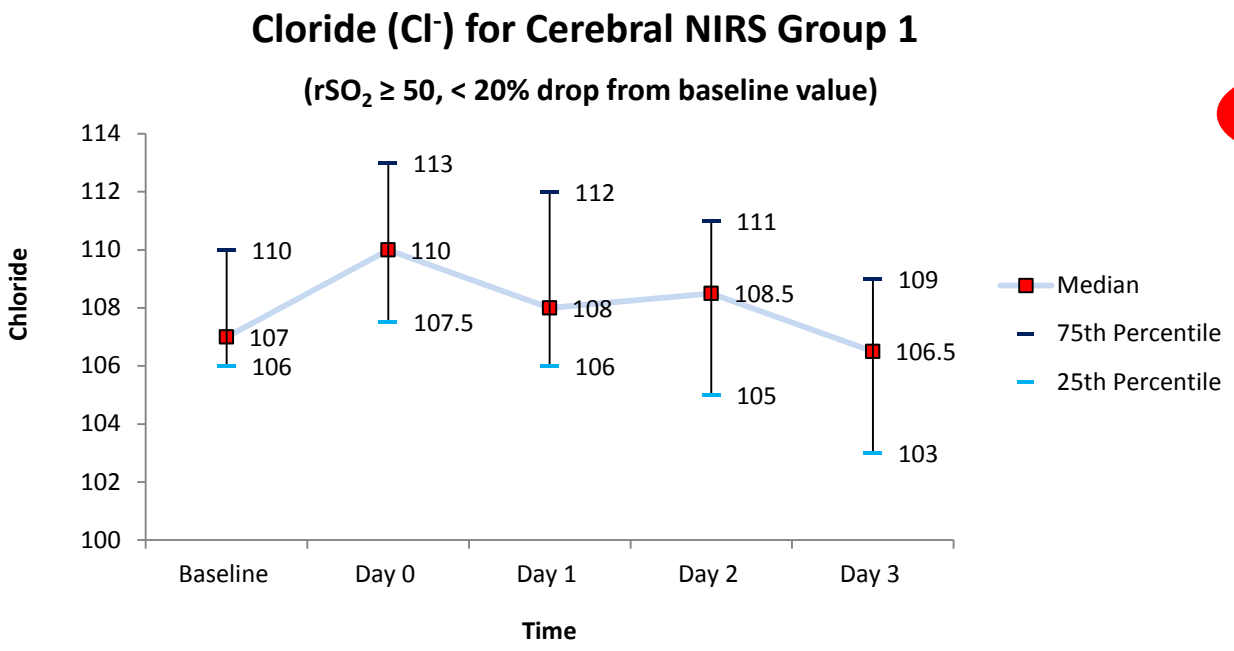


Figure 4.4 Chloride for Cerebral NIRS Group 1 irrespective of surgical technique

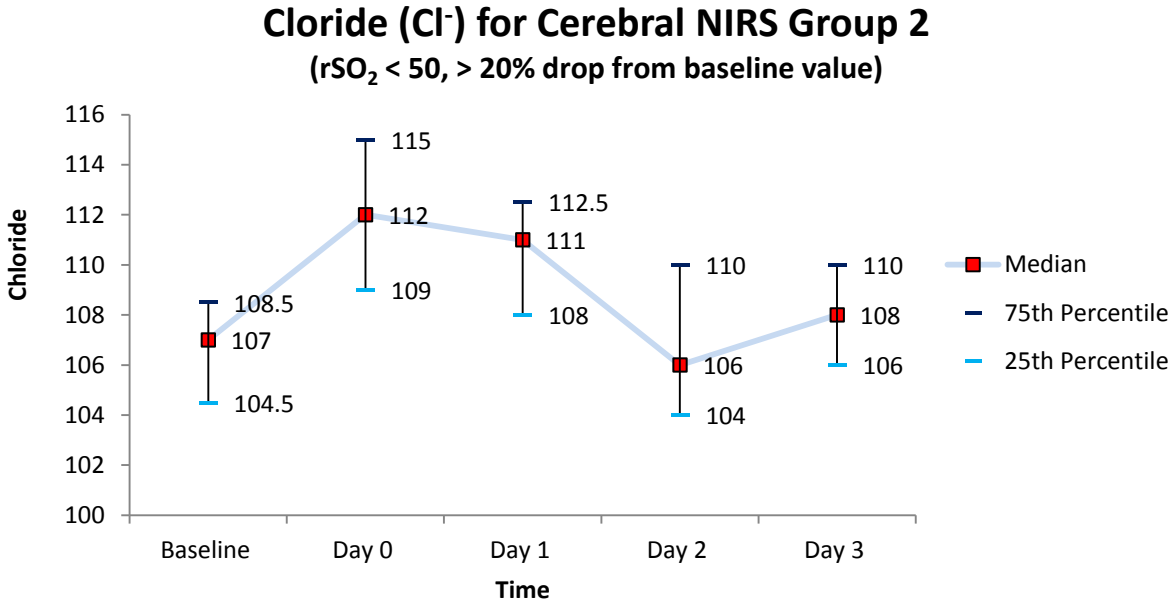


Figure 4.5 Chloride for Cerebral NIRS Group 2 irrespective of surgical technique

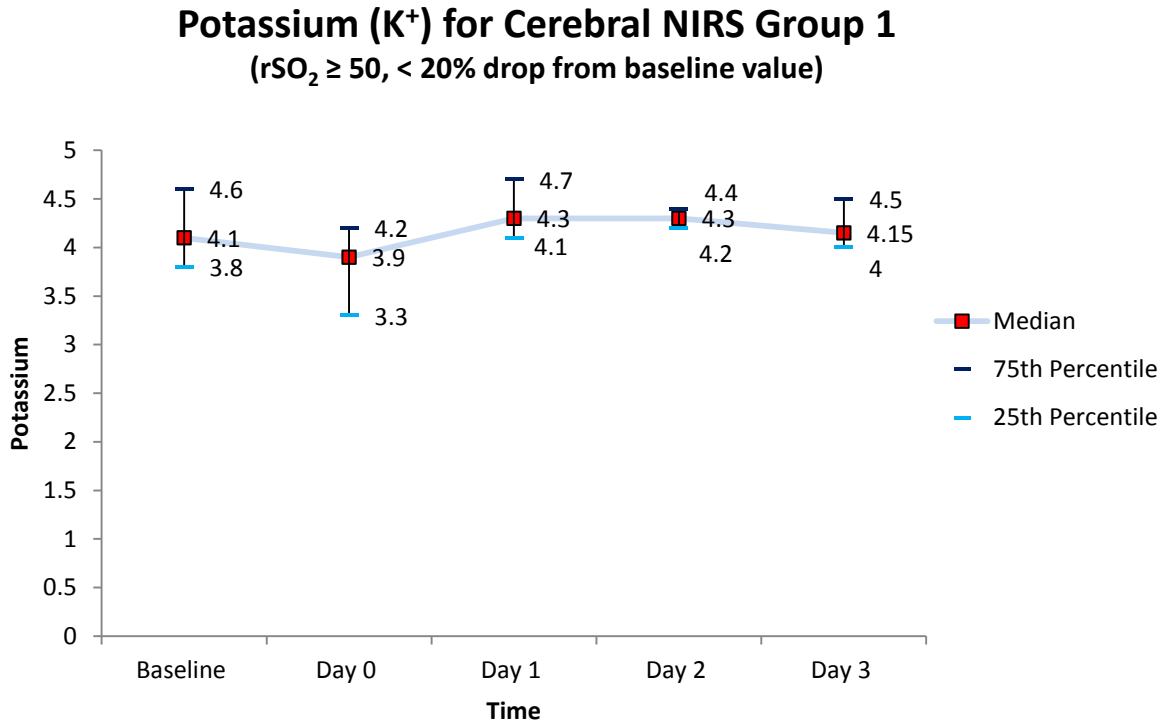


Figure 4.6 Potassium for Cerebral NIRS Group 1 irrespective of surgical technique

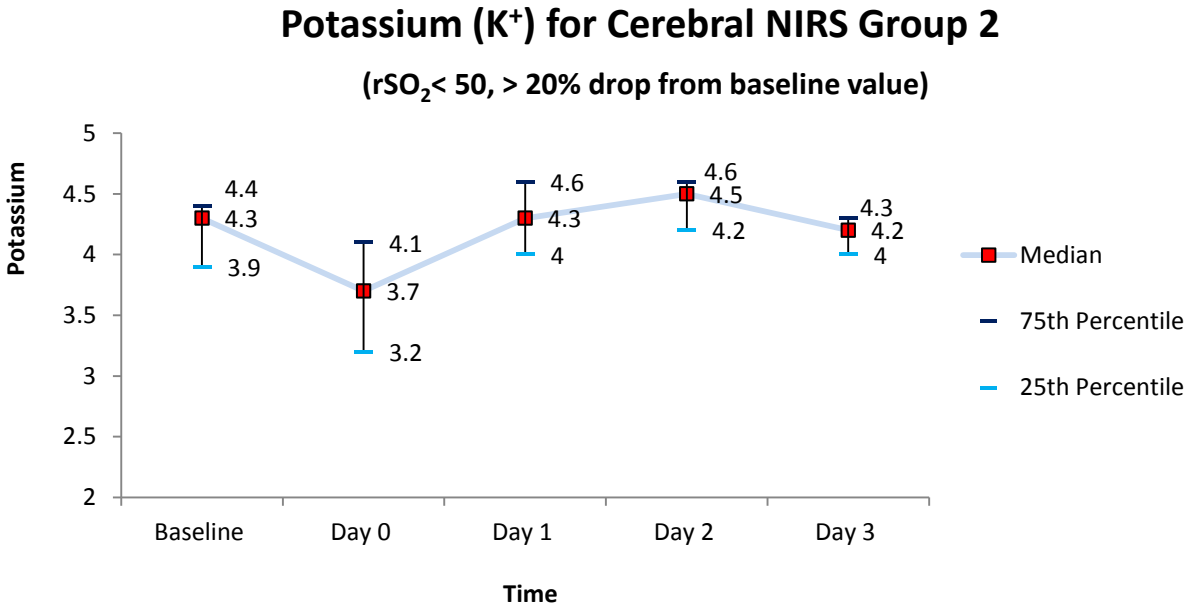


Figure 4.7 Potassium for Cerebral NIRS Group 2 irrespective of surgical technique

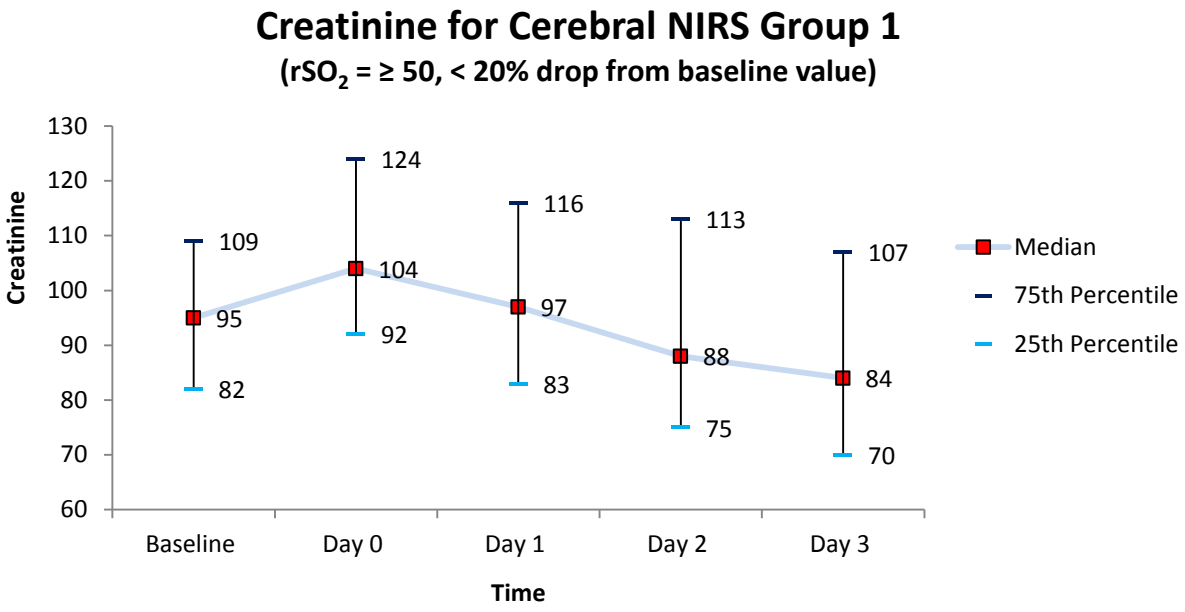


Figure 4.8 Creatinine for Cerebral NIRS Group 1 irrespective of surgical technique

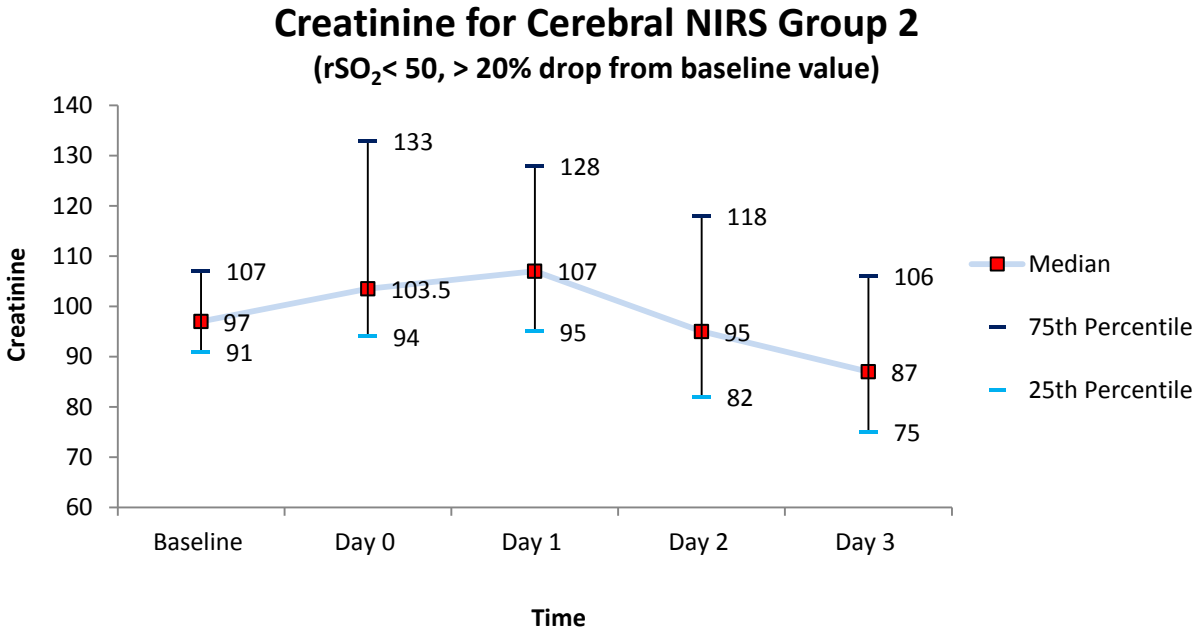


Figure 4.9 Creatinine for Cerebral NIRS Group 2 irrespective of surgical technique

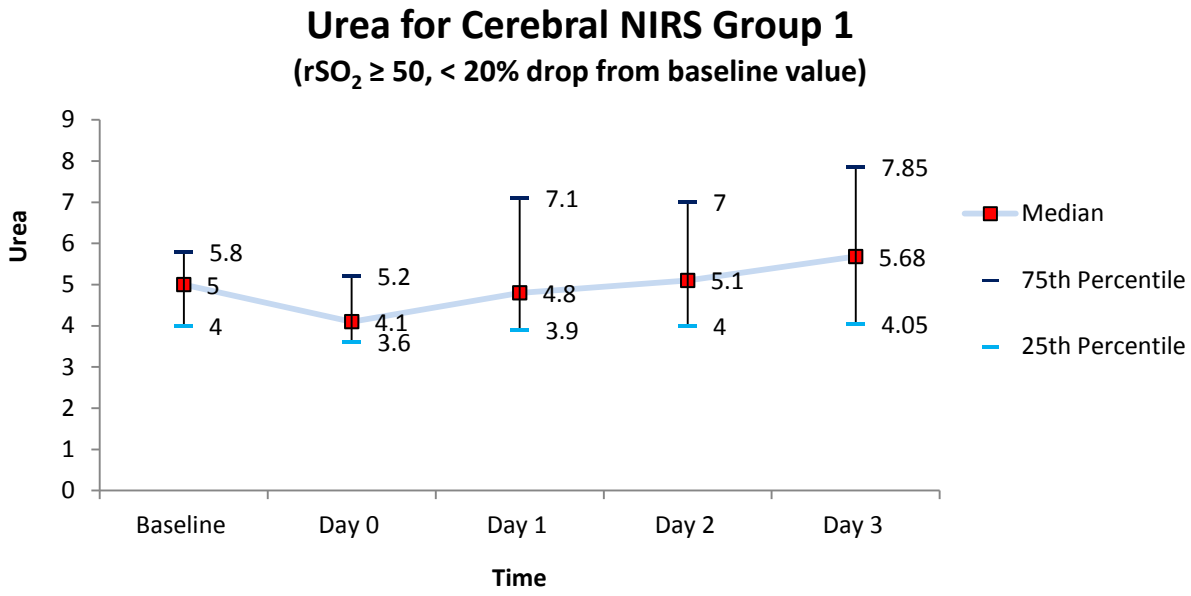


Figure 4.10 Urea for Cerebral NIRS Group 1 irrespective of surgical technique

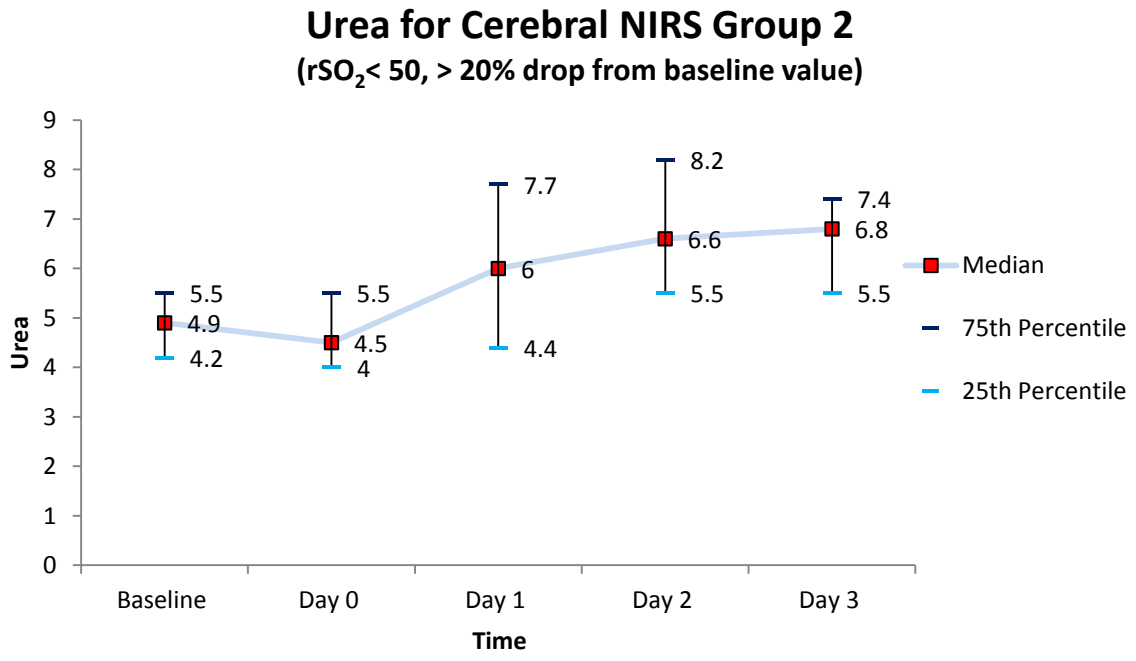


Figure 4.11 Urea for Cerebral NIRS Group 2 irrespective of surgical technique

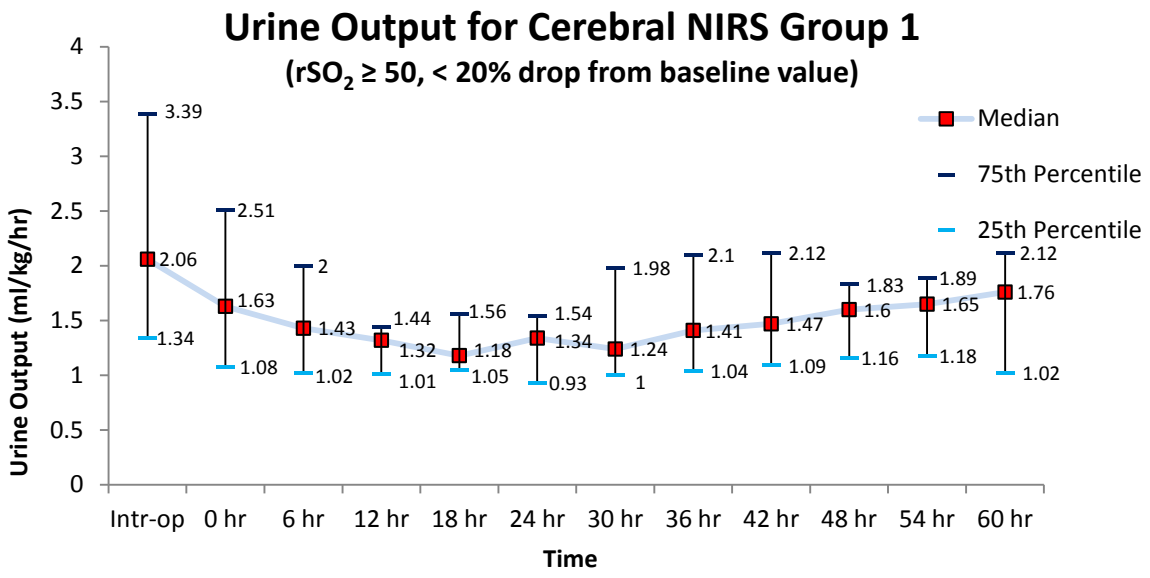


Figure 4.12 Urine Output for Cerebral NIRS Group 1 irrespective of surgical technique

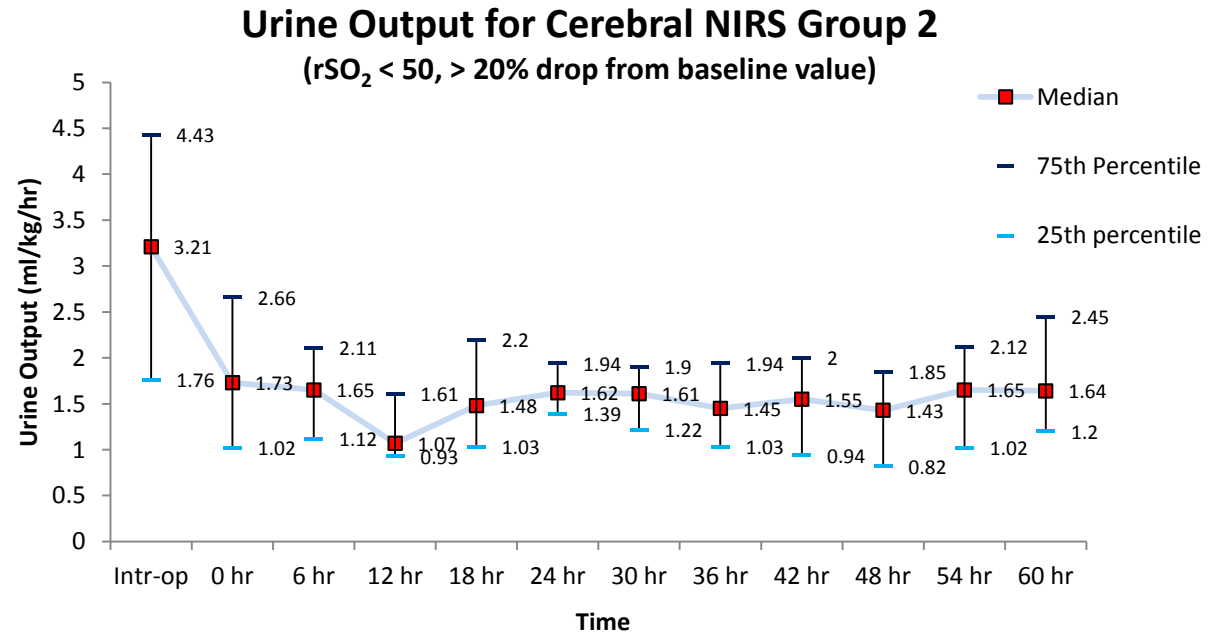


Figure 4.13 Urine Output for Cerebral NIRS Group 2 irrespective of surgical technique

4.3.2.4 *Renal Function: Group 1 vs. Group 2 irrespective of Surgical Technique*

In comparison the overall U&E and creatinine values of the two groups showed no statistical significant differences for potassium and chloride at baseline level, day 1, day 2 and day 3 respectively (Table 4.8). There was a statistical significant difference for sodium (Table 4.8) between group 1 and group 2 on day 2 (p = 0.0486).

Table 4.8 Renal function: Group 1 vs. Group 2 irrespective of surgical technique

U&E, CREATININE, URINE OUTPUT	GROUP 1 (n = 29) Min/Max	GROUP 2 (n=31) Min/Max	p-VALUE
Sodium (mEq/L)			
Baseline	135/145	130/145	0.6921
Day 0	135/152	135/151	0.2744
Day 1	139/152	129/148	0.1749
Day 2	133/144	130/148	**0.0486**
Day 3	131/145	131/146	0.0572
Potassium (mEq/L)			
Baseline	2.5/4.8	3.1/4.9	0.5577
Day 0	2.7/4.9	2.7/8.8	0.2327
Day 1	3.6/6.4	3.8/5.6	0.8916
Day 2	3.7/5.2	3.8/5.1	0.1356
Day 3	3.6/5.2	3.2/4.7	0.6566
Chloride (mEq/L)			
Baseline	102/117	95/112	0.4107
Day 0	102/118	102/116	0.2125
Day 1	100/115	101/119	0.0998
Day 2	103/115	100/116	0.3010
Day 3	100/112	98/117	0.3514
Urea (mEq/L)			
Baseline	1.6/7.4	2.8/9.4	0.7842
Day 0	2.2/6.4	2.7/7.1	0.1690
Day 1	1.7/9.1	3.0/11.5	0.1124
Day 2	1.5/11.6	2.9/17.6	**0.0263**
Day 3	2.8/12.4	2.7/20.5	0.3290
Creatinine (mEq/L)			
Baseline	63/131	54/148	0.5008
Day 0	67/151	62/138	0.5649
Day 1	71/157	42/204	0.1867
Day 2	66/176	52/230	0.3856
Day 3	65/199	40/217	0.8726

Urine Output (ml/kg/hr)			
Intra-operative	0.58/15.69	0.39/8.09	0.1179
0 hours	0.4/6.4	0.6/11.76	0.9925
6 hours	0.65/2.86	0.68/3.12	0.4280
12 hours	0.67/2.63	0.54/3.35	0.3172
18 hours	0.37/2.27	0.46/4.16	0.1087
24hours	0.22/2.76	**0.51/2.84**	**0.0108**
30 hours	0.48/3.58	0.36/3.25	0.3451
36 hours	0.73/5.21	0.48/2.74	0.5658
42 hours	0.8/3.68	0.71/3.33	0.8200
48 hours	0.59/2.66	0.55/2.6	0.5658
54 hours	0.69/1.51	0.33/3.2	0.7952
60 hours	0.68/3.17	0.33/3.36	0.9224

The data was given as median with 25th and 75th percentile. The p-values were calculated with t-test and the Kruskal-Wallis-Test. Categorical variables are demonstrated with an n-value and percentages. The p-values were calculated with Chi-square test. A $p < 0.05$ indicates statistical significance. [mEq/L = mill equivalents per litre; ml/kg/hr- millilitres per kilogram per hour]

On day 2, the urea values between the 2 groups indicated a statistical significant difference (p=0.0263). Urine output was evaluated in ml/kg/hour, and showed a statistical significant difference at 24 hours between group 1 and group 2 (p = 0.0108). These differences showed that a NIRS reduction of more than 20 % from baseline and values of less than 50, did have an impact on post–operative renal function. The median value however was 63 (Table 4.8) The elevated urea value, with higher sodium and urine output might reflect a polyuric phase of early renal dysfunction. The creatinine values were however not different between the groups. The results demonstrated a weak association and therefore this warrants further investigation.

4.3.2.5 Post-operative Complications and Outcomes: Group 1 vs. Group 2 irrespective of Surgical Technique

The mortality rate in the study was very low, only two patients died in group 1 (6.90%) and no mortality was reported in group 2 (0%). The first patient was a 59-year-old

white male who underwent off-pump CABG surgery. According to his EuroSCORE (1.56%) he was a low-risk patient. After a stable intra-operative and early post-operative course, the patient developed unexplained Acute Respiratory Distress Syndrome (ARDS). He died 96h post-operatively in the ICU due to untreatable respiratory failure. The second patient was an 80-year-old male who also underwent off-pump CABG surgery. The patient had a logistic EuroSCORE predicted risk percentage of 10.99% (high-risk patient). The patient developed post-operative kidney failure, respiratory failure, and pump failure with dysrythmia. The patient died after six days in the ICU due to multiple-organ failure and septic shock.

Table 4.9 Post-operative Outcomes and Complications: Group 1 vs. Group 2 irrespective of Surgical Technique

OUTCOME VARIABLES	GROUP 1 (n=29)	GROUP 2 (n=31)	p-VALUE
Mortality			
Yes	2 (6.90%)	-	0.2294
No	27 (93.10%)	31 (100%)	
Return to ICU			
Yes	1 (3.45%)	-	0.4833
No	28 (96.55%)	31 (100%)	
Re-intubation			
Yes	-	1 (3.23%)	1.000
No	29 (100%)	30 (96.77)	
Re-operation			
Yes	1 (3.45%)	1 (3.32%)	1.000
No	28 (96.55%)	30 (96.77%)	
Post-operative MI			
Yes	-	-	-
No	29 (100%)	31 (100%)	
Pulmonary complications			
Yes	-	2 (6.45%)	0.4921
No	29 (100%)	29 (93.55%)	
Neurological complications			
Yes	-	-	-
No	29 (100%)	31 (100%)	
Renal complications			
Yes	1 (3.45%)	-	0.4833
No	28 (96.55%)	31 (100%)	
GIT complications			
Yes	1 (3.45%)	1 (3.32%)	1.000
No	28 (96.55%)	30 (96.77%)	
Multi system failure			
Yes	1 (3.45%)	-	0.4833

No	28 (96.55%)	31 (100%)	
Post-operative dissection of major arteries			
Yes	-	-	-
No	29 (100%)	31 (100%)	
Acute limb ischemia			
Yes	-	-	-
No	29 (100%)	31 (100%)	
Heart block			
Yes	-	-	-
No	29 (100%)	31 (100%)	
Atrial fibrillation			
Yes	1 (3.45%)	1 (3.32%)	1.000
No	28 (96.55%)	30 (96.77%)	
Cardiac arrest			
Yes	-	-	-
No	29 (100%)	31 (100%)	
Anticoagulant complications			
Yes	-	-	-
No	29 (100%)	31 (100%)	
Tamponade			
Yes	-	-	-
No	29 (100%)	31 (100%)	
Sternal wound infection			
Yes	-	1 (3.23%)	1.000
No	29 (100%)	30 (96.77)	
Septicaemia			
Yes	1 (3.45%)	1 (3.32%)	1.000
No	28 (96.55%)	30 (96.77%)	
Post-operative blood transfusion			
Yes	7 (24.14%)	14 (45.16%)	0.1369
No	21 (72.41%)	17 (54.84%)	
Length of hospital stay (days)			
Median	8.00	8.00	0.5111
25th percentile	6.00	7.00	-
75th percentile	11.00	10.00	-
Length of ICU stay (days)			
Median	3.00	3.00	0.3029
25th percentile	2.00	3.00	-
75th percentile	3.00	3.00	-
Ventilation time (hours)			
Median	10.00	12.00	**0.0099**
25th percentile	6.00	12.00	-
75th percentile	14.00	16.00	-

The data is given as median with 25th and 75th percentile. The p-values were calculated with t-test and the Kruskal-Wallis-Test. Categorical variables are demonstrated with an n-value and percentages. The p-values were calculated with Chi-square test. A $p < 0.05$ indicates statistical significance. [MI: Myocardial infarction; ICU: Intensive Care Unit; GIT: Gastro-intestinal system].

Two patients in group 2 had pulmonary complications (6.45%) and none in group 1 (0%) respectively. One patient in each group presented with gastro-intestinal complications, atrial fibrillation, and septicaemia. None of the patients presented with post-operative myocardial infarction, neurological complications, acute limb

ischemia, heart block, cardiac arrest, anticoagulant complications, tamponade, or dissection of the major arteries (Table 4.9).

Most importantly, no statistical significant difference were found between the 2 groups in regards to length of hospital stay (p = 0.5111) and length of ICU stay (p = 0.3029). However, ventilation time showed a statistical significant difference between the 2 groups (p-value = 0.0099), demonstrating a 2 hour longer post-operative ventilation time in group 2 (Table 4.9).

4.3.3 Comparison of Cerebral NIRS values between Group 1 (rSO2 > 50; < 20% drop from baseline value) & Group 2 (rSO2 ≤ 50; > 20% drop from baseline value) in patients receiving On-Pump CABG surgery (Analysis 3)

All on-pump CABG patients (n = 30) were subdivided into 2 cerebral NIRS groups (group 1 = rSO_2 > 50; < 20% from baseline value and group 2 = rSO_2 ≤ 50; > 20% from baseline value). These groups were then compared with the MMSE (Table 4.10), intra-operative hemodynamic data (Table 4.11), renal function (Figure 4.14 – 4.25 and Table 4.12), and all other post-operative complications/outcomes (Table 4.13).

Thirty patients received on-pump CABG surgery of which 13.33% (n = 4) fell in group 1 and 86.67% (n = 26) in group 2. Therefore, it is important to note that 86.67% of on-pump patients had reduced or compromised cerebral blood flow, as reflected in reductions in cerebral NIRS values of more than 20%, or absolute values of less than 50.

4.3.3.1 Mini-Mental State Examination (MMSE): Group 1 vs. Group 2 (on-pump CABG surgery)

No statistical significant differences were found in pre- and post-operative MMSE between the two groups that received on-pump CABG surgery (Table 4.10). The number of patients that received the MMSE pre-operatively in group 1 was 75% (n=3) and in group 2 were 80.76% (n=21). Post-operatively 75% (n=3) in group 1 received the MMSE and 76.92% (n=20) in group 2. The difference in numbers are ascribe to patients refusing to take the test and if the patient already received his/her pre-operative medication the test was also not performed (patients were not excluded due to this reason). However, by interpreting the existing data the reduction in cerebral NIRS values were not linked to adverse neurological outcomes (the median scores were equal or above 27 for both group 1 and group 2 which indicates normal neurological function).

Table 4.10 MMSE: Group 1 vs. Group 2 (on-pump CABG surgery)

	GROUP 1				GROUP 2				p-VALUE
	n	median	25th percentile	75th percentile	n	median	25th percentile	75th percentile	
Pre	3	29.00	29.00	30.00	21	28.00	24.00	29.00	0.1419
Post	3	29.00	24.00	30.00	20	26.50	23.50	28.50	0.4078
Diff	3	0	0	5.00	20	1.00	0	1.50	0.8516

Interpretation of data (Normal – any score above 27 out of 30; Some cognitive impairment – a score between 20 and 26 out of 30 and Moderate to severe cognitive impairment – a score between 10 and 19). The continuous variables are given as median with 25th and 75th percentile. The p-values were calculated with t-test and the Kruskal-Wallis-Test. A $p < 0.05$ indicates statistical significance. [Pre: pre-operative MMSE; Post: post-operative MMSE; Diff: difference between pre-operative MMSE and post-operative MMSE].

4.3.3.2 *Intra-operative Hemodynamic Monitoring: Group 1 vs. Group 2 (on-pump CABG surgery)*

Intra-operative observations of heart rate, mean arterial pressure, systolic pressure, cardiac output, haemoglobin concentration, oxygen saturation (O_2SAT), and partial pressure of oxygen (pO_2) were recorded for every patient that received a NIRS analysis. These observations revealed no statistical significant difference between group 1 and group 2 (Table 4.11). This table clearly demonstrates the limitation of hemodynamic data in detecting subtle changes in tissue perfusion compared to cerebral NIRS values and trends.

Table 4.11 Intra-operative Hemodynamic Data: Group 1 vs. Group 2 (on-pump CABG surgery)

INTRA-OPRATIVE DATA	GROUP 1 (n=4)	GROUP 2 (n=26)	p-VALUE
Heart Rate (beats/min)			
Median	62.50	69.00	0.3756
25th percentile	62.00	63.00	-
75th percentile	74.50	84.00	-
Mean Arterial Pressure (mmHg)			
Median	85.135	94.535	0.6255
25th percentile	80.045	71.84	-
75th percentile	98.35	119.38	-
Systolic Pressure (mmHg)			
Median	123.49	131.81	0.9514
25th percentile	117.31	100.56	-
75th percentile	148.325	145.90	-
Cardiac Output (l/min)			
Median	4.705	4.84	0.7518
25th percentile	4.345	4.34	-
75th percentile	5.185	5.09	-
Haemoglobin (kPa)			
Median	13.35	14.55	0.3758
25th percentile	12.40	13.90	-
75th percentile	15.55	15.40	-
O_2SAT (%)			

Median	95.10	95.50	0.6672
25th percentile	94.60	93.80	-
75th percentile	98.10	96.10	-
pO_2 (kPa)			
Median	89.80	71.15	0.4456
25th percentile	67.95	64.90	-
75th percentile	162.05	77.70	-

The data is given as median with 25th and 75th percentile. The p-values were calculated with t-test and the Kruskal-Wallis-Test. A $p < 0.05$ indicates statistical significance. [O_2SAT: Oxygen Saturation; PO_2: Partial Pressure of Oxygen; min: minute; mmHg: millimetres mercury; l/min: litres per minute; %: percentage; kPa: kilopascal].

4.3.3.3 Renal Function: Group 1 vs. Group 2 (on-pump CABG surgery)

No statistical significant differences were found between the two groups with reference to sodium, urea, and urine output (Table 4.12). However, the statistical significant difference in creatinine [day 1 ($p = 0.0398$)] showed that a NIRS reduction of more than 20 % in baseline and values of less than 50, did have an association with post–operative renal function.

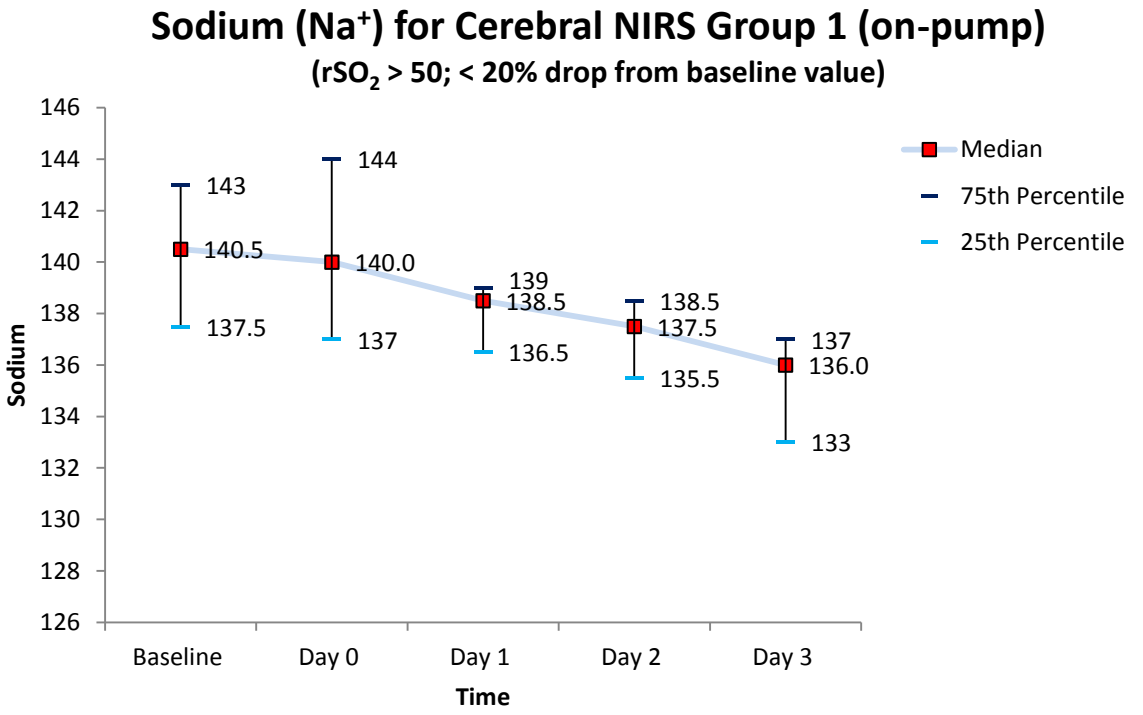


Figure 4.14 Sodium for Cerebral NIRS Group 1 (on-pump CABG surgery)

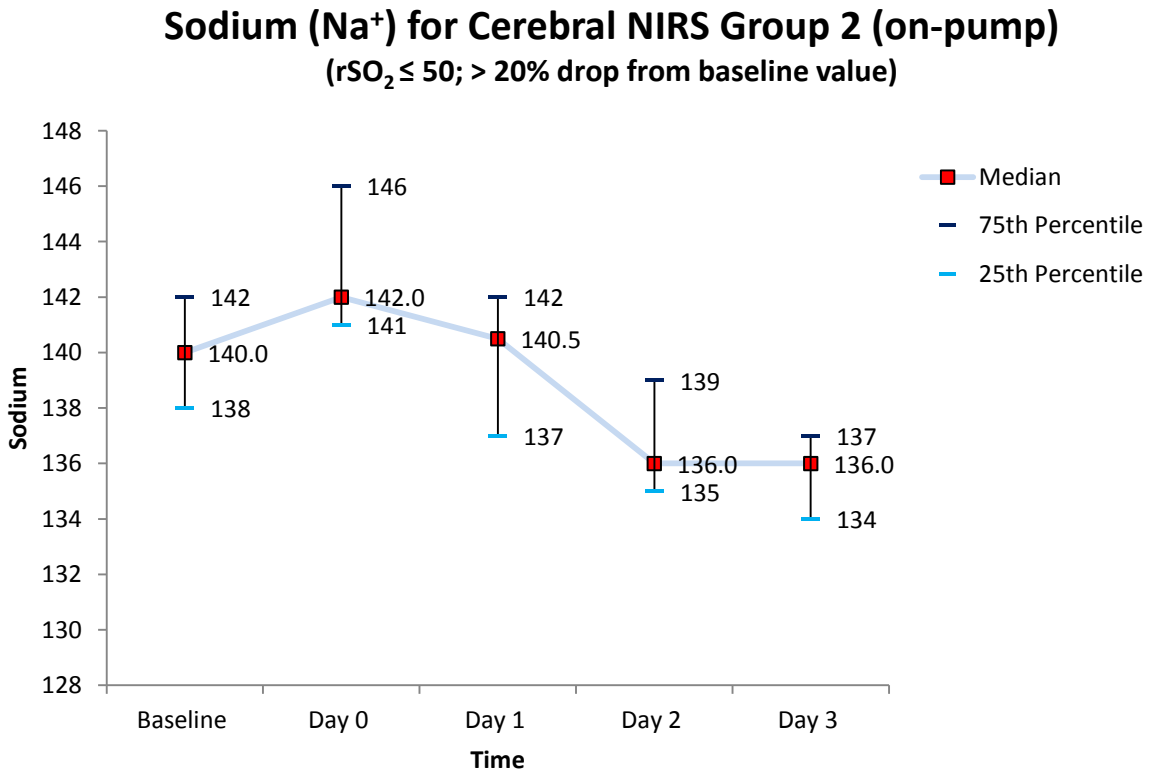


Figure 4.15 Sodium for Cerebral NIRS Group 2 (on-pump CABG surgery)

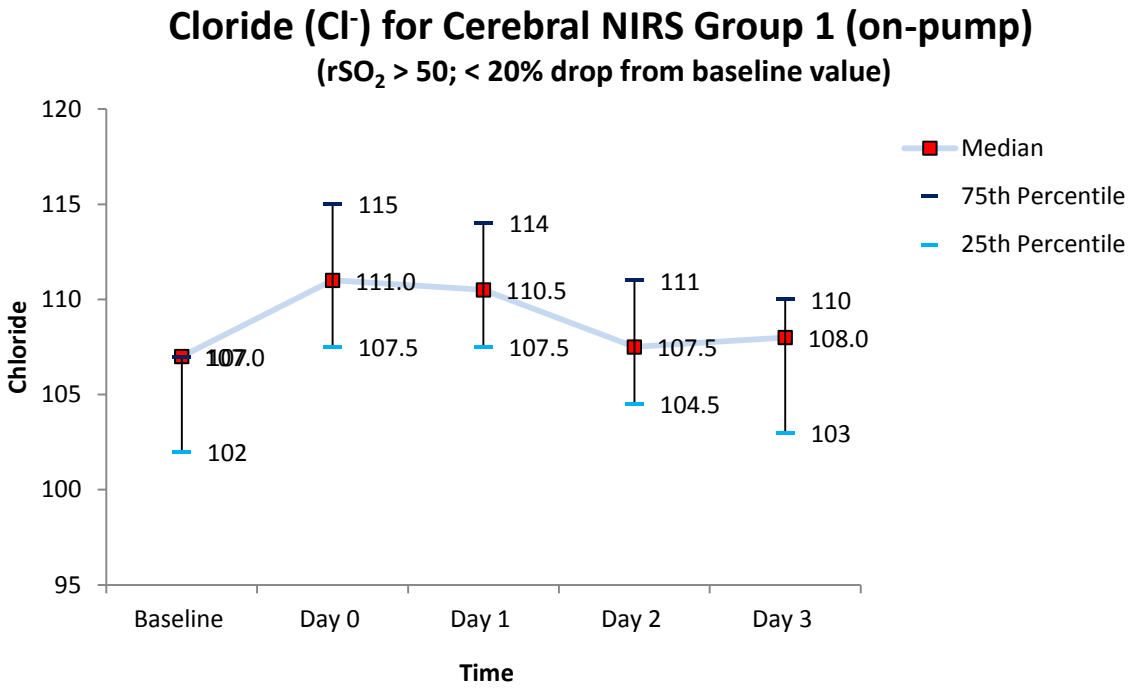


Figure 4.16 Chloride for Cerebral NIRS Group 1 (on-pump CABG surgery)

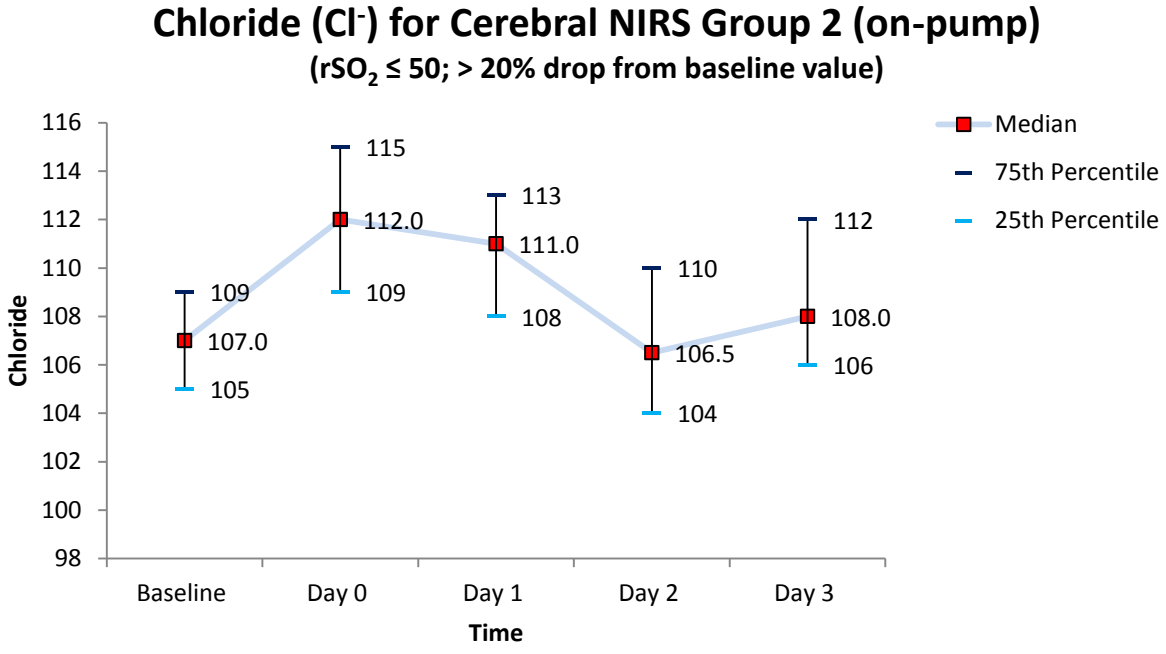


Figure 4.17 Chloride for Cerebral NIRS Group 2 (on-pump CABG surgery)

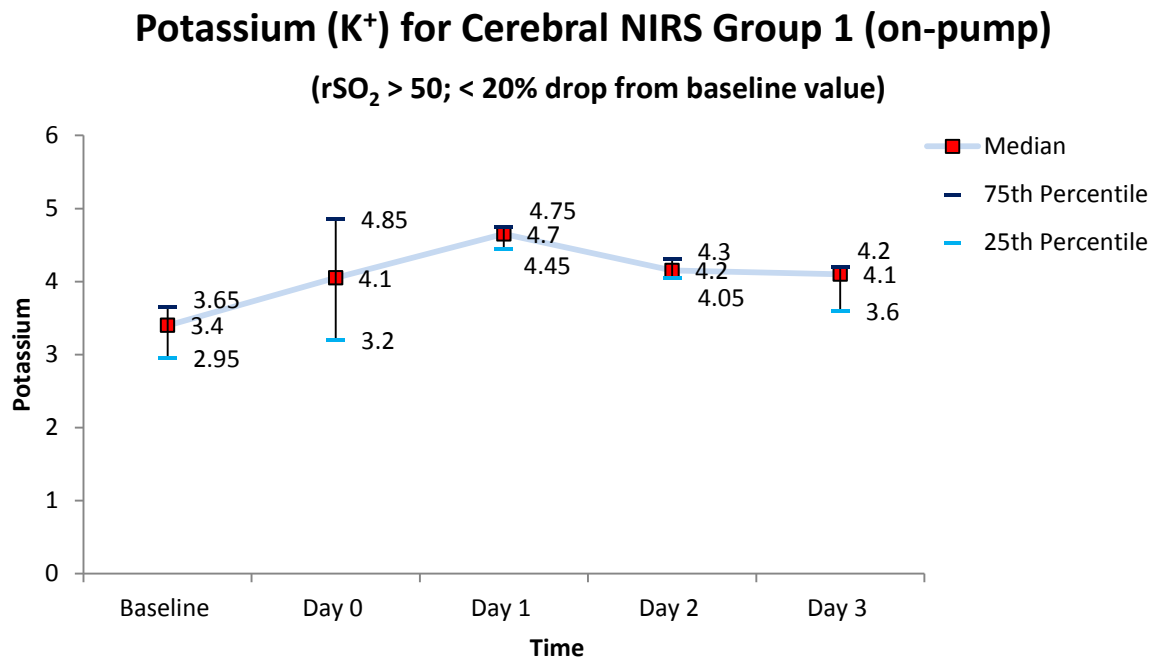


Figure 4.18 Potassium for Cerebral NIRS Group 1 (on-pump CABG surgery)

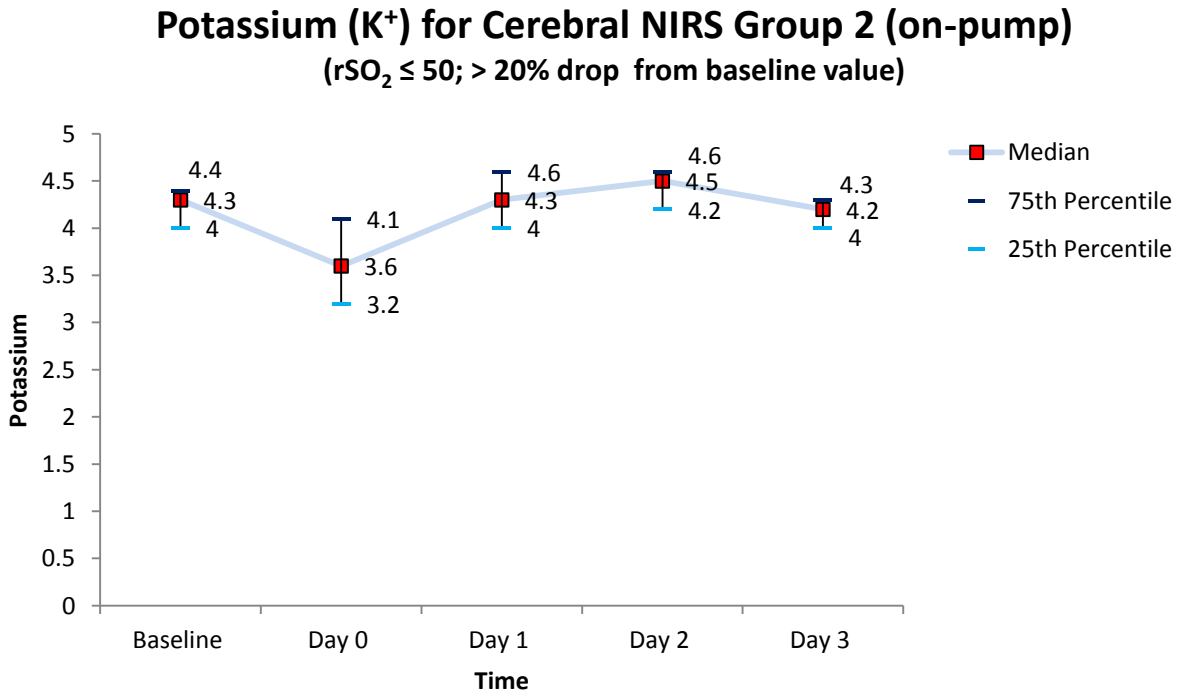


Figure 4.19 Potassium for Cerebral NIRS Group 2 (on-pump CABG surgery)

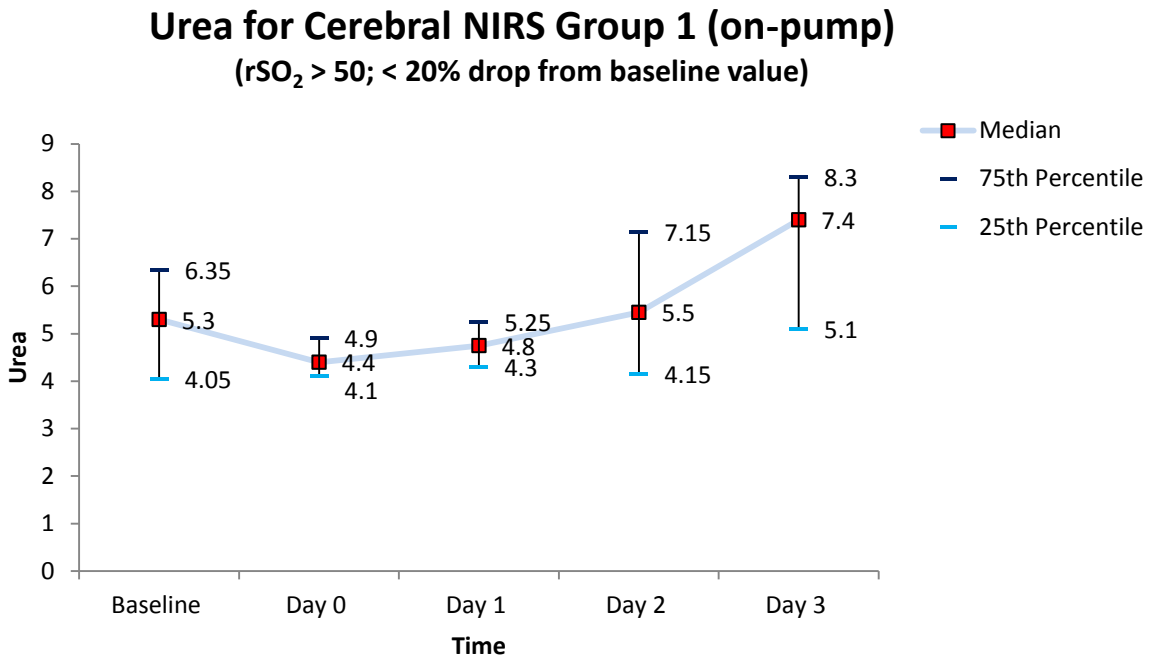


Figure 4.20 Urea for Cerebral NIRS Group 1 (on-pump CABG surgery)

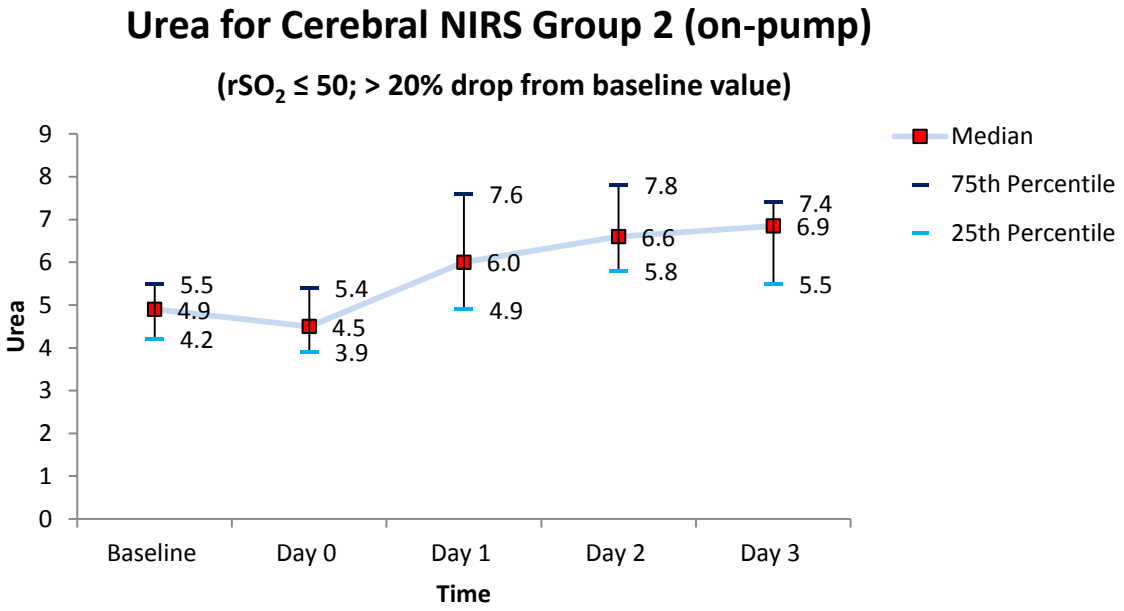


Figure 4.21 Urea for Cerebral NIRS Group 2 (on-pump CABG surgery)

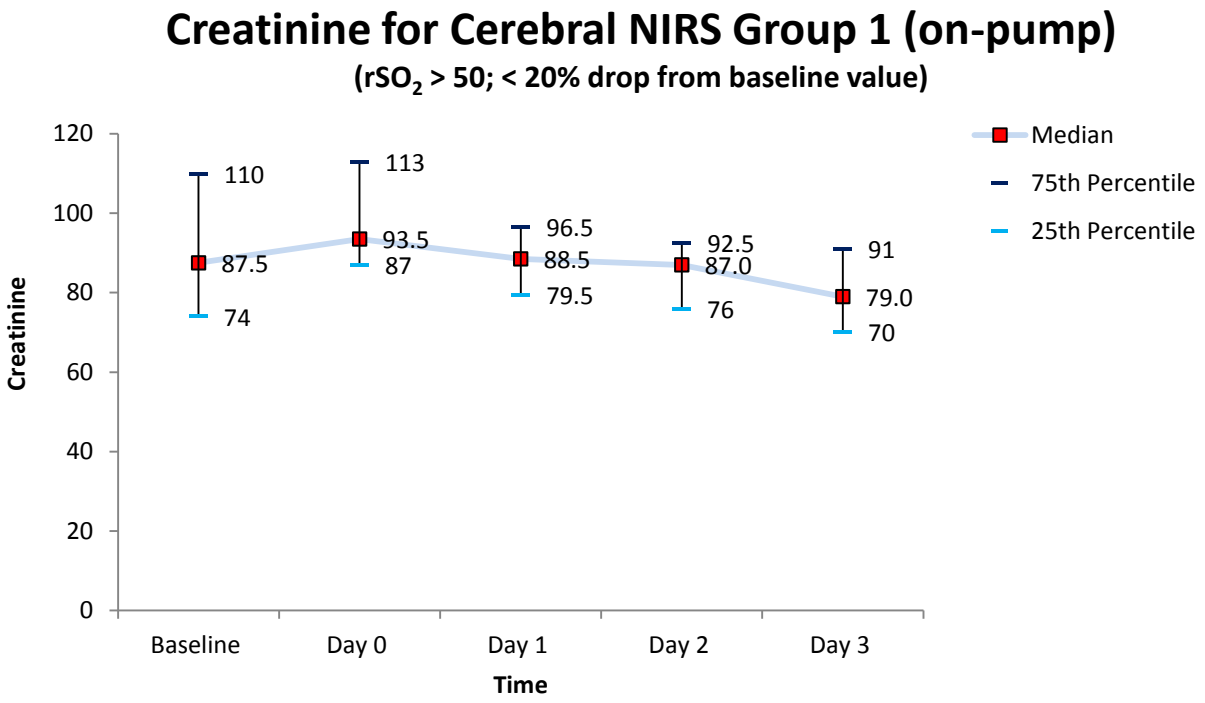


Figure 4.22 Creatinine for Cerebral NIRS Group 1 (on-pump CABG surgery)

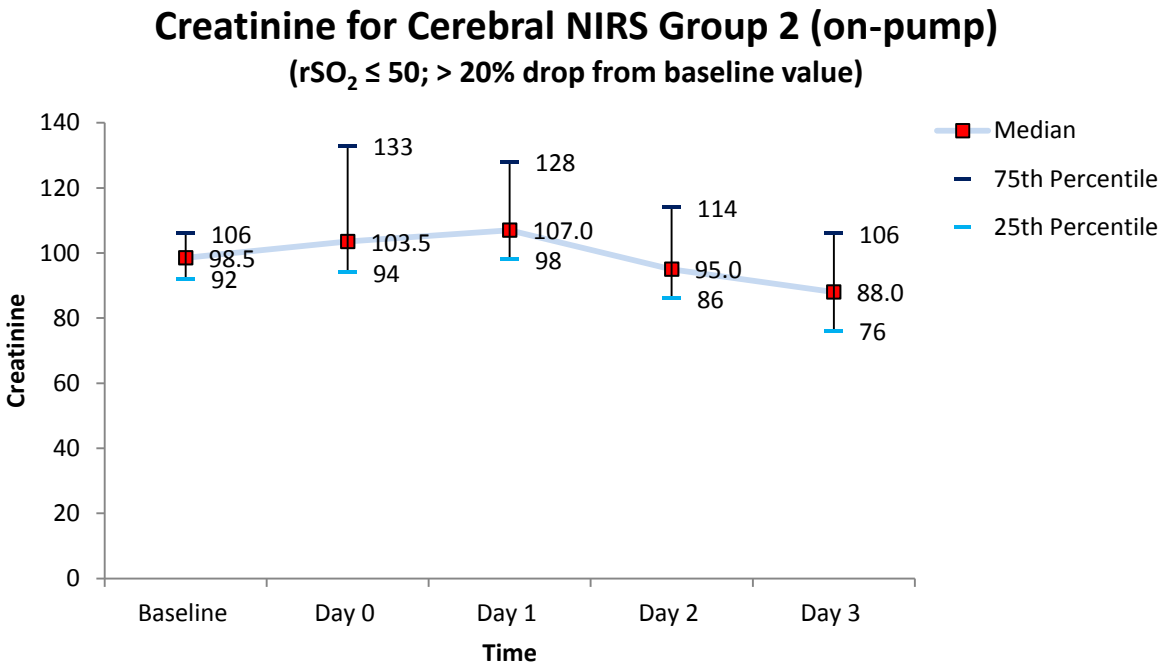


Figure 4.23 Creatinine for Cerebral NIRS Group 2 (on-pump CABG surgery)

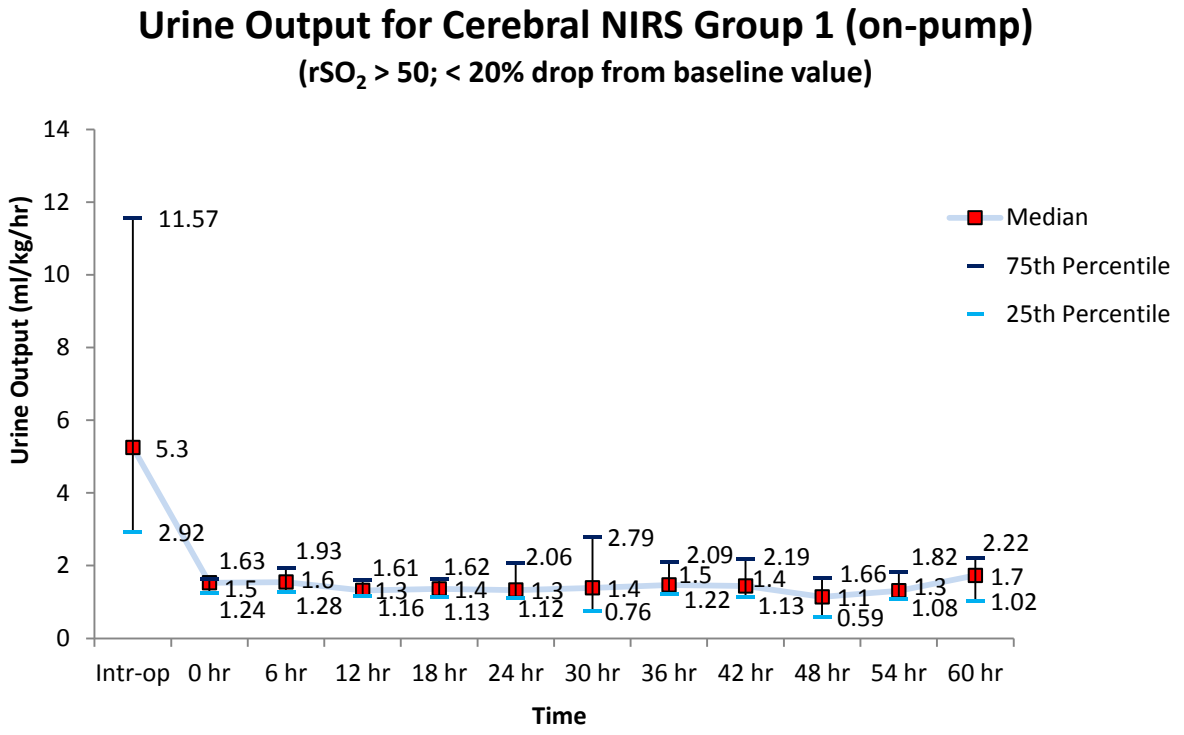


Figure 4.24 Urine Output for Cerebral NIRS Group 1 (on-pump CABG surgery)

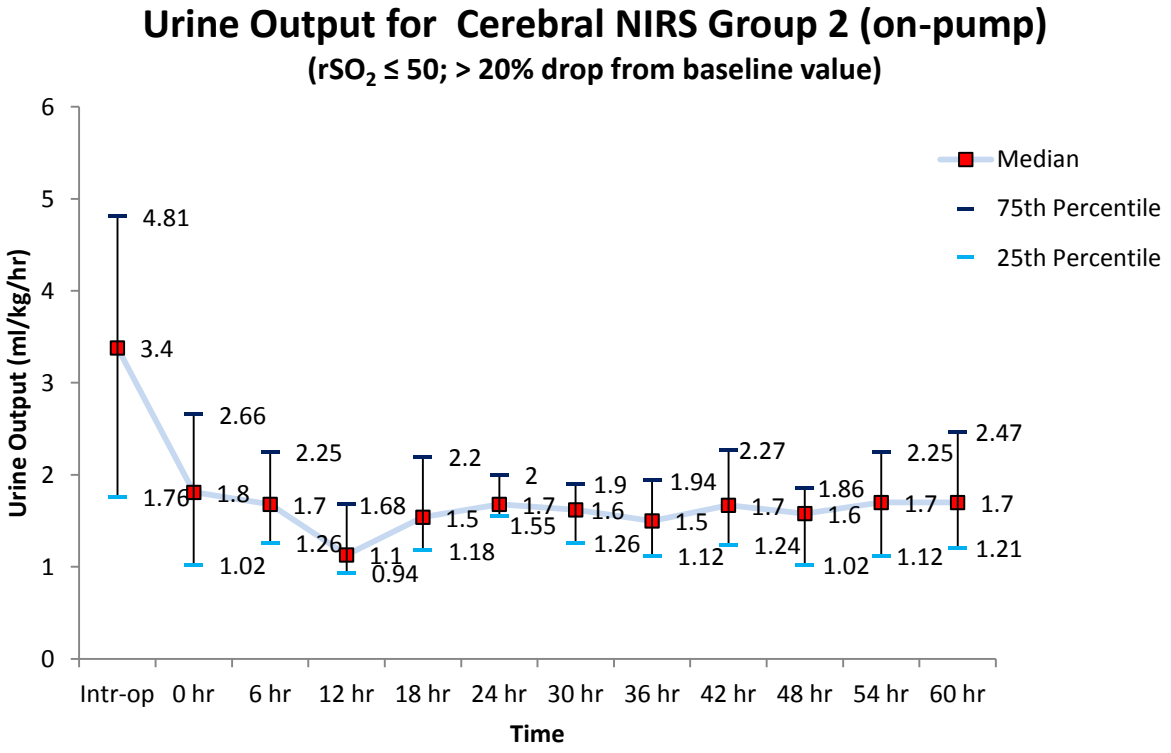


Figure 4.25 Urine output for Cerebral NIRS Group 2 (on-pump CABG surgery)

Table 4.12 Renal Function: Group 1 vs. Group 2 (on-pump CABG surgery)

U&E, CREATININE, URINE OUTPUT	GROUP 1 (n=4) Min/Max	GROUP 2 (n=26) Min/Max	p-VALUE
Sodium (mEq/L)			
Baseline	135/145	135/145	0.8058
Day 0	136/146	136/151	0.3404
Day 1	135/139	129/148	0.2092
Day 2	134/139	131/148	0.7991
Day 3	133/137	131/146	0.8653
Potassium (mEq/L)			
Baseline	2.5/3.9	3.1/4.9	**0.0089**
Day 0	3.1/4.9	2.7/8.8	0.4615
Day 1	4.3/4.8	3.8/5.6	0.2088
Day 2	4.0/4.4	3.8/5.0	0.0559
Day 3	3.6/4.2	3.8/4.7	0.3111
Chloride (mEq/L)			
Baseline	102/107	102/112	0.2697
Day 0	105/118	102/116	0.9510
Day 1	107/115	101/119	1.000
Day 2	104/112	103/116	0.8860
Day 3	103/110	98/117	0.7007
Urea (mEq/L)			
Baseline	3.7/6.5	2.8/9.4	0.7835
Day 0	4.0/5.2	2.7/7.1	0.8546
Day 1	3.9/5.7	3.5/11.5	0.1210
Day 2	3.5/8.2	3.2/17.6	0.2291
Day 3	5.1/8.3	3.3/20.5	0.7061
Creatinine (mEq/L)			
Baseline	68/125	76/137	0.3138
Day 0	82/131	79/138	0.2459
Day 1	71/104	74/204	**0.0398**
Day 2	66/97	66/230	0.1944
Day 3	70/91	54/217	0.4513
Urine Output (ml/kg/hr)			
Intra-operative	2.79/15.69	0.39/8.09	0.2001
0 hours	1.02/1.66	0.60/11.76	0.4127
6 hours	1.15/2.18	0.68/3.12	0.7329
12 hours	1.11/1.80	0.60/3.35	0.4528
18 hours	1.08/1.71	0.46/4.16	0.4528
24hours	1.11/2.58	0.97/2.84	0.3393
30 hours	0.75/3.58	1.04/3.25	0.7329
36 hours	1.04/2.63	0.83/2.74	0.7848
42 hours	1.09/2.67	0.83/3.33	0.8312
48 hours	0.59/1.66	0.55/2.60	0.2712
54 hours	1.08/1.82	0.63/3.20	0.4730
60 hours	1.02/2.22	0.62/3.36	0.8110

The data was given as median with 25th and 75th percentile. The p-values were calculated with t-test and the Kruskal-Wallis-Test. Categorical variables are demonstrated with an n-value and percentages. The p-values were calculated with Chi-square test. A $p < 0.05$ indicates statistical significance. [mEq/L: mill equivalents per litre; ml/ kg/ hr: millilitres per kilogram per hour]

4.3.3.4 Post-operative Complications/Outcomes: Group 1 vs. Group 2 (on-pump CABG surgery)

The patients in group 1 had no post-operative complications. The post-operative complications reported for group 2 were: re-intubation 3.85% (n=1), pulmonary complications 3.58% (n=1), GIT complications 3.58% (n=1), atrial fibrillation 3.58% (n=1), sternal wound infection 3.58% (n=1), and septicaemia 3.58% (n=1). Seventy five percent (n=3) of patients in group 1 had a post-operative blood transfusion and 50% (n=13) in group 2. Because of the small sample size in group 1, statistical analysis is senseless and therefore data is displayed in a frequency table (Table 4.13).

Table 4.13 Post-operative Outcomes and Complications: Group 1 vs. Group 2 (on-pump CABG surgery)

OUTCOME VARIABLES	GROUP 1 (n=4)	GROUP 2 (n=26)
Mortality		
Yes	-	-
No	4 (100%)	26 (100%)
Return to ICU		
Yes	-	-
No	4 (100%)	26 (100%)
Re-intubation		
Yes	-	1 (3.85%)
No	4 (100%)	25 (96.15%)
Re-operation		
Yes	-	1 (3.85%)
No	4 (100%)	26 (100%)
Post-operative MI		
Yes	-	-
No	4 (100%)	26 (100%)
Pulmonary complications		
Yes	-	1 (3.85%)
No	4 (100%)	25 (96.15%)
Neurological complications		
Yes	-	-
No	4 (100%)	26 (100%)
Renal complications		
Yes	-	-
No	4 (100%)	26 (100%)
GIT complications		

Yes	-	1 (3.85%)
No	4 (100%)	25 (96.15%)
Multi system failure		
Yes	-	-
No	4 (100%)	26 (100%)
Post-operative dissection of major arteries		
Yes	-	-
No	4 (100%)	26 (100%)
Acute limb ischemia		
Yes	-	-
No	4 (100%)	26 (100%)
Heart block		
Yes	-	-
No	4 (100%)	26 (100%)
Atrial fibrillation		
Yes	-	1 (3.85%)
No	4 (100%)	25 (96.15%)
Cardiac arrest		
Yes	-	-
No	4 (100%)	26 (100%)
Anticoagulant complications		
Yes	-	-
No	4 (100%)	26 (100%)
Tamponade		
Yes	-	-
No	4 (100%)	26 (100%)
Sternal wound infection		
Yes	-	1 (3.85%)
No:	4 (100%)	25 (96.15%)
Septicaemia		
Yes	-	1 (3.85%)
No	4 (100%)	25 (96.15%)
Post-operative blood transfusion		
Yes	3 (75.00%)	13 (50.00%)
No	1 (25.00%)	13 (50.00%)
Length of hospital stay (days)		
Median	8.00	8.00
25th percentile	6.50	7.00
75th percentile	10.00	12.00
Length of ICU stay (days)		
Median	3.00	3.00
25th percentile	2.50	3.00
75th percentile	3.50	3.00
Ventilation time (hours)		
Median	13.00	12.00
25th percentile	10.00	12.00
75th percentile	14.00	16.00

The data is given as median with 25th and 75th percentile. The p-values were calculated with t-test and the Kruskal-Wallis-Test. Categorical variables are demonstrated with an n-value and percentages. The p-values were calculated with Chi-square test. A $p < 0.05$ indicates statistical significance. [MI: Myocardial infarction; ICU: Intensive Care Unit; GIT: Gastro-intestinal system].

4.3.4 Comparison of Cerebral NIRS values between Group 1 *(rSO2 > 50; < 20% drop from baseline value)* & Group 2 *(rSO2 ≤ 50; > 20% drop from baseline value)* in patients receiving Off-Pump CABG surgery (Analysis 4)

In analysis 4 all off-pump CABG patients (n=30) were subdivided into two cerebral NIRS groups (group 1 = rSO_2 > 50; < 20% from baseline value and group 2 = rSO_2 ≤ 50; > 20% from baseline value). The cerebral NIRS values of the two groups were then compared with MMSE (Table 4.14), intra-operative hemodynamic data (Table 4.15), renal function (Figure 4.26 - 4.37; Table 4.16), and all other post-operative complications/outcomes (Table 4.17). Thirty patients received off-pump CABG surgery of which 83.33% (n=25) fell in group 1 and 16.67% (n = 5) in group 2. It is important to note that 83.33% of patients undergoing off-pump surgery, had satisfactory NIRS values.

4.3.4.1 Mini-Mental State Examination (MMSE): Group 1 vs. Group 2 (off-pump CABG surgery)

Again, no statistical significant differences were found in the pre- and post-operative MMSE between the 2 groups of the patients that received off-pump CABG surgery (Table 4.14). The number of patients that received the MMSE pre-operatively in group 1 was 72% (n=18) and in group 2 were 100% (n=5). Post-operatively 64% (n=16) in group 1 received MMSE and 100% (n=5) in group 2. The difference in numbers are ascribe to pre-operative sedation medication and refusal of the patients to take the test.

Table 4.14 MMSE: Group 1 vs. Group 2 (off-pump CABG surgery)

	GROUP 1				GROUP 2				p-VALUE
	N	median	25th percentile	75th percentile	n	median	25th percentile	75th percentile	
Pre	18	28.00	27.00	29.00	5	29.00	24.00	29.00	0.8785
Post	16	28.00	25.50	29.50	5	25.00	23.00	28.00	0.1905
Diff	16	0	-1.5	1.50	5	4.00	1.00	1.00	0.2218

The continuous variables are given as median with 25th and 75th percentile. The p-values were calculated with t-test and the Kruskal-Wallis-Test. A $p < 0.05$ indicates statistical significance. Pre: pre-operative MMSE; Post: post-operative MMSE; Diff: difference between pre-operative MMSE and post-operative MMSE.

4.3.4.2 Intra-operative Hemodynamic Monitoring: Group 1 vs. Group 2 (off-pump CABG surgery)

The intra-operative hemodynamic data displayed no statistical significant differences between the two groups receiving off-pump CABG surgery (Table 4.15).

Table 4.15 Intra-operative Hemodynamic Data: Group 1 vs. Group 2 (off-pump CABG surgery)

VARIABLES	GROUP 1 (n=25)	GROUP 2 (n=5)	p-value
Heart Rate (beats/min)	n=24		
Median	68.00	69.00	0.6645
25th percentile	59.50	68.00	-
75th percentile	76.00	72.00	-
Mean Arterial Pressure (mmHg)	n=24		
Median	101.195	81.59	0.5637
25th percentile	79.43	80.53	-
75th percentile	123.49	106.10	-
Systolic Pressure (mmHg)	n=24		
Median	142.53	125.44	0.4884
25th percentile	109.855	121.31	-
75th percentile	174.30	161.71	-
Haemoglobin (kPa)			
Median	13.70	12.30	0.4519
25th percentile	12.50	12.30	-
75th percentile	14.90	12.60	-
O_2SAT (%)			
Median	95.00	95.50	0.7595
25th percentile	93.90	93.20	-
75th percentile	96.60	97.00	-
pO_2 (kPa)			
Median	71.80	69.30	0.5222
25th percentile	66.70	61.30	-
75th percentile	107.30	126.10	-

The data is given as median with 25th and 75th percentile. The p-values were calculated with t-test and the Kruskal-Wallis-Test. A $p < 0.05$ indicates statistical significance. [min: minute; mmHg: millimetres mercury; kPa: kilopascal; O_2SAT: Oxygen Saturation; %: percentage PO_2: Partial Pressure of Oxygen]

4.3.4.3 Renal Function: Group 1 vs. Group 2 (off-pump CABG surgery)

No statistical significant differences were seen between group 1 and 2 with reference to potassium, urea and creatinine for the patients that received off-pump CABG surgery (Table 4.16).

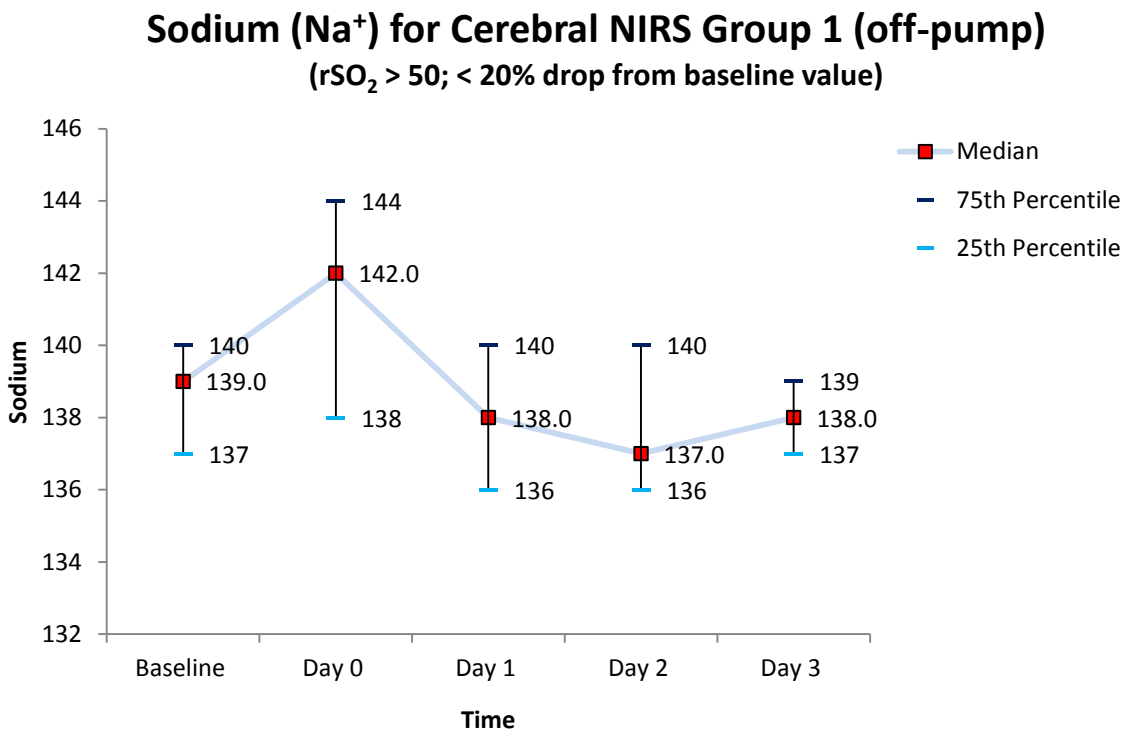


Figure 4.26 Sodium for Cerebral NIRS Group 1(off-pump CABG surgery)

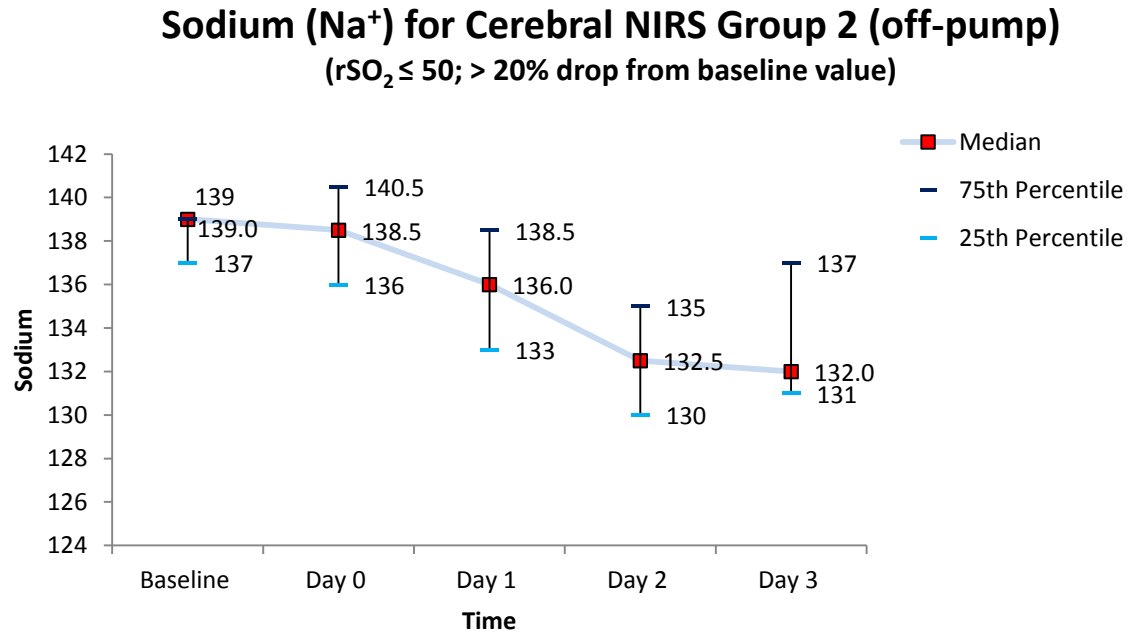


Figure 4.27 Sodium for Cerebral NIRS Group 2 (off-pump CABG surgery)

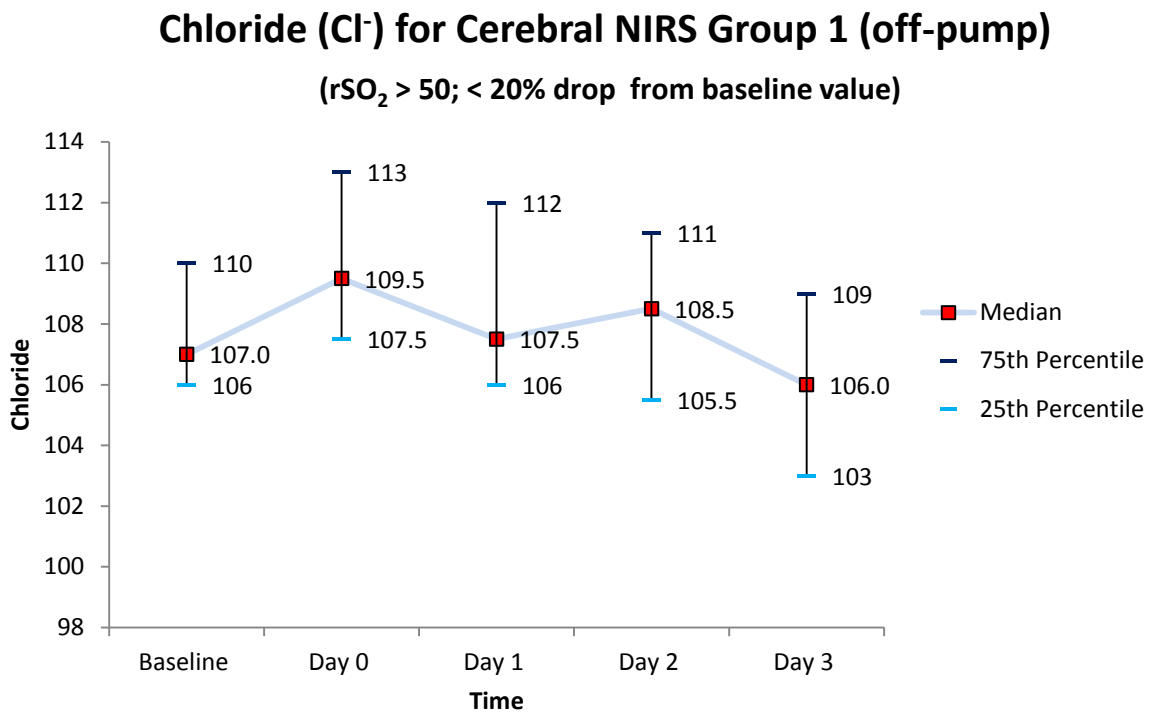


Figure 4.28 Chloride for Cerebral NIRS Group 1 (off-pump CABG surgery)

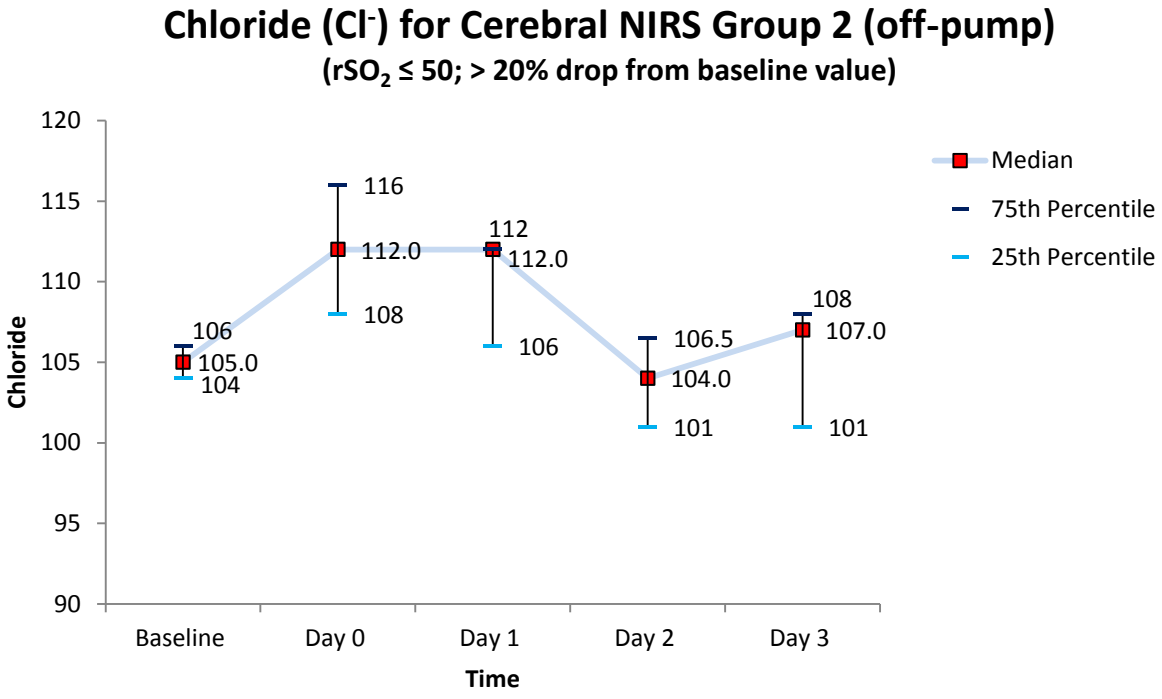


Figure 4.29 Chloride for Cerebral NIRS Group 2 (off-pump CABG surgery)

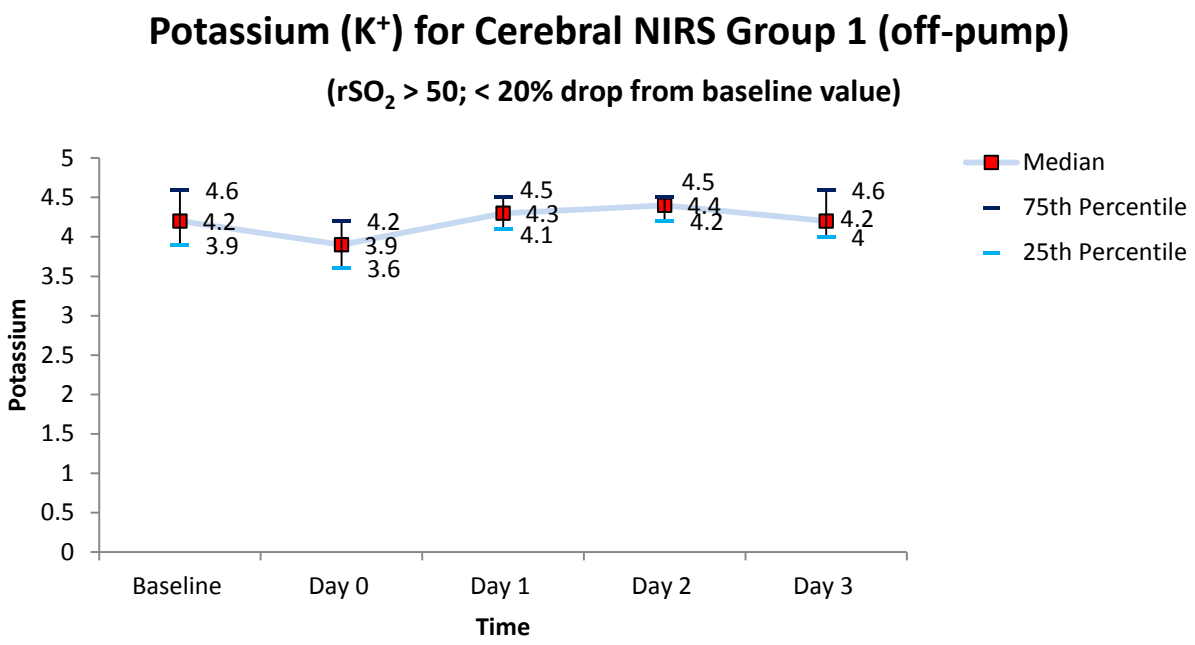


Figure 4.30 Potassium for Cerebral NIRS Group 1 (off-pump CABG surgery)

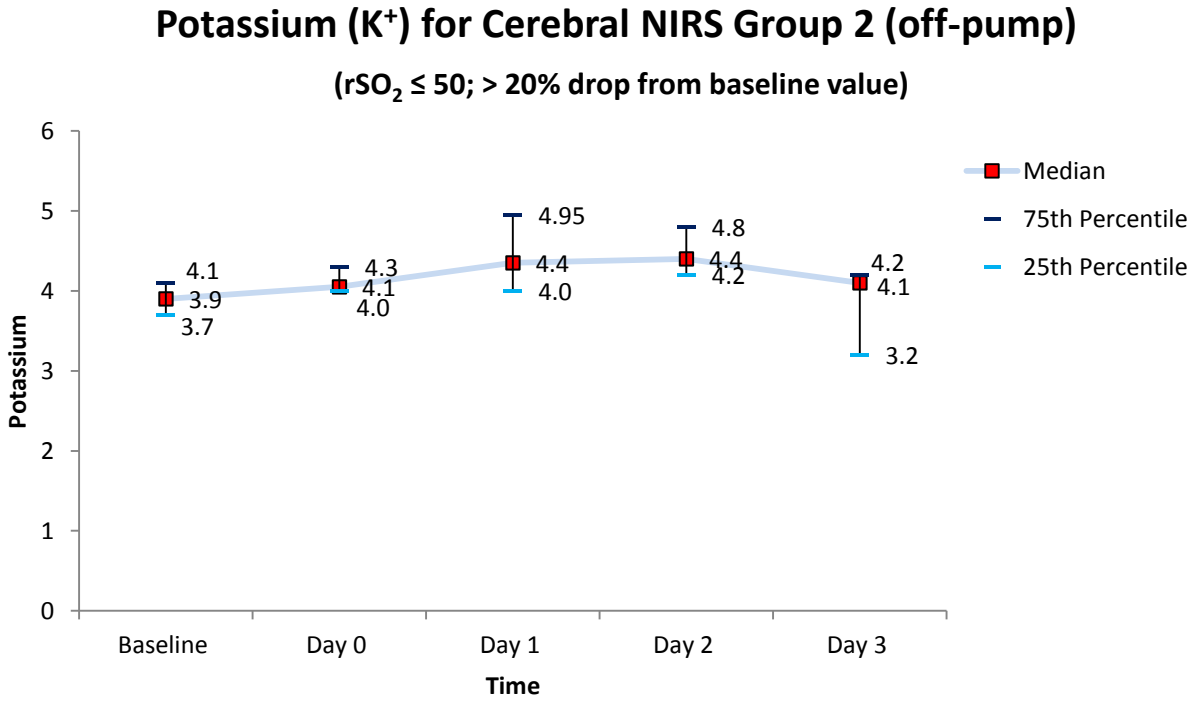


Figure 4.31 Potassium for Cerebral NIRS Group 2 (off-pump CABG surgery)

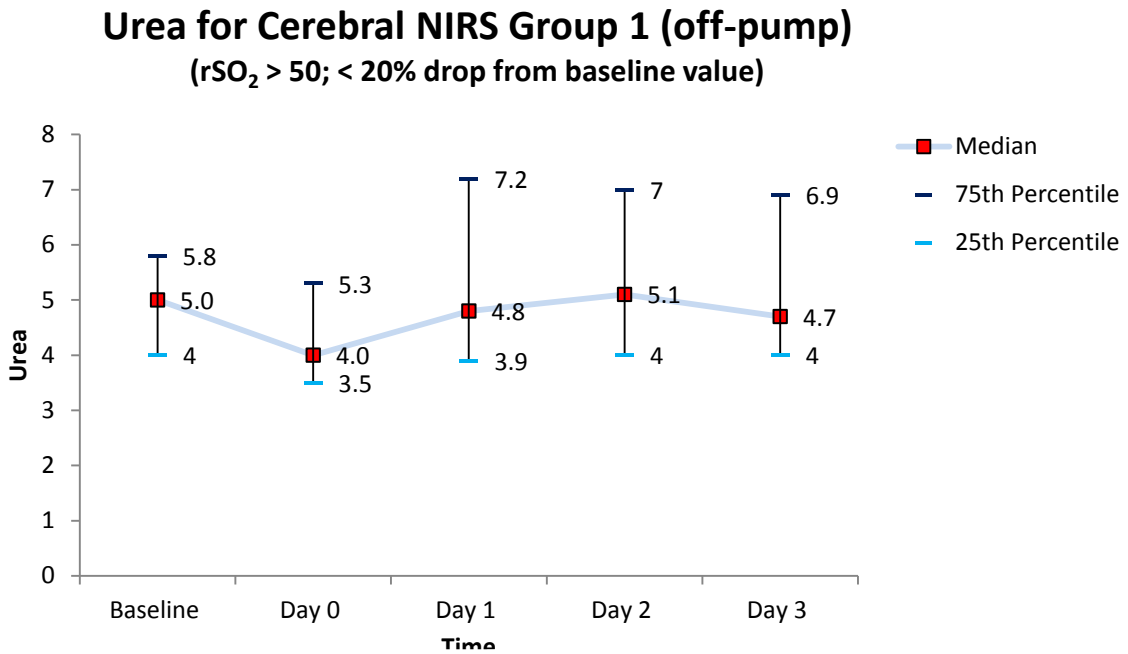


Figure 4.32 Urea for Cerebral NIRS Group 1 (off-pump CABG surgery)

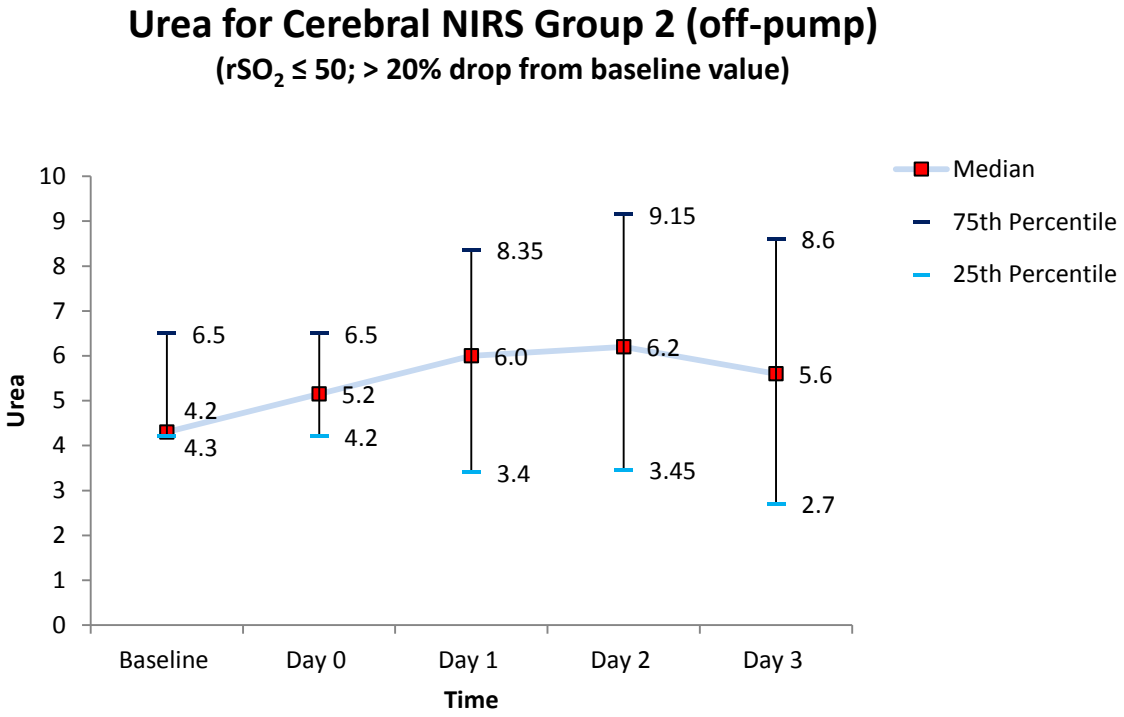


Figure 4.33 Urea for Cerebral NIRS Group 2 (off-pump CABG surgery)

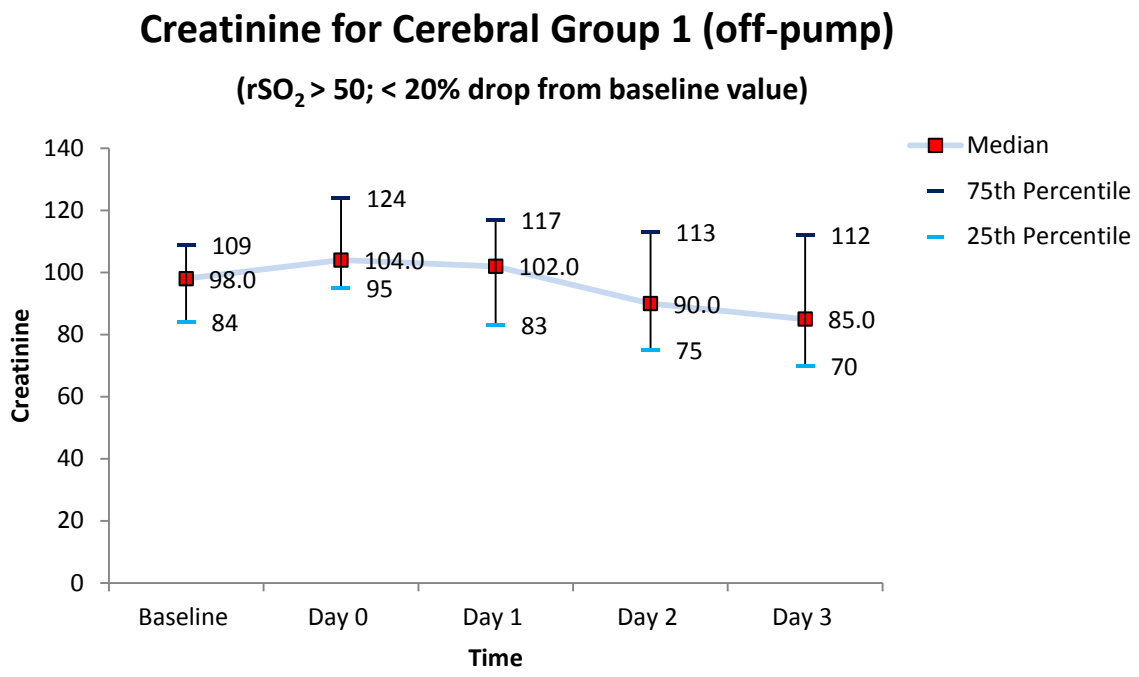


Figure 4.34 Creatinine for Cerebral NIRS Group 1 (on-pump CABG surgery)

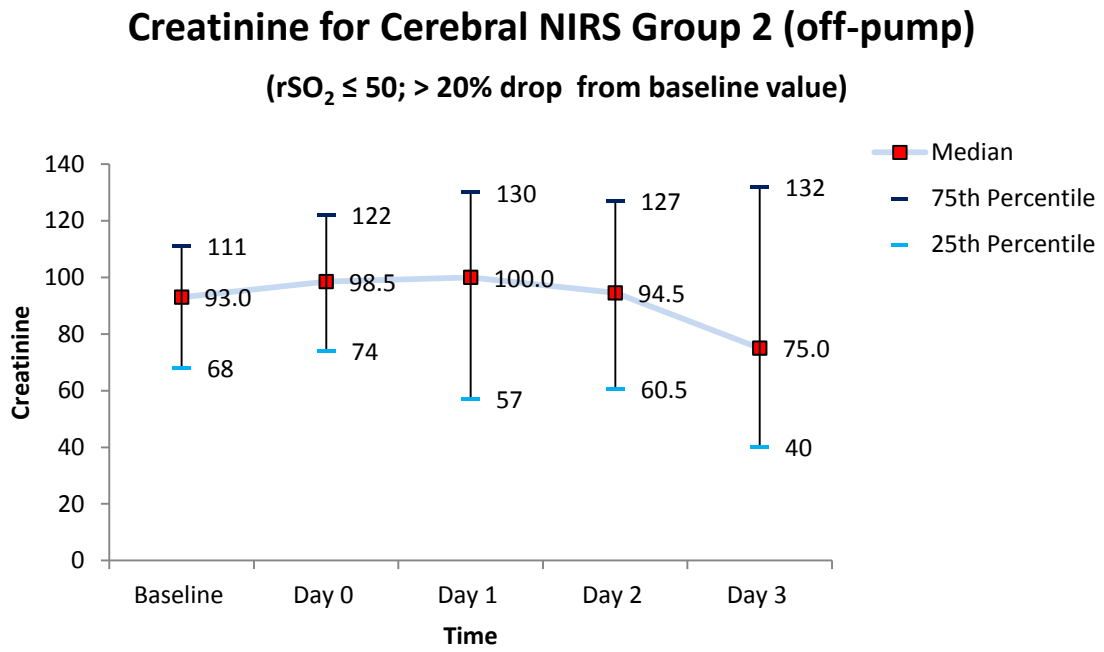


Figure 4.35 Creatinine for Cerebral NIRS Group 2 (off-pump CABG surgery)

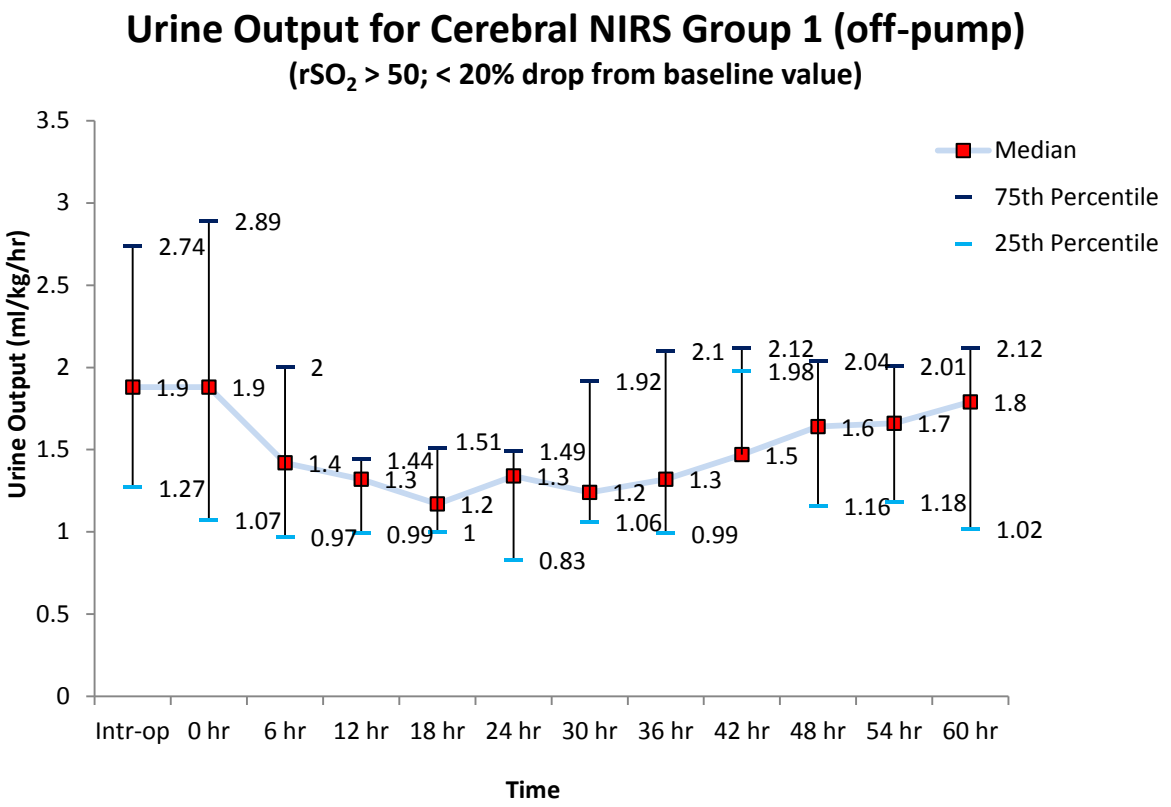


Figure 4.36 Urine output for Cerebral NIRS Group 1 (off-pump CABG surgery)

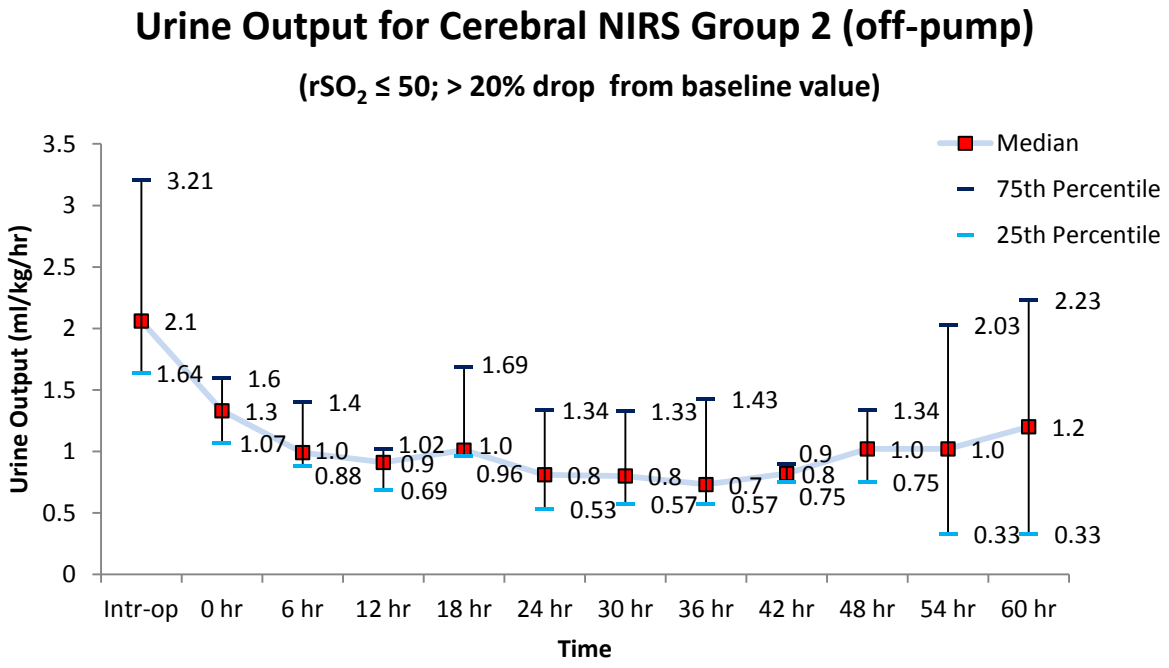


Figure 4.37 Urine output for Cerebral NIRS Group 2 (off-pump CABG surgery)

The increased urine output at 12 hrs (p=0.0440), 42 hrs (p=0.0064) and 48hrs (p=0.0357) post-operatively might once again reflect a period of polyurea secondary to impaired renal flow, but the creatinine values showed no difference (Table 4.3.4.3). It might also reflect mobilization of sequestrated fluid post-operatively.

Table 4.16 Renal Function: Group 1 vs. Group 2 (off-pump CABG surgery)

U&E, CREATININE, URINE OUTPUT	GROUP 1 (n=25) Min/Max	GROUP 2 (n=5) Min/Max	p-VALUE
Sodium (mEq/L)			
Baseline	136/144	130/139	0.1647
Day 0	135/152	135/141	0.1593
Day 1	130/152	132/139	0.3018
Day 2	133/144	130/135	**0.0057**
Day 3	131/145	131/137	0.0661
Potassium (mEq/L)			
Baseline	3.3/4.8	3.6/4.5	0.1984
Day 0	2.7/4.8	4.0/4.5	0.2044
Day 1	3.6/6.4	3.9/5.3	0.8640
Day 2	3.7/5.2	4.1/5.1	0.6811
Day 3	3.8/5.2	3.2/4.2	0.3094
Chloride (mEq/L)			
Baseline	102/117	95/106	**0.0250**
Day 0	102/118	108/116	0.4634
Day 1	100/114	106/112	0.5825
Day 2	103/115	100/107	0.0517
Day 3	100/112	101/108	0.7550
Urea (mEq/L)			
Baseline	1.6/7.4	3.7/8.9	0.6359
Day 0	2.2/6.4	4.2/6.9	0.0941
Day 1	1.7/9.1	3.0/8.5	0.8377
Day 2	1.5/11.6	2.9/9.9	0.7385
Day 3	2.8/12.4	2.7/8.6	0.7364
Creatinine (mEq/L)			
Baseline	63/131	54/148	0.7807
Day 0	67/151	62/133	0.6820
Day 1	71/157	42/132	0.6820
Day 2	67/176	52/134	0.7108
Day 3	65/199	40/132	0.5449
Urine Output (ml/kg/hr)			
Intra-operative	0.58/5.58	0.54/3.86	0.8625
0 hours	0.40/6.40	0.90/1.78	0.3526
6 hours	0.65/2.86	0.85/1.72	0.3139
12 hours	0.67/2.63	0.54/1.07	**0.0440**
18 hours	0.37/2.27	0.92/2.34	0.6421

24hours	0.22/2.76	0.51/1.60	0.3139
30 hours	0.48/2.43	0.36/1.83	0.0744
36 hours	0.73/5.21	0.48/2.06	0.0744
42 hours	0.80/3.62	0.71/0.94	**0.0064**
48 hours	0.80/2.66	0.73/1.40	**0.0357**
54 hours	0.69/3.12	0.33/2.03	0.3918
60 hours	0.68/3.17	0.33/2.23	0.4835

The data was given as median with 25th and 75th percentile. The p-values were calculated with t-test and the Kruskal-Wallis-Test. Categorical variables are demonstrated with an n-value and percentages. The p-values were calculated with Chi-square test. A $p < 0.05$ indicates statistical significance. [mEq/L: mill equivalents per litre; ml/kg/hr: millilitre per kilogram per hour]

4.3.4.4 Post-operative Complications/Outcomes: Group 1 vs. Group 2 (off-pump CABG surgery)

Statistical analysis revealed no statistical differences in post-operative complications/outcomes between group 1(n=25) and group 2 (n=5) for patients that received off-pump CABG surgery (Table 4.17).

The post-operative complications reported for group 1 were: mortality rate 8% (n=2); re-admission to ICU 4% (n=1); re-operation 4% (n=1), renal complications 4% (n=1) and the same for gastro-intestinal complications, multi system failure, atrial fibrillation, and septicemia. Sixteen percent (n=4) of the patients in group 1 had a post-operative blood transfusion. The number of complications for the patients that fell in group 2 was much less. Only 20% (n=1) had post-operative pulmonary complications and 20% (n=1) had a blood transfusion after surgery. The ventilation times ranged from 6 to 9 hours in group 1 and 12 to 18 hours in group 2 with a borderline p-value of 0.0596.

Because of the small sample size in group 2, a statistical analysis is senseless and therefore data is displayed in a frequency table (Table 4.17).

Table 4.17 Post-operative Outcomes and Complications: Group 1 vs. Group 2 (off-pump CABG surgery)

OUTCOME VARIABLES	GROUP 1 (n=25)	GROUP 2 (n=5)
Mortality		
Yes	2 (8.00%)	-
No	23 (92.00%)	5 (100%)
Return to ICU		
Yes	1 (4.00%)	-
No	24 (96.00%)	5 (100%)
Re-intubation		
Yes	-	-
No	25 (100%)	5 (100%)
Re-operation		
Yes	1 (4.00%)	-
No	24 (96.00%)	5 (100%)
Post-operative MI		
Yes	-	-
No	25 (100%)	5 (100%)
Pulmonary complications		
Yes	-	1 (20.00%)
No	25 (100%)	4 (80.00%)
Neurological complications		
Yes	-	-
No	25 (100%)	5 (100%)
Renal complications		
Yes	1 (4.00%)	-
N	24 (96.00%)	5 (100%)
GIT complications		
Yes	1 (4.00%)	-
No	24 (96.00%)	5 (100%)
Multi system failure		
Yes	1 (4.00%)	-
No	24 (96.00%)	5 (100%)
Post-operative dissection of major arteries		
Yes	-	-
No	25 (100%)	5 (100%)
Acute limb ischemia		
Yes	-	-
No	25 (100%)	5 (100%)
Heart block		
Yes	-	-
No	25 (100%)	5 (100%)
Atrial fibrillation		
Yes	1 (4.00%)	-
No	24 (96.00%)	5 (100%)
Cardiac arrest		
Yes	-	-
No	25 (100%)	5 (100%)
Anticoagulant complications		
Yes	-	-
No	25 (100%)	5 (100%)
Tamponade		
Yes	-	-
No	25 (100%)	5 (100%)

Sternal wound infection		
Yes	-	-
No	25 (100%)	5 (100%)
Septicaemia		
Yes	1 (4.00%)	-
No	24 (96.00%)	5 (100%)
Post-operative blood transfusion		
Yes	4 (16.00%)	1 (20.00%)
No	20 (80.00%)	4 (80.00%)
Length of hospital stay (days)		
Median	8.00	7.00
25th percentile	6.00	6.00
75th percentile	11.00	8.00
Length of ICU stay (days)		
Median	3.00	3.00
25th percentile	2.00	3.00
75th percentile	3.00	4.00
Ventilation time (hours)		
Median	9.00	12.00
25th percentile	6.00	12.00
75th percentile	12.00	18.00

The data is given as median with 25th and 75th percentile. The p-values were calculated with t-test and the Kruskal-Wallis-Test. Categorical variables are demonstrated with an n-value and percentages. The p-values were calculated with Chi-square test. A $p < 0.05$ indicates statistical significance. MI: Myocardial infarction; ICU: Intensive Care Unit; GIT: Gastro-intestinal system.

Chapter 5

DISCUSSION

5.1 INTRODUCTION

The Somanetics® INVOS® Cerebral Oximeter presents a new "vital sign" called regional saturation of oxygen (rSO_2). The system alerts clinicians of cerebral desaturation and gives an early warning of regional oxygen imbalances that may be encountered in surgery or in the cardiac laboratory. A decline in cerebral oximeter values, during CPB, occurs frequently in cardiac surgery and reflect the changing hemodynamic profile of balance between brain oxygen delivery and consumption. Since low rSO_2 values correlate with adverse neurological outcome, continuous assessment via cerebral oximetry, using near-infrared spectroscopy, is a valuable patient management tool and low values can be corrected with simple interventions.

A decline in rSO_2 below 50, or a decline of more than 20 percent from baseline is cause for concern and warrants the initiation of intervention. Absolute values, below 40 and a drop of more than 25 percent from baseline, are associated with neurological dysfunction and other adverse outcomes. A $rSO_2 < 50$ or drop of 25% from baseline are linked to cerebral hypoperfusion and is associated with post-operative neurological dysfunction. In this study the cerebral values were interpreted using the threshold values of $rSO_2 >50$ or < 20% drop from baseline and $rSO_2 < 50$ or > 25% drop from baseline as published by Edmonds and co-workers, (2004).

5.2 PRE-OPERATIVE DEMOGRAPHIC AND CLINICAL DATA (ON-PUMP VERSUS OFF-PUMP)

Essentially the patients in the on-pump and off-pump groups were considered to be similar regarding risk factors and co-morbidities. No differences could be demonstrated between the on-pump and off-pump group with regard to pre-operative demographics. The only difference between the groups was the amount of pre-operative acute MI's [on-pump (n=14; 47%) versus off-pump (n=22; 73%)]. Therefore, we conclude that the study population was similar in nature with no clear distinguishable factors between the on-pump and off-pump groups.

The pre-operative Mini-mental State examination showed no difference between the two groups and no cognitive impairment could be demonstrated using either technique. Both the on-pump and off-pump group had a median value above 27. It was very difficult to accurately interpret the data due to patients refusing to take the test, educational level, and pre-operative medication. Another factor that could contribute was the fact that the examination was done by a perfusionist and not a qualified occupational therapist with professional interview and interpretation skills.

5.3 CEREBRAL NIRS PERFORMED ON ON-PUMP AND OFF-PUMP CABG GROUPS (ANALYSIS 1)

5.3.1 Cerebral Near Infrared Spectroscopy (NIRS)

It is clear from the results that patients that received on-pump CABG surgery had more compromised (compromised = rSO_2 <50; ≥ 20% drop from baseline) cerebral flow than those patients that received off-pump CABG surgery. In the on-pump group 86.87% (n=26) had compromised cerebral blood flow and only 16.67% (n=5) in the off-pump group had compromised cerebral blood flow. It is important to note that of all cerebral NIRS vales recorded the lowest NIRS value of each patient was used for data analysis in both the on-pump and off-pump groups. The median values between the on-pump and off-pump were 69 and 65.5 respectively with no statistical significant difference between the two groups (p=0.3398).

5.3.2 Cerebral NIRS linked to intra-operative events (on-pump versus off-pump)

The cerebral NIRS values of the on-pump and off-pump groups were linked to pre-determined intra-operative events in order to reflect the hemodynamic impact of events during these procedures on oxygen delivery (as reflected in NIRS values). While events are non-comparable between groups, time lines were used and median values were compared between on and off-pump groups. No statistical significant difference could be demonstrated between the time lines (events) between the on-pump and off-pump groups.

5.4 COMPARISON OF CEREBRAL NIRS VALUES BETWEEN GROUP 1 (rSO_2= ≥ 50, < 20% drop from baseline value) AND GROUP 2 (rSO_2 < 50, > 20% drop from baseline value) IRRESPECTIVE OF SURGICAL TECHNIQUE (ANALYSIS 2)

5.4.1 Cerebral Near Infrared Spectroscopy (NIRS)

Of the 60 patients 29 patients fell in group 1 and 31 patients in group 2. The NIRS values showed a statistical significant difference (p=0.0004) between group 1 and group 2. It is important to note that the majority of patients with reduced cerebral flow/oxygen delivery (group 2) as reflected in cerebral NIRS, had on-pump CABG procedures (84% of risk group 2).

5.4.2 Mini-mental State Examination

The cerebral NIRS values in group 1 was above 27 (median score 28, pre- and postoperative), therefore none of the patients in group 1 showed any cognitive decline after CABG surgery. On the other hand the median pre-operative score for group 2 was 28 but after CABG surgery it dropped to 26 indicative of mild cognitive impairment (Lopez *et al*., 2005). This corresponds with the cerebral NIRS values because group 2 had compromised cerebral flow during surgery (rSO_2 < 50, > 20% drop from baseline value). The MMSE revealed no statistical significant difference between the two groups.

5.4.3 Renal Function

A statistical significant difference was found for urinary output (p=0.0108) on day 1 and in sodium (p = 0.0486) and urea values (p=0.0263) on day 2 between the two groups.

Group 2 had a higher sodium, urea and urinary output minimum maximum range than group 1. Therefore, these differences show that a NIRS reduction of more than 20 % in baseline and values of less than 50, with a median NIRS value of 63 can possibly be associated with a decline in post–operative renal function. The elevated urea value, with higher sodium and urine output might reflect a polyuric phase of early renal dysfunction. The creatinine values were however not different between the groups.

The reason why the creatinine remained relatively stable could be attributed to the compensatory mechanism of the kidneys. Serum creatinine level is a late indicator of renal injury. According to McBride and Skoyles (2004) a patient can lose up to 50% of his renal tubular function before his creatinine levels will start to decline.

5.4.4 Post-operative Outcomes and Complications

No major post-operative differences could be demonstrated between the two groups. The only difference between the two groups was recorded for the ventilation time. Although group 2 demonstrated longer post-operative ventilation

times (median group 2 = 12.00 versus median group 1 = 10.00) the median length of stay for group 1 and 2 was exactly the same (8 days).

5.5 COMPARISON OF CEREBRAL NIRS VALUES BETWEEN GROUP 1 (rSO2 > 50; < 20% drop from baseline value) & GROUP 2 (rSO2 ≤ 50; > 20% drop from baseline value) IN PATIENTS RECEIVING ON-PUMP CABG SURGERY (ANALYSIS 3)

5.5.1 Cerebral Near Infrared Spectroscopy (NIRS)

All on-pump CABG patients (n=30) were subdivided into group 1 (satisfactory cerebral oxygenation) and group 2 (compromised cerebral oxygenation). Although median NIRS values were above 50, a total of 26 (86.67%) patients fell in group 2. It is important to take note that the times spend "under the curve" was restricted due to intervention by the perfusionist and anaesthesiologist.

5.5.2 Mini-mental State Examination

The MMSE results of Group 1 pre- and post-operatively were both 29 therefore no cognitive decline were present after surgery [score ≥ 27 = normal (Lopez *et al*., 2005)]. However the number of patients that fell in group 1 was only 4 of which 3 received MMSE pre- and post-operatively.

Although group 2 had compromised cerebral blood flow (more than 20% drop from baseline) the MMSE scores were also ≥ 27. The decline in cerebral NIRS values in group 2 (pre-operatively = 28, post-operatively = 27) was not sufficient enough to cause cognitive impairment in these patients. The MMSE revealed no difference

between the two groups (p>0.05) but factors as previously stated could have contributed to compromised data and should be taken into consideration.

5.5.3 Renal Function

A statistical significant difference was found for creatinine (p=0.0398) on day 1 and a statistical baseline difference for potassium (p = 0.0089).

In Group 2 we found an increase in both urea and creatinine levels as well as a decrease in urine output post-operatively, which suggest that a NIRS reduction of more than 20 % in baseline and values of less than 50 during CABG surgery, with a minimum median NIRS value of 51 has no association with post–operative renal function.

5.5.4 Post-operative Outcomes and Complications

No major post-operative differences could be demonstrated between the two groups. Due to small sample size in group 1, statistical data was counterintuitive.

5.6 COMPARISON OF CEREBRAL NIRS VALUES BETWEEN GROUP 1 (rSO2 > 50; < 20% drop from baseline value) & GROUP 2 (rSO2 ≤ 50; > 20% drop from baseline value) IN PATIENTS RECEIVING OFF-PUMP CABG SURGERY (ANALYSIS 4)

5.6.1 Cerebral Near Infrared Spectroscopy (NIRS)

All off-pump CABG patients (n=30) were subdivided into group 1 (satisfactory cerebral oxygenation) and group 2 (compromised cerebral oxygenation). Only 5 of these patients had a decrease in cerebral oxygen delivery (group 2) with a minimum median value of 52, therefore above 50, but had a more than 20% drop from the baseline value.

5.6.2 Mini-mental State Examination

The decline in cerebral NIRS values in the group 1 was not sufficient enough to cause cognitive impairment in these patients. Both the median pre- and post-operative MMSE scores were above 27. The patients in group 2 did display cognitive decline because the pre-operative score of 29 dropped to 25 post-operatively. However only 5 patients fell in group 2.

Pre- and post-operatively no statistical difference were found between group 1 and group 2 ($p>0.05$).

5.6.3 Renal Function

In off-pump CABG patients, a statistical significant difference was found for sodium (p=0.0057)) on day 2 and in urine output (p = 0.0440, p = 0.0064, p = 0.0357 respectively) at 12, 42, and 48 hours post-operatively between the two groups.

In both groups a decrease in post-operative urinary output was observed. Both groups also showed an increase in urea levels, but an increase in creatinine levels could only be found in group 1. Ascione and colleagues (2001) reported that although off-pump CABG surgery minimizes renal injury, surgical manipulation can cause a definite degree of post-operative renal dysfunction.

5.6.4 Post-operative Outcomes and Complications

No major post-operative differences could be demonstrated between the two groups. The only notable difference between the two groups was recorded for the ventilation time. Group 2 demonstrated longer post-operative ventilation times (median group 2 = 12.00 versus median group 1 = 9.00).

5.7 GENERAL DISCUSSION

Whether or not off-pump surgery is better than on-pump surgery is widely debatable. Although some differences were found during on- and off-pump surgery, there were no significant differences regarding post-operative outcomes and complication between the two groups.

No neurological impairment took place in any of the patients, which can be due to the small amount of time spent under the curve (decrease 20% from baseline or values below 50) due to interventions by the perfusionist and anaesthesiologist. If no corrective action was taken to restore decrease NIRS values the time spend under the curve could have been calculated using Slater's formula (Slater *et al*., 2009).

rSO_2 score = 50%; rSO_2 - current rSO_2 (%) x time (seconds)

The rSO_2 score generated is an area under the curve measurement, which accounts for both depth and duration of desaturation below the 50% saturation threshold. However, in this study the researcher did notice that NIRS could be associated with early tubular kidney function impairment in CABG surgery, which led to the polyuric phase. Cerebral NIRS should be further investigated as a marker for more than just cerebral microcirculation.

MMSE didn't show any differences between the two groups. A decline in the MMSE scores were reported for the patients that fell in group 2 who had compromised cerebral oxygenation. To state that these patients had mild cognitive impairment as indicated by the criteria published by Lopez *et al.*, (2005) is debatable. The data

was compromised due to several factors: (a) the number of participants in some of these groups were limited to only 3 patients (b) the assessments were made by multiple perfusionists who were not neurologists or occupational therapists that lack interview and interpretation skills (c) a complete battery of neurocognitive tests were not administered, only MMSE.

Mortality between on- and off-pump groups was not significant and no patterns regarding mortality could be found. Death occurred post-operatively and no NIRS monitoring took place after the patients left the operation room.

Cardiopulmonary bypass is associated with post-operative neurological dysfunction due to microemboli and hypoperfusion (Edmonds *et al.,* 2004), and although OPCAB has become popular over the years, surgical techniques and manipulation of the heart can result in compromised cerebral blood flow (Murkin *et al.,* 2000).

Non-pulsatile CPB, inflammatory responses to bypass, hemodilution, and the release of free radicals contribute to post-operative renal failure (de Jaegere and Suyker, 2002). Ascione and co-workers (2001) suggested that OPCAB technique minimizes renal injury; anaesthesia and manipulation of the heart may cause a definite degree of post-operative renal injury.

Our results indicated that no statistical significant intra-operative events caused a decline in cerebral blood flow. In both groups there were patients with minimum rSO_2 values below 50. In our investigation we did not have a specific algorithm to prevent cerebral desaturation or to restore rSO_2 levels to normal ($rSO_2 > 50$). In

regards to our findings in Analysis 1, there were no differences between on- and off-pump patients.

Chapter 6

CONCLUSION

6.1 GENERAL

Although the study population was relatively small, the use of cerebral oximetry intra-operatively, (especially in on-pump cardiac surgery patients), showed a tendency towards less renal function impairment in patients with absolute NIRS values > 50 or where there was < 20% drop from baseline. However, the absolute values remained mostly within the normal range. It is probably important to consider the time spend below 50 or a drop of more than 20%, and to make use of the Slater score to determine whether or not the patients were at increase risk for post-operative complications (Slater *et al*., 2007) and with an increased study population, this is recommended.

Although Ascione and co-workers (2001) stated that OPCAB is associated with less neurological dysfunction and renal insufficiency, this could not be proven by the present study. Whether or not OPCAB is better than on-pump CABG surgery is still debatable and as this study was underpowered, we cannot draw a definitive conclusion from our results.]\

The Somanetic INVOS system seems to be an important tool in theatres, and with active interventions to keep values > 50 and to prevent a drop of more than 20% from baseline, it may improve patient outcomes. It is recommended that anaesthesiologists and perfusionists make use of the proposed algorithm presented

by Denault and colleagues (2007) (Appendix C) as a guideline to optimalize cerebral perfusion and oxygen transfer.

During the research study, fluctuations in NIRS values led to perfusion as well as anaesthetic interventions. These interventions limited the periods spend "under the curve" and may in itself been a limitation of the study.

In order to elucidate the value of NIRS further, a larger study population will be required and a larger absolute number of patients with significant reductions in NIRS values for an extended period of time as described by Slater and co-workers (2007).

The role and usefulness of NIRS has been demonstrated in that timely intervention as occurred during this observational study, lead to similar clinical outcomes , even in the groups of patients that did spent some time, however limited, with impaired NIRS values.

The value of routine NIRS monitoring during cardiac surgery has been re-confirmed in this study.

6.1.1 LIMITATIONS

1. Observational study design.
2. Small sample size.
3. MMSE not done by professional psychiatrist/neurologist.
4. Insufficient number of patient with extended periods of impaired flow.

6.1.2 RECOMMENDATIONS

1. Randomized trial.
2. Increase study population.
3. MMSE assessment done by a qualified neurologist/psychiatrist and repeat the test during the 6 week follow-up.
4. Include additional neuropsychological assessments.

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Appendix A

INFORMED CONSENT

EVALUATION OF NEAR-INFRARED SPECTROSCOPY VALUES BETWEEN ON-PUMP AND OFF-PUMP CORONARY ARTERY BYPASS GRAFT SURGERY IN PATIENTS WITH ACUTE CORONARY SYNDROME.

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 VAN OXIMETRIE WAARDES 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)

Letsatsi: _____

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**

Appendix B

INFORMATION LEAFLETS

EVALUATION OF NEAR-INFRARED SPECTROSCOPY VALUES BETWEEN ON-PUMP AND OFF-PUMP CORONARY ARTERY BYPASS GRAFT SURGERY IN PATIENTS WITH ACUTE CORONARY SYNDROME.

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 patient 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 echocardioFigure and an angiogram at the catheter lab on the second floor, Universitas Hospital. **(Routine practice for ACS).**

C) 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.

D) Mini-Mental state examination (MMSE)

This is a very brief 30 point questionnaire test that will be used to assess cognition. Ms Lindy Liebenberg will conduct this test before and after the intervention procedures and it will take about 10 minutes.

Risks

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

INLIGTINGSDOKUMENT

EVALIASIE VAN OXIMETRIE WAARDES 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) 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.

D) Kognitiewe toestand evalueringstoets

Hierdie is a vinnige 30-punt vraelys wat gebruik gaan word om kognitiewe funksie te evalueer. Me Lindy Liebenberg sal hierdie toets uitvoer voor en na die intervensie en dit sal slegs ongeveer 10 minute neem.

Risiko's

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

Appendix C
PROPOSED CLINICAL ALGORITHM for NIRS

PROPOSED CLINICAL ALGORITHM FOR NIRS

Declining cerebral oximeter values, regarding decreased Cerebral oximetry during CPB, occurs frequently in cardiac surgery and reflect the changing hemodynamic profile of balance between brain oxygen delivery and consumption. Since low rSO_2 values correlate with adverse neurological outcome, continuous assessment via cerebral oximeter, using near-infrared spectroscopy, is a valuable patient management tool. Low cerebral oximeter values can be corrected with simple interventions (Somanetics 2005).

Step 1 : Mechanical obstruction

Arterial malperfusion – The first and most important step when rSO_2 decrease = rule out mechanical obstruction to cerebral blood flow.

Example : Ascending aortic dissection with occlusion in carotid lumen

: Kinking or obstruction, during cerebral perfusion, of the perfusion cannula.

Superior Vena Cava obstruction **– Cerebral venous obstruction via dislocation of heart or venous cannula malposition.**

CPP (Cerebral Perfusion Pressure) = MAP – jugular venous pressure (difference between inflow and outflow pressures) (Denault, Deschamps and Murkin, 2007).

Step 2: ↑ Mean Arterial Pressure

With brain desaturation the most common intervention is to maintain cerebral perfusion pressure (CPP) and MAP within 15% of baseline using vasopressors during CPB (Denault *et al*., 2007).

Step 3: Systemic Oxygenation

- Presence or absences of peripheral desaturation can be identified by NIRS in a variety of clinical settings.
- Oximetry has been used during CPB to detect vaporizer failure.
- In such cases, if all else fails, the inspired oxygen fraction would be increased during CPB (Denault *et al.*, 2007).

Step 4: Normal $PaCO_2$

- Hyperventilation decreases brain oximetry.
- Hypoventilation increases brain oximetry.
- **$PaCO_2$ – powerful determinant of CBF.**
- Most common causes of ↓ rSO_2 : Hyperventilation
  : Rewarming on CPB
- When $PaCO_2$ is below 35 mmHg – normalize $PaCO_2$ ≥ 35 mmHg (Denault *et al.*, 2007).

Step 5: Optimize Hemoglobin

- Hemoglobin (Hb) is the key element of oxygen transfer in the body.
- **Decrease Hemoglobin = Decrease rSO_2**
- With onset of CPB, hemodilution causes a decrease in Hb and a decrease in MAP due to decrease in viscosity, resulting in a decrease in rSO_2.
- A decrease in rSO_2 can be used as an indication for blood transfusion (Denault *et al.*, 2007).

Step 6: Cardiac Function

- Decrease cardiac performance = increase in brain oxygen extraction = lower oximetry values
- Increasing your pump flow during CPB is a good technique to correct cerebral desaturation (Denault *et al.*, 2007).

Step 7 : Decrease Cerebral Metabolic Rate of Oxygen ($CMRO_2$)

- Decrease rSO_2 = Increase in $CMRO_2$.
- This may occur after rewarming during CPB.
- $CMRO_2$ can be reduced through deepening of anaesthesia (Denault *et al.*, 2007).

Step 8: Other

- **Laminar Flow vs. Pulsatile Perfusion** = Laminar flow decreases CBF during CPB, therefore during CPB, pulsatile perfusion may be introduced when rSO_2 is low. Denault and colleagues (2007) have noted that in certain patients there was an improvement in rSO_2 when pulsatile perfusion was introduced (Denault *et al.*, 2007).

PROPOSED ALGORITHM IN THE USE OF BRAIN OXIMETRY

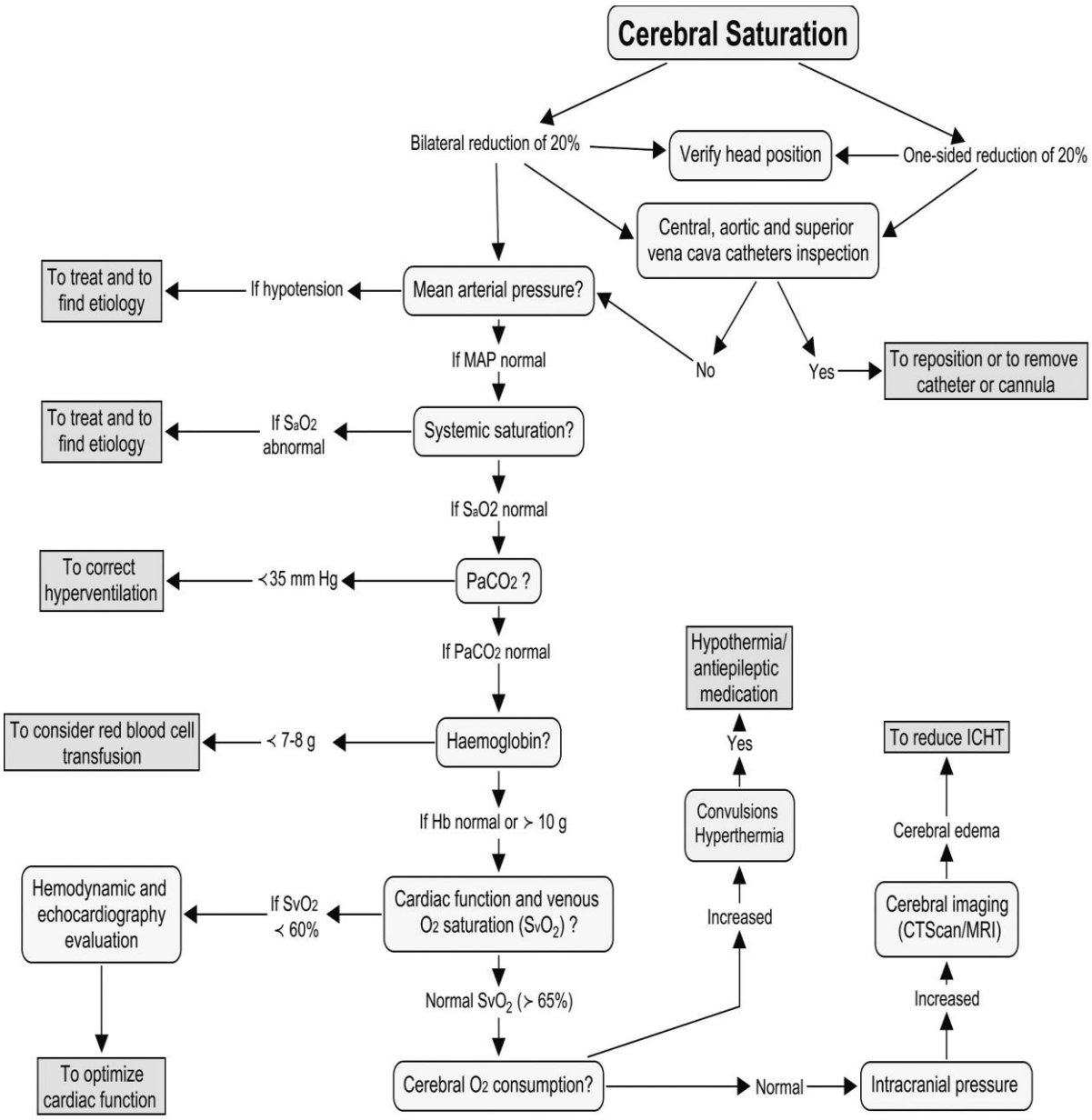

Figure 2.3 **Proposed algorithm in the use of Brain Oximetry** (CT – computed tomoFigurey; ICHT – intracranial hypertension; MAP – mean arterial pressure; MRI – magnetic resonance imaging) (Adapted from Denault *et al;* 2007)

Appendix D

DEPARTMENT CARDIOTHORACIC SURGERY UFS SURGICAL DATABASE

DEPARTMENT CARDIOTHORACIC SURGERY
SURGICAL DATABASE DATA SHEET
CARDIAC SURGERY

Sticker

PATIENT IDENTIFICATION & DEMOGRAPHICS

First name(s)			
Surname			
Title		**Language**	
Gender	Male O Female O	**ID Number**	
DOB	m m / d d / y y y y	Age	years
Folder #	UM	**Reference**	
Practitioner		**Location**	
Category	Private O Academic O		
Funder / Medical aid			
Status	Current O Inactive O	Hospital O	Deceased O
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**	

ADULT CARDIAC - HISTORY
Cardiac History

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

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

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

Previous Cardiothoracic or Vascular Surgical Intervention

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

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

Recent failed intervention	Yes	O	No	O							
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	O	Active	O																	
Immuno-supressed																					

INVESTIGATION
Catheterisation

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

Haemodynamics

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

Thrombolysis

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

Coronary Anatomy

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

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%)	O	Fair (40 - 49%)	O	Poor (< 40%)	O	Not measured	O													
Method	LV Gram	O	Radio-nucluide	O	Echo	O	Estimate	O													
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 O	2 O	3 O	4 O
Valve	**Aortic**	**Mitral**	**Tricuspid**	**Pulmonary**
Haemodynamic pathology	Stenosis O Regurgitation O Mixed O	Stenosis O Regurgitation O Mixed O	Stenosis O Regurgitation O Mixed O	Stenosis O Regurgitation O Mixed O
Explant type	Native valve O Mechanical O Biological O Homograft O Autograft O Ring O	Native valve O Mechanical O Biological O Homograft O Autograft O Ring O	Native valve O Mechanical O Biological O Homograft O Autograft O Ring O	Native valve O Mechanical O Biological O Homograft O Autograft O Ring O
If Native valve, pathology	Native valve not present O Congenital O Degenerative O Active infective endocarditis O Previous infective endocarditis O Rheumatic O Annuloaortic ectasia O	Native valve not present O Congenital O Degenerative O Active infective endocarditis O Previous infective endocarditis O Rheumatic O Annuloaortic ectasia O	Native valve not present O Congenital O Degenerative O Active infective endocarditis O Previous infective endocarditis O Rheumatic O Annuloaortic ectasia O	Native valve not present O Congenital O Degenerative O Active infective endocarditis O Previous infective endocarditis O Rheumatic O Annuloaortic ectasia O

	Calcific degeneration ○ Ischaemia ○ Functional regurgitation ○ Other native valve pathology ○	Calcific degeneration ○ Ischaemia ○ Functional regurgitation ○ Other native valve pathology ○	Calcific degeneration ○ Ischaemia ○ Functional regurgitation ○ Other native valve pathology ○	Calcific degeneration ○ Ischaemia ○ Functional regurgitation ○ 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

AORTA
Aortic Procedures

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

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

MYOCARDIAL
Myocardial Protection

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

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						○
	Re-operation for bleeding post-op						○
	Re-operation for valvular dysfunction						○
	Re-operation for graft procedure						○
	Re-operation for other cardiac procedure						○
	Re-operation for other non-cardiac procedure						○
	Peri-operative MI						○
	Sternum resuturing sterile						○
	Surgery for deep sternal sepsis						○
New post-operative stroke	None	○	Transient stroke	○	Permanent stroke	○	Disoriented ○
Renal complications	Dialysis	○	Renal failure	○	Creatinine / urea up	○	
Infection	Sternum superficial	○	Sternum deep	○	Leg	○	IABP ○
	Septicemia	○	Wound drainage	○	Urinary tract infection	○	

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

Cardiac Factors

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

Operation Factors

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

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

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

Examination

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
	Other							

Special investigations

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

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 E

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

Research Division
Internal Post Box G40
☎(051) 4052812
Fax nr (051) 4444359

E-mail address: gndkhs.md@mail.uovs.ac.za

Ms H Strauss

2007-06-14

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

Dear Prof Smit

ETOVS NR 51/07B
RESEARCHER: PROF FE SMIT AND OTHERS
PROJECT TITLE: EVALUATION OF OXIMETRY VALUES DURING CABG ON-PUMP, CABG OFF-PUMP AND PCI

- 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
Ms L Liebenberg, Dept of Cardiothoracic Surgery, Faculty of Health Sciences, UFS

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2007-06-14

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CHAIR: ETHICS COMMITTEE

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APPENDICES