THE EFFECT OF OPTIMIZING CEREBRAL TISSUE OXYGEN SATURATION ON MARKERS OF NEUROLOGICAL INJURY DURING CORONARY ARTERY BYPASS GRAFT SURGERY

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AUTHORS DECLARATION

This study represents original work by the author. It has not been submitted to any other Tertiary Institution. Where use of the work of others was made, it has been duly acknowledged in the text.

The research described in this dissertation was carried out in the Department of Clinical Technology, Faculty of Health Sciences, Durban University of Technology under the supervision of Professor J K Adam (Head of the Clinical Technology programme) and the Department of Cardiothoracic Surgery, Inkosi Albert Luthuli Central Hospital, Durban, South Africa under the supervision of Professor A Reddi (Head of Department and Chief Surgeon, Cardiothoracic Surgery, Nelson Mandela School of Medicine).

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DEDICATION

I dedicate this work to:

My late Brother, Mr Avishkar Harilall, for the uncompromising principles that guided his life. He taught me to persevere and to face challenges with faith and humility. His spirit will be my guiding beacon in all my endeavours.

My mother and father, for leading their children into intellectual pursuits. They taught me that even the most mammoth task can be accomplished if it is done one step at a time. Your words were etched with wisdom.

My wife Charlene, for her magnificent devotion to her family. She has been the epitome of patience and support whilst witnessing my academic journey. There have been numerous nights and weekends that I have spent, conducting research or writing, time that I otherwise could have spent with her and our two beautiful children Anshul and Ariana, they make everything worthwhile.

ABSTRACT

Introduction

Surgical revascularization of the coronary arteries is a cornerstone of cardiothoracic surgery. The enduring nature of coronary artery bypass grafting (CABG) bespeaks of its history and proven efficacy. However, cerebral deoxygenation during on-pump coronary artery bypass graft surgery may be associated with adverse neurological sequelae. Advanced age and the incidence of preoperative co-morbidity in patients presenting for coronary artery bypass graft surgery increases the potential for stroke and other adverse perioperative outcomes (Murkin, Adams, Quantz, Bainbridge and Novick, 2007). It is hypothesized, that by using the brain as an index organ, interventions to improve cerebral oxygenation would have systemic benefits for cardiac surgical patients. In an attempt to predict those patients that are predisposed to cerebral complications, investigators have used neurological monitoring ie, Near infrared spectroscopy (NIRS) to enhance detection of hypoxic conditions associated with neurological injury (Hoffman, 2006). Serum S100B protein has been used as a biochemical marker of brain injury during cardiac surgery. Elevated levels serve as a potential marker of brain cell damage and adverse neurological outcomes (Einav, Itshayek, Kark, Ovadia, Weiniger and Shoshan, 2008).

Aims and Objectives of the study

This prospective, quantitative, interventional study was carried out to maintain cerebral tissue oxygen saturation during cardiopulmonary bypass above 75% of the baseline level by implementation of a proposed interventional protocol. The analysis of S100B which is a marker of neurological injury and optimization of regional cerebral oxygen saturation would allow for the formulation of an algorithm which could be implemented during on-pump coronary artery bypass

graft surgery as a preventive clinical measure further reducing the risk of neurological injury. Central venous lines (CVP) are inserted routinely during cardiac surgery. Central venous oxygen saturation is a global marker of tissue oxygenation. A secondary aim of the study was to determine if a correlation existed between central venous and cerebral tissue oxygen saturations. If a positive correlation existed then central venous oxygen saturation could be used as a surrogate measure of cerebral tissue oxygen saturation during on-pump coronary artery bypass graft surgery. This study is one of the first done in the South African population group.

Methods

Forty (40) patients undergoing on-pump coronary artery bypass graft surgery were recruited at Inkosi Albert Luthuli Central Hospital. Patients were randomized into a control group (n=20) and interventional group (n=20) using a sealed envelope system. The envelope contained designation to either group. Envelopes were randomly chosen. Intraoperative regional cerebral oxygen saturation (rSO_2) monitoring with active display and treatment intervention protocol was administered for the interventional group. In the control group regional cerebral oxygen saturation monitoring was not visible to the perfusionist operating the heart lung machine during cardiopulmonary bypass (blinded). Recording of regional cerebral saturation was conducted by an independent person (another perfusionist) who was not involved in the management of the case so as to ensure that no interventions were carried out on the control group.

Arterial blood samples for the measurement of serum S100B were taken pre and postoperatively. An enzyme immunoassay (ELISA) was used for the quantitative and comparative measurement of human S100B concentrations for both groups. Central venous oxygen saturation was monitored from the CVP using the Edwards Vigileo monitor. Cerebral monitoring constituted the use of Near infrared spectroscopy monitoring using the Invos 5100c, Somonetics Corp, Troy MI monitor.

Adhesive optode pads were be placed over each fronto- temporal area for cerebral oxygen measurement.

During cardiopulmonary bypass, eight time period measurements of mean arterial pressure (MAP), heart rate, temperature, activated clotting time (ACT), patient oxygen saturation (SpO_2), partial pressure of carbon dioxide (pCO_2), haematocrit, lactate, pH, haemoglobin (Hb), base excess (BE), potassium (K^+), sodium (Na^+), glucose, calcium (Ca^{2+}), central venous oxygen saturation ($ScvO_2$), cerebral tissue oxygen saturation (rSO_2), fraction inspired oxygen (FiO_2), sweep rate, pump flow rate (cardiac index), and percentage isoflurane per patient were taken. The time periods when data was recorded included: 5 minutes after onset of cardiopulmonary bypass, aortic cross clamping, after cardioplegic arrest, during distal anastomosis, during proximal anastomosis, during rewarming, after aortic cross clamp release and before termination of cardiopulmonary bypass. Baseline measurements were also taken.

Clinical data recorded for both groups included: the number of grafts performed, cardiopulmonary bypass time, cross clamp time, red blood cells administered (packed cells), amount of adrenalin infused and total cerebral desaturation time. A prioritized intraoperative management protocol to maintain rSO_2 values above 75% of the baseline threshold during cardiopulmonary bypass was followed. Cerebral desaturation was defined as a decrease in saturation values below 70% of baseline for more than one minute. Interventions commenced within 15 seconds of decrease below 75% of baseline value.

Results

The results of the study show that there was a highly significant difference in the change in S100B concentrations pre and post surgery between the interventional and control groups. The intervention

group showed a smaller increase in S100B concentration of 37.3 picograms per millilitre (pg/ml) while the control group showed a larger increase of 139.3 pg/ml. Therefore, the control group showed a significantly higher increase in S100B concentration over time than the intervention group ($p < 0.001$).

Maximizing pump flow rates was the most common intervention used (45 times) followed by maintaining partial pressure of carbon dioxide to approximately 40 mmHg (28 times), increasing mean arterial pressure by administration of adrenalin (11 times) and administration of red blood cells to increase haematocrit (11 times). There was a highly statistically significant treatment effect within the intervention group for each of the above interventions compared with no intervention. The above mentioned interventions significantly affected right and left cerebral oxygen saturations. However, administration of red blood cells was not found to significantly increase right ($p = 0.165$) and left ($p = 0.169$) cerebral oxygen saturation within the intervention group.

The study highlighted a significant difference between the intervention and control groups in terms of cerebral desaturation time ($p <0.001$). The mean desaturation time for the control group was 63.85 minutes as compared to 24.7 minutes in the interventional group. Cerebral desaturation occurred predominantly during aortic cross clamping, distal anastomosis of coronary arteries and aortic cross clamp release.

Predictors of cerebral oxygen desaturation included, partial pressure of carbon dioxide (pCO_2), temperature, pump flow rate (LMP), mean arterial pressure (MAP), haematocrit, heart rate (HR) and patient oxygen saturation (SpO_2). Central venous oxygen saturation was not significantly related to right ($p = 0.244$) or left ($p = 0.613$) cerebral oxygen saturations. Therefore central venous oxygen saturation cannot be used as a surrogate measure of cerebral tissue oxygen saturation during on-pump coronary artery bypass graft surgery.

Conclusion

These findings demonstrate the positive effect of optimizing cerebral oxygen saturation using an interventional protocol on markers of neurological injury (S100B). Optimization of pump flow rate, partial pressure of carbon dioxide and mean arterial pressure would result in increased cerebral oxygen saturation levels and a reduction in neurological injury. Therefore, an algorithm incorporating these interventions can be formulated. Monitoring specifically for brain oxygen saturation together with an effective treatment protocol to deal with cerebral desaturation during on-pump CABG must be advocated.

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LIST OF ABBREVIATIONS

ACT - Activated clotting time

AF - Atrial fibrillation

ATP - Adenosine triphosphate

BBB - Blood brain barrier

BE - Base excess

BFV - Blood flow velocity

BHS - Beating heart surgery

BMI - Body mass index

CABG - Coronary artery bypass graft

CBF - Cerebral blood flow

CEA - Carotid endarterectomy

CI - Cardiac index

CI - Confidence interval (Statistical)

CMR - Cerebral metabolic rate

$CMRO_2$ - Cerebral metabolic rate of oxygen consumption

CNS - Central nervous system

CPB - Cardiopulmonary bypass

CSF - Cerebrospinal fluid

CT - Computed tomography

CVA - Cerebrovascular accident

CVP - Central venous line

Cx - Circumflex artery

DCT - Double aortic cross clamp

DOS - Delirium observational screening scale

DRS - Delirium rating scale

DWI - Diffusion weighted imaging

ECAD - Extracranial atherosclerotic disease

EEG - Electroencephalogram

ELISA - Enzyme-Linked Immuno-Sorbent Assay

Euroscore - European system for cardiac operative risk evaluation

FCD - Functional capillary density

GEE - Generalized estimating equations

Hb - Haemoglobin

Hct - Haematocrit

HITS - High intensity transient signals

HR - Heart rate

IABP - Intra aortic balloon pump

IALCH - Inkosi Albert Luthuli Central Hospital

ICA - Internal carotid artery

ICAD - Intracranial atherosclerotic disease

ICEM - International council for emboli measurement

ICP - Intracranial pressure

LAP - Left atrial pressure

LD - Leukocyte depleting

LED - Light emitting diode

LVEDP - Left ventricular end diastolic pressure

MAP - Mean arterial pressure

MCA - Middle cerebral artery

MRI - Magnetic resonance imaging

NIRS - Near infrared spectroscopy

NP - Neuropsychologic impairment

OPCAB - Off pump coronary artery bypass graft surgery

OR - Odds ratio

PCI - Percutaneous coronary intervention

pCO_2 - Partial pressure of carbon dioxide

pO_2 - Partial pressure of oxygen

POCD - Post operative cognitive dysfunction

PWI - Perfusion weighted imaging

QL - Quality of life

RAP - Right atrial pressure

REM - Rapid eye movement

rSO_2 - Cerebral oxygen saturation

RVEDP - Right ventricular end diastolic pressures

S100B - Serum S100 beta protein

SAH - Subarachnoid haemorrhage

SCADs - Small capillary arteriolar dilatations

SCT - Single aortic cross clamp

$ScvO_2$ - Central venous oxygen saturation

SNP - Single nucleotide polymorphisms

SpO_2 - Patient saturation

SvO_2 - Mixed venous saturation

T1 - Nasopharyngeal temperature

T2 - Bladder temperature

TBI - Traumatic brain injury

TCD - Transcranial Doppler ultrasonography

TIA - Transient ischaemic attack

TOE - Transoesophageal echocardiography

TOI - Tissue oxygen index

VA - Visual acuity

CHAPTER ONE – INTRODUCTION

The use of cardiopulmonary bypass (CPB) as a surgical technique to oxygenate and subsequently recirculate blood diverted away from the heart and lungs was clinically introduced by Gibbon in 1953. It became the mainstay of cardiac surgery, facilitating a variety of complex cardiac procedures. (Gibbon, 1954; Murkin, Boyd, Ganapathy, Adams, Peterson, Morgan and Lok, 1999). Yearly, an increasing number of people throughout the world undergo coronary artery bypass graft surgery (CABG) (Selnes, Goldsborough, Louis, Borowicz, McKhann and Guy, 1999). The development of coronary artery bypass grafting with the use of cardiopulmonary bypass and its effect on angina pectoris was the product of a series of technical and scientific advances involving surgical, anaesthetic, and perfusion strategies (Selnes et al., 1999). The practice of CPB continues to be refined since its advent in the 1950s (Shann, Likosky, Murkin, Baker, Baribeau, Defoe, Dickinson, Gardner, Grocott, O'Conner, Rosinski, Sellke and Willcox, 2006). Despite these advances, the established undesirable effects of cardiopulmonary bypass remain and add to adverse neurobehavioral outcomes in the post-operative patient. The increasing number of patients undergoing cardiac surgery who are of advanced age and who have co-morbid medical conditions underscores the significance of complications for overall patient outcomes. The persistence of adverse neurologic episodes following coronary artery bypass graft surgery continues to confound cardiac surgeons seeking to improve procedural outcomes (Greinecker, 2003). This reinforces the need for continuous ongoing refinement of all aspects of management (Curtis, Vora and Ohri, 2010).

Currently neurological complications are of greatest interest due to their association with operative mortality, longer hospitalization, health resource utilization, and impaired quality of life after cardiac surgery (Hogue, Gottesman and Stearns, 2008). Adverse neurological episodes after cardiac surgery are now recognized as a serious and costly healthcare problem in need of urgent attention (Wolman, Nussmeier, Aggarwal, Kanchuger, Roach and Newman, 1999). The severity of neurological injury ranges from subtle changes in personality, behaviour and cognitive function to fatal brain injury – 'cerebral catastrophe' (Arrowsmith, Grocott, Reeves and Newman, 2000). The incidence of stroke post cardiopulmonary bypass (CPB) ranges from 0.9% to 5.4% and the incidence of neuropsychologic impairment (NP) ranges from 28%-79%, with persistent impairment at six months in 19-57% of the cases (Stump, Rogers, Hammon and Newman, 2000). Roach and colleagues (1996), in their large scale multi institutional study documented a 6.1% incidence of serious adverse neurological events. This was concluded by a survey of 2,108 patients undergoing CABG surgery at twenty four United States institutions (Roach, Mangano, Newman, Nussmeier, Aggarwal, Katherine, Graham, Ley, Ozanne, Magano, Herskowitz, Katseva and Sears, 1996). The exact cause of CPB-related neurologic injury remains unclear. Major debates attribute neurological insult to CPB-related hypoperfusion or microvascular embolization. In addition, extracorporeal circulation is associated with a complex inflammatory cascade, which may contribute to the development of postoperative neurologic morbidity.

The neurobehavioral outcomes range from the well documented incidence of stroke to the less well-delineated postoperative delirium and cognitive difficulties such as memory loss and visuospatial deficits (Omar and Taggart, 2009). The major focus of

cardiac surgery has shifted from the postoperative status of the heart to the effects of CABG on the brain and thought processes (Selnes et al., 1999). In an attempt to predict those patients that are predisposed to cerebral complications, investigators have encouraged the use of neurological monitoring, in particular Near infrared spectroscopy (NIRS) during cardiopulmonary bypass (Nagdyman, Fleck, Barth, Khaliq, Stiller, Ewert, Huebler, Kuppe and Lange, 2004).

Scientific literature demonstrates that the application of specific monitoring may be able to enhance the detection of hypoxic conditions associated with neurological sequelae and would allow intervention on individual patients and drive refinements in strategies to reduce patients at risk (Hoffman, 2006). The primary goal for the application of NIRS monitoring is to detect and hence optimize factors that affect cerebral oxygen supply and demand. Suggested factors include position of the vascular cannula, perfusion pressure, arterial oxygen content, partial pressure of carbon dioxide, haemoglobin, cardiac output, mean arterial pressure and cerebral metabolic rate of oxygen (Denault, 2007).

The use of biochemical markers for the detection and monitoring of organ damage is widespread. In order to link processes of care with markers of neurological injury, investigators have highlighted the role of biochemical markers of brain injury which would increase the sensitivity and timelines of diagnosing injury (Groom, Quinn, Lennon, Welch, Kramer, Ross, Beaulieu, Brown, Malenka, O'Conner and Likosky, 2010). S100B protein is abundant in the nervous system where it is predominantly expressed in astrocytes, oligodendrocytes and Schwann cells (Einav, Itshayek, Kark, Ovadia, Weiniger and Shoshan, 2008). The clinical values have been demonstrated in

stroke, cerebral complications association with cardiac arrest and in patients with severe as well as minor head injury (Jonsson, Per Johnsson, Backstrom, Alling, Dautovic-Bergh and Blomquist, 2004). High concentrations of S100B have been demonstrated in brain injury, ischaemia and hypoxia (Fazio, Bhudia, Marchi, Aumayr and Janigro, 2004). S100B can be used as a marker and early indicator of brain injury during and after cardiopulmonary bypass (Einav et al., 2008).

The aim of the study is to optimize cerebral tissue oxygen saturation using an interventional protocol and to assess the effect on serum S100B protein which is a marker of neurological injury during coronary artery bypass graft surgery. The principle objective is to increase regional cerebral oxygen saturation monitored by Near Infrared Spectroscopy (NIRS) during cardiopulmonary bypass using an interventional protocol. Thus, an algorithm can be formulated which could be implemented during cardiopulmonary bypass to increase low levels of cerebral oxygen saturation and decrease adverse neurological injury after coronary artery bypass. Neurological injury can therefore be prevented if monitoring detects potentially harmful conditions early enough to allow initiation of effective interventions before irreversible injury has occurred.

Central venous lines (CVP) are inserted routinely during cardiac surgery. Central venous oxygen saturation is a global marker of tissue oxygenation. A secondary objective is to determine if a correlation exists between central venous oxygen saturation, measured from the CVP, regional cerebral oxygen saturation and serum S100B. If a strong correlation is established then central venous oxygen saturation could be used as a marker of brain injury during cardiopulmonary bypass.

Considering that CABG represents more than half the workload in adult cardiac surgery worldwide, cerebral protection is an important issue that affects our decision making process and impacts on our daily practice. The multifactorial dimensions of neurologic injury during cardiac surgery warrant the need for clinical trials capable of yielding definitive answers.

CHAPTER TWO: STUDY BACKGROUND AND LITERATURE REVIEW

2.1 STUDY BACKGROUND

2.1.1 INTRODUCTION

Operative revascularization of the coronary arteries remains the foundation of surgery for ischaemic heart disease. The enduring nature of coronary artery bypass grafting bespeaks of its history and proven efficacy. It is a technique that can be reproducibly performed by different surgeons with varying degrees of technical skill and acumen with generally favourable results. Current advancements in surgical technique, anaesthetic protocols and cardiopulmonary bypass technology have reduced overall morbidity associated with cardiac surgery and widened the spectrum of patients being considered for CABG. However, conventional bypass grafting utilizing cardiopulmonary bypass and cardioplegic arrest continues to be associated with neurological outcomes that may negate an otherwise successful procedure (Dewey and Mack, 2003). Neurological complications and cognitive deficits are preoccupations in cardiac surgery because of their frequency, variety and long-term impact. Therefore, central nervous system injury remains a devastating and debilitating complication for those who undergo cardiac surgery (Baker, Hallsworth and Knight, 2005). The persistence of these adverse neurological episodes after CABG continues to confound cardiothoracic surgeons who continuously seek to improve procedural outcomes (Greinecker, 2003).

Myocardial revascularization with the use of cardiopulmonary bypass (CPB) is reported to be associated with significant cerebral morbidity (Van Dijk, Jansen, Hijman, Nierich, Diephuis, Moons, Lanpor, Borst, Keizer, Nathoe, Grobee, Jagere, and Kalkman, 2002). Neurological

injury in the form of stroke or neurocognitive impairment is a frequent and potentially devastating complication that may affect patients undergoing CABG. The aetiology of CABG- associated neurological injury is multifactorial, with the phenomena of cerebral hypoperfusion and embolism being major contributors. Recent studies indicate that the incidence of cognitive decline ranges from 3% - 50%, depending on patient characteristics, definition of deficit, and timing of neuropsychologic assessment (Roach, Kanchuger, Mangano, Newman, Nussmeier, Wolman, Aggarwal, Katherine, Graham, Ley, Ozanne, Magano, Herskowitz, Katseva and Sears, 1996; Newman, Kirchner, Phillips–Bute, Graver Vincent, Grocott, Jones, Malk, Reves and Blumenthal, 2001). A recent pooled analysis of six comparable studies yielded a proportion of 23% of patients with cognitive decline two months after surgery (Van Dijk, Keizer, Diephuis, Durand, Vos and Hijman, 2000). Although the degree of decline does not affect most patients in functional terms, a small percentage of patients with cognitive decline become sufficiently disabled thus preventing their return to employment (Roach et al., 1996).

Performing CABG without cardiopulmonary bypass has indicated a decrease in risk of perioperative stroke. The decrease has been seen, especially in high risk patients like the elderly (Scarbrough, White, Derilus, Mathew, Newman, Stamou, Sotiris, Hill, Dangas, Pfister, Boyce, Dullum, Bafi and Corso, 2005). Whether off pump CABG reduces the incidence of less severe neurocognitive impairment has not yet been clearly established and merits further investigation. Bowles and colleagues suggested that avoiding the use of CPB could lead to reduced cerebral microemboli during coronary revascularization, as measured by intraoperative transcranial Doppler ultrasonography (Bowles, Lee, Dang, Taoka, Johnson, Lau and Nekomoto, 2001).

In neonates, recognition of the brain as a potential target of injury has been identified. The magnitude of the problem is of a large scale, with estimates of post CPB neurologic injury ranging from 2% to 30% (du Plessis, 1997; Limperopoulos 2002). Ferry (1990), reported that transient and permanent neuropsychiatric injury occured in as many as 25% of all infants undergoing hypothermic CPB with severe abnormalities presented in <10% of cases. Recently the focus has shifted from patient mortality to long term functional disability of which neurocognitive performance is an important determinant. Currently the emphasis on mechanisms of neurological injury during cardiac surgery and proposed strategies to prevent or reduce the number of patients exposed to peri-operative brain damage remains a priority which has to be rigorously investigated (du Plessis, 1997).

2.1.2 NEUROPHYSIOLOGY

2.1.2.1 CEREBRAL PHYSIOLOGY

The adult human brain weighs approximately 1350g which represents about 2% of the total body weight. It also receives between 12-15 % of the cardiac output. Under Normal physiologic conditions blood flow through the brain of an adult person ranges between 50 to 65 milliliters per 100 grams of brain tissue every minute. The consistent high blood flow rate is a direct reflection of the brain's high metabolic rate. Under resting conditions, the brain consumes oxygen at an average rate of about 3.5 ml/100g/min. The entire brain tissue oxygen consumption is about 47 ml/min. Normal cerebral physiologic values for the various regions of the brain are shown in Table 1 and Figure 1 below.

Table: 1 Normal cerebral Physiologic Values

Normal Cerebral Physiologic Values	
Global	45 -55ml/100g/min
Cortical	75 -80ml/100g/min
Sub - cortical	~20ml/100g/min
Cerebral metabolic rate of oxygen	3 -3.5ml/100g/min
Cerebral vascular resistance	1.5 -2.1ml/100g/min
Cerebral Venous Oxygen	32-44 mmHg
Cerebral Venous Oxygen Saturation	55 -70%
Intracranial Pressure	8 -12 mmHg

(Patel, 2007)

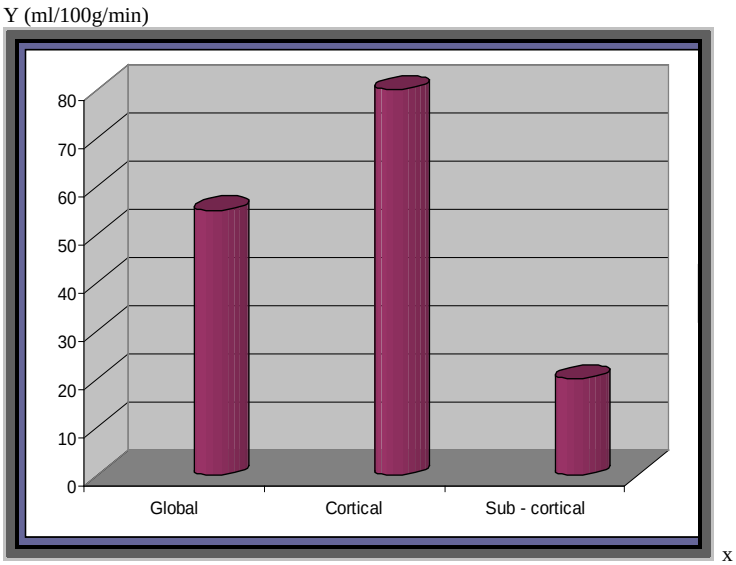


Figure: 1 Graph showing normal cerebral physiological values for different parts of the brain (Y.Harilall, 2010)

Approximately 60% of the brain energy consumption accounts for the generation of adenosine triphosphate (ATP) to support electrophysiological function (Malcom, 1991). Energy requirements of the brain can be compartmentalized into basal and functional needs. Basal energy is required for maintenance of cell integrity with electrochemical gradients and the production, storage, release, and reuptake of transmitters. Energy that is expended in neuronal functioning also includes generation of electrical activity by the pyramidal cells. Approximately 40% of the energy is used for basal needs, whereas functional activity consumes 60% (Figure 2) (Morgan & Mikhail, 2002).

The cell population of the brain is heterogeneous in its oxygen requirements. Glial cells constitute half of the brain's volume and require less energy than neurons. Besides providing a physical support latticework for the brain, the glial cells play an important role in the reuptake of neurotransmitters and in the delivery and removal of metabolic substrates and wastes (Rod, Trent and Stephens, 2006).

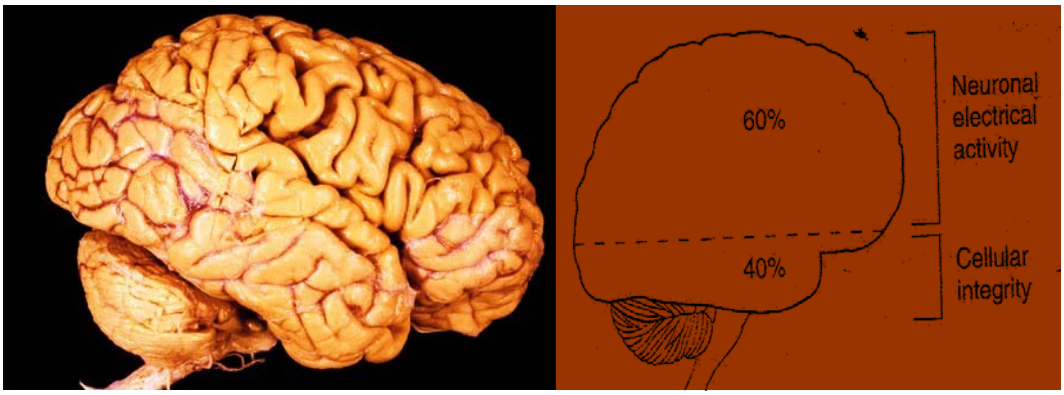


Figure: 2 Normal brain oxygen requirements (Morgan & Mikhail, 2002: p553)

2.1.3 CEREBRAL METABOLISM

Cerebral metabolic rate (CMR) is commonly expressed in terms of oxygen consumption ($CMRO_2$), which averages 3-3.8 ml/100g/min. In the awake, resting state, brain metabolism accounts for about 15% of the total metabolism of the body. Although the brain constitutes 2% of total body mass, metabolism per unit mass of brain tissue is about 7.5 times the average metabolism in non-neural tissue. Cerebral metabolic rate of oxygen extraction is greatest in the grey matter of the cerebral cortex which generally parallels cortical electrical activity. Because of the brain's relatively high oxygen consumption and the absence of significant oxygen reserves, interruption of cerebral perfusion usually results in unconsciousness within ten seconds as oxygen tension drops below 30 mmHg. Therefore, the brain is dependant upon a constant supply of oxygen (aerobic metabolism) and glucose

(glycolysis) by blood (perfusion). If blood flow is not established within 3 to 8 minutes at normothermia, ATP stores become depleted resulting in irreversible cellular injury. Neuronal cells normally utilize glucose as a primary source of energy. Brain glucose consumption is approximately 5 mg/100g/min, of which 99% is metabolized aerobically. Cerebral metabolic rate of oxygen consumption ($CMRO_2$), therefore, correlates with glucose consumption. Acute hypoglycaemia which is sustained is equally devastating as brain hypoxia. Paradoxically, hyperglycaemia can exacerbate global brain tissue injury. The mechanism of action is by accelerating cerebral acidosis and cellular injury (Guyton, 1991).

2.1.4 CEREBRAL BLOOD FLOW

A fundamental characteristic of the brain is that, despite its high metabolic rate, it does not have substantial reserves of oxygen and energy substrates. The central nervous system is therefore intolerant to a reduction in cerebral blood flow. Cerebral blood flow (CBF) is tightly coupled to cerebral oxygen metabolism thus ensuring appropriate oxygen delivery and consumption (Brown, Wade and Marshall, 1985; Gupta, Hutchinson, Al-Rawi, Gupta, Swart, Kirkpatrick, Menon and Datta, 1999; Johnston, Steiner, Gupta and Menon, 2003). The brain is exquisitely sensitive to hypoxia. Abrupt failure in oxygen delivery will lead to loss of consciousness within ten seconds and irreversible ischaemic injury occurring within minutes. Thus the primary function of cerebral circulation is to ensure that supply of oxygen to the brain is uninterrupted (Groves, 2003).

The threshold of cerebral blood flow (CBF) is constantly maintained at a relative rate of 50 ml/100g/min, flow in gray matter is about 80 ml/100g/min whilst flow in white matter is estimated to be 20 ml/100g/min. Total Cerebral blood flow (CBF) in adults averages

750 ml/min (15 -20 % of cardiac output). Flow rates below 20 – 25 ml/100g/min are usually associated with cerebral impairment, as evident by slowing on the electroencephalogram (EEG). Cerebral blood flow (CBF) rates between 15 -20 ml/100g/min typically produce a flat (isoelectric) EEG (Figure 3), while values below 10 ml/100g/min are usually associated with irreversible brain damage (Morgan & Mikhail, 2002)**.**

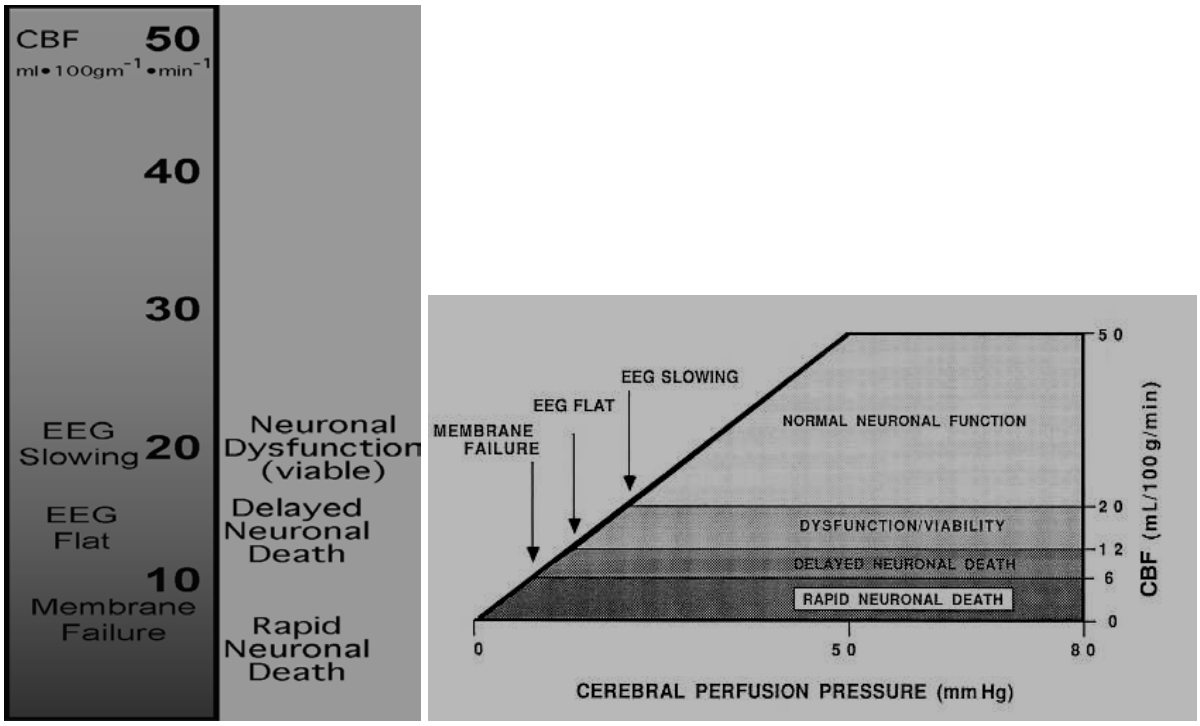


Figure: 3 Illustration of neuronal dysfunction at flow rates of 20ml/100g/min which progresses to membrane failure and neuronal death at lower cerebral blood flow rates (Patel, 2007)

2.1.4.1 CEREBRAL BLOOD FLOW – METABOLISM COUPLING

In the absence of pathology, cerebral blood flow (CBF) is closely coupled to cerebral metabolism. This occurs at both, global and regional levels. This was first demonstrated by Kety and Schmidt in normal awake individuals more than 60 years ago. They found that CBF autoregulates to maintain a constant CBF at perfusion pressures varying between 50 and 150 mmHg (Kety and Schmidt, 1945). Cerebral blood flow increases during periods of central

nervous system activation in order to accommodate for the rapid increase in cerebral metabolic rate for oxygen ($CMRO_2$) necessitated by the increased energy requirements for synaptic transmission. Flow- metabolism coupling is therefore an important control of cerebral circulation. It is regarded as robust mechanism that is also preserved during sleep and during general anaesthesia (Madsen, Schmidt, Wildschiodz, Friberg, Holm, Vorstrup and Lassen, 1991; Lenzi, Zoccoli, Walker and Franzini, 2000; Lam, Matta, Mayberg and Strebel, 1995). The mechanism of flow- metabolism coupling can be observed at different stages of sleep where light or deep sleep is associated with declines in CBF. Rapid eye movement (REM) during sleep shows cerebral blood flow similar to the awake state (Madsen et al., 1991). Figure 4 below demonstrates the effect of local neuronal activity on cerebral blood flow. An increase in occipital blood flow is observed in a cat's brain when intense light is shone into its eyes for one and a half minutes (Guyton and Hall, 2006).

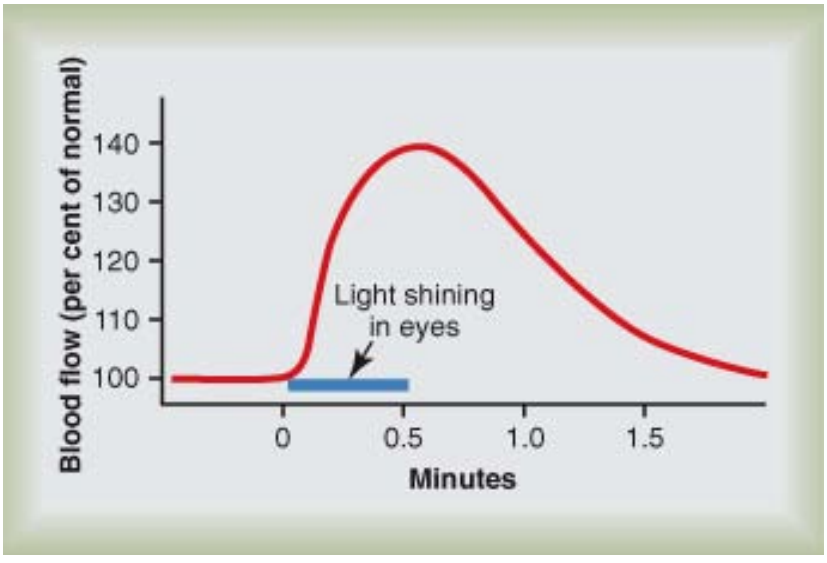


Figure: 4 Increase in blood flow to the occipital regions of a cat's brain when light is shined into its eyes (Guyton and Hall, 2006)

2.1.5 CEREBRAL PERFUSION PRESSURE (CPP)

Cerebral perfusion pressure (CPP) is the difference between mean arterial pressure (MAP) and intracranial pressure (ICP) or cerebral venous pressure. Cerebral perfusion pressure = MAP – ICP (When cerebral venous pressure is significantly higher than intracranial pressure, perfusion pressure becomes the difference between the measure of mean arterial pressure and cerebral venous pressure). Cerebral perfusion pressure is normally 80 to 100 mmHg. Moderate to severe increases in intracranial pressure can compromise cerebral perfusion and cerebral blood flow although the mean arterial pressure may be normal. Patients with CPP values less than 50 mmHg demonstrate a slowing on the EEG, those with a CPP of 25-40 mmHg typically have a flat EEG. Sustained perfusion pressures less than 25 mmHg result in irreversible brain damage (Morgan & Mikhail, 2000).

2.1.6 AUTOREGULATION OF CEREBRAL BLOOD FLOW

The human brain, like the heart and kidneys can tolerate swings in blood pressure with minimal change in the rate of cerebral blood flow. Fog (1937), was the first to observe the homeostatic mechanism of cerebral autoregulation with *in vivo* vasoconstriction and vasodilation in response to changes in blood pressure. Under normal physiological conditions, change in mean arterial pressures (MAP) in the range of 60 mmHg – 160 mmHg demonstrates little or no change as demonstrated in a study conducted by Paulson, Strandgaard and Edvinsson, (1990). Cerebral blood flow is well autoregulated between mean arterial pressure limits of 60 mmHg and 140 mmHg. Thus in patients who are hypertensive autoregulation is still intact when mean arterial pressures increase to as high as 180 mmHg (Guyton and Hall, 2006).

Figure 5 demonstrates cerebral blood flow in normal patients and hypertensive as well as hypotensive individuals.

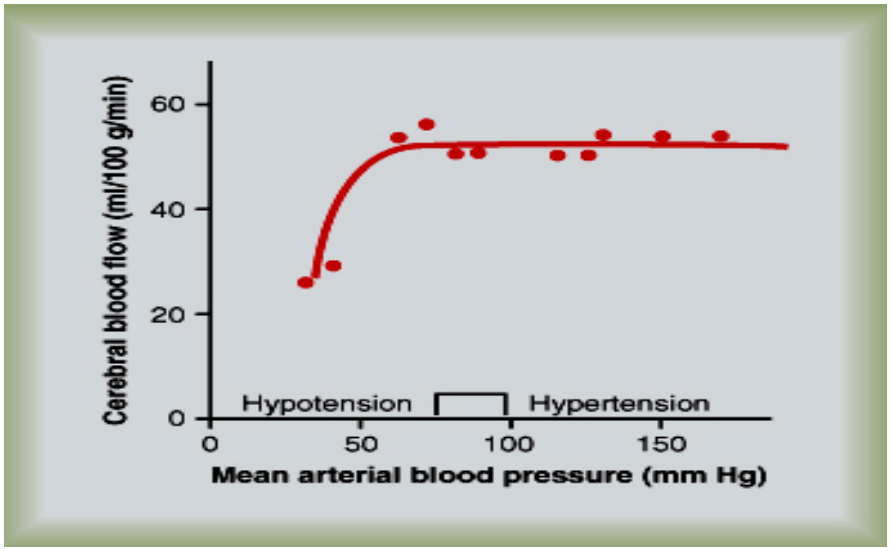


Figure: 5 Effect of differences in MAP, from hypotensive to hypertensive level on cerebral blood flow in different human beings (Guyton and Hall, 2006)

The cerebral vasculature can adapt rapidly within a time frame of 10-60 seconds to changes in cerebral perfusion pressure. However, sudden or abrupt changes in MAP can lead to transient changes even when autoregulation is intact. Autoregulation ensures that as MAP increases there is a direct increase in the resistance from a reduction in the calibre of the small cerebral arteries and arterioles. Therefore, changes in cerebral perfusion pressure occur as a result of vasodilation due to decreased perfusion pressure or vasoconstriction due to elevations in perfusion pressure (Ganong, 2003). Beyond these limits of autoregulation, CBF is directly proportional to MAP and is described as a pressure dependant system. Elevations in blood pressure above the upper limits of autoregulation can cause rupture of cerebral blood vessels, sometimes resulting in serious brain oedema or cerebral haemorrhage. There are certain areas of the brain that are more susceptible to ischaemia than others. The watershed areas between the anterior, middle and posterior cerebral arteries, including the areas

between the superior and inferior cerebellar arteries are more prone to ischaemia as mean arterial pressure decreases below the lower limits of autoregulation. These territories are said to have resting mean arterial pressures that are lower compared to more proximal territories supplied by major arteries and are the first to reach a critical threshold when systemic MAP decreases. When CBF reaches the upper limit of autoregulation “Breakthrough,” vessels may leak into the extravascular space (Strandgaard, Mackenzie, Sengupta, Rowan, lassen and Harper, 1974).

2.1.7 ABNORMAL AUTOREGULATION

Hypoxaemia, hypercapnia, trauma and high-dose volatile anaesthetic agents are some of the causes that lead to impaired or abolished autoregulation in patients. Physiologically, hypercapnia (pCO_2 > 60 mmHg) impairs cerebral autoregulation (McCulloch, Visco, and Lam, 2000). Ischaemic cerebrovascular disease, subarachnoid haemorrhage, and traumatic brain injury (TBI) are clinical neurological disorders that contribute to the pathophysiology. Abnormal autoregulation can range from minimal impairment to complete absence and is classified as ‘intact,” “impaired,” or totally “abolished.” In the absence of autoregulation, systemic hypertension may result in cerebral haemorrhage and oedema formation, whilst deceases in blood pressure may turn already ischaemic areas into areas of infarction. Patients that present with subarachnoid haemorrhage, induced hypertension may improve outcome by ameliorating ischaemic deficits. Patients with traumatic brain injury often lose cerebral autoregulation and suffer from ischaemia. In this instance elevation of MAP is indicated because the compensatory mechanism of vasoconstriction mediated by autoregulation decreases intracranial pressure. The limits of autoregulation can be seen in chronic

hypertensive patients where the autoregulatory curve seen in Figure 5 above is shifted to the right and MAP >160 mmHg may not increase cerebral blood flow.

2.1.8 PATHOPHYSIOLOGY OF CEREBRAL ISCHAEMIA

The high energy utilization of the brain and a very limited energy storage capacity makes it very vulnerable to injury in the face of substrate supply interruption. Ischaemia can be focal or global. Reduced cerebral blood flow below threshold level quickly results in the brain losing its metabolic substrate which triggers a cascade of events causing cell death. In the absence of oxygen, cells are forced into anaerobic metabolism and lactic acid production. Fig 6 provides a graphic overview of the changes at cellular level during cerebral ischaemia.

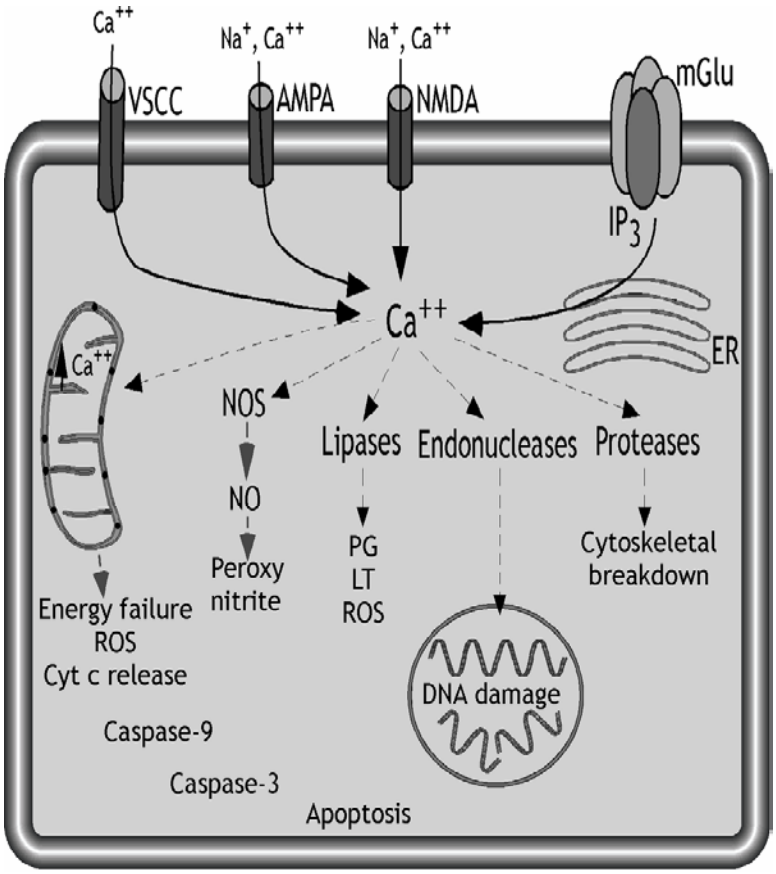


Figure: 6 Pathophysiological mechanisms operative in cerebral ischaemia (Patel, 2007)

The ATP produced is inadequate for cellular homeostasis and the ionic pumps cease to function. During ischaemia, ATP depletion results in neuronal depolarization and the subsequent release of super normal levels of neurotransmitters, especially glutamate. Glutamate toxicity occurs due to over excitation of NMDA (N-methyl d-aspartate receptor) and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors, further increasing the levels of calcium and sodium. These toxic levels activate endonucleases, proteases and lipases which cause a breakdown of the cytoskeleton of neurons and the release of fatty acids and phospholipases. Lipases damage plasma membrane lipids and release arachadonic acid, which is metabolized by the cyclooxygenase and lipooxygenases to yield free radicals and other mediators of cell injury. Nitric oxide produced by the activation of Nitric oxide synthase, subsequently forms peroxynitrite, a highly reactive free radical, and activated endonucleases that damage DNA, and subsequently renders the cell susceptible to apoptosis. Neuronal injury occurs rapidly and resuscitation becomes increasingly difficult as the period of ischaemia increases. The vulnerability of neurons to ischaemia varies. Neurons in the hippocampus, layer three of the cerebral cortex, the striatum and the purkinje cells of the cerebellum have a higher vulnerability and are referred to as selectively vulnerable (Patel, 2007; Vavilala, Lorri and Arthur, 2002; Murdoch and Hall, 1990).

2.1.9 FACTORS THAT AFFECT CEREBRAL BLOOD FLOW

2.1.9.1 Partial pressure of carbon dioxide

An increase in carbon dioxide concentration in the arterial blood perfusing the brain greatly increases cerebral blood flow (Murkin, 2007). The cerebral circulation is exquisitely sensitive to changes in pCO_2. In normal individuals cerebral blood flow increases linearly by

2% to 4% per mmHg pCO_2 within the range of 25 mmHg to 75 mmHg. Thus pCO_2 is the most potent physiologic cerebral vasodilator.

Changes in CBF occur within seconds after pCO_2 is changed, and complete equilibration is said to occur within two minutes (Severinghaus and Lassen, 1967). The immediate response of the cerebral vasculature to carbon dioxide (CO_2) is caused by the rapid diffusion of arterial CO_2 across the blood-brain barrier (BBB) and into the perivascular fluid and cerebral vascular smooth muscle cell. Carbon dioxide (CO_2) reduces the perivascular pH which in turn leads to cerebral vasodilation and increased CBF. Carbon dioxide and bicarbonate ions exert their effects on the cerebrovasculature via changes in the extracellular fluid pH and not by direct action (Kontos, Raper and Patterson, 1977). Although CO_2 is a potent cerebral vasodilator, arterial hydrogen ions do not affect the cerebrovasculature. It does not readily diffuse across the intact blood brain barrier (BBB) and therefore, cannot lower the perivascular pH of the cerebral vessels. Consequently, metabolic acidosis and alkalosis do not affect vascular tone, as do respiratory acidosis and alkalosis (Harper and Bell, 1963). The changes in CBF associated with alterations of arterial CO_2 are not maintained for prolonged periods. During chronic hypercapnia maintained for 6 hours in dogs, Warner, Turner and Kassell, (1987), demonstrated an adaptive increase in the cerebrospinal fluid (CSF) pH that was associated with a decrease in CBF. The change in pH was accompanied by an increase in the CSF bicarbonate ions. Similarly, Muizelaar, Poel, Li, Kontos and Levasseur, (1988) found that during chronic hypocapnia, the pH of CSF gradually decreased toward baseline and CSF bicarbonate concentration also decreased. The relationship of change between arterial pCO_2 and CBF is demonstrated in Figure 7. A 70% increase in arterial pCO_2 approximately doubles the cerebral blood flow.

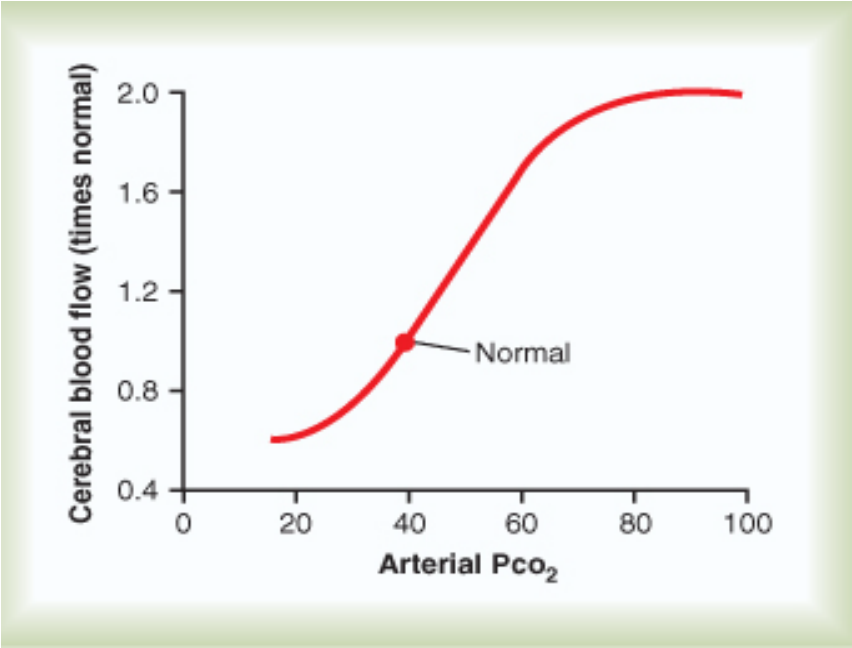


Figure: 7 Relationship between arterial PCO_2 and cerebral blood flow (Guyton and Hall, 2000; p 710)

Although cerebral blood flow is altered in response to changes in pCO_2, these changes are not sustained for a long period. During a time period of 6 to 8 hours cerebral blood flow returns to normal because cerebrospinal fluid pH gradually normalizes due to the extrusion of bicarbonate. Acute normalization of pCO_2 results in increased cerebral blood flow rate which could potentially increase intracranial pressure. Other negative effects of hypocapnia such as neurotoxicity and reperfusion injury are demonstrated in Figure 8.

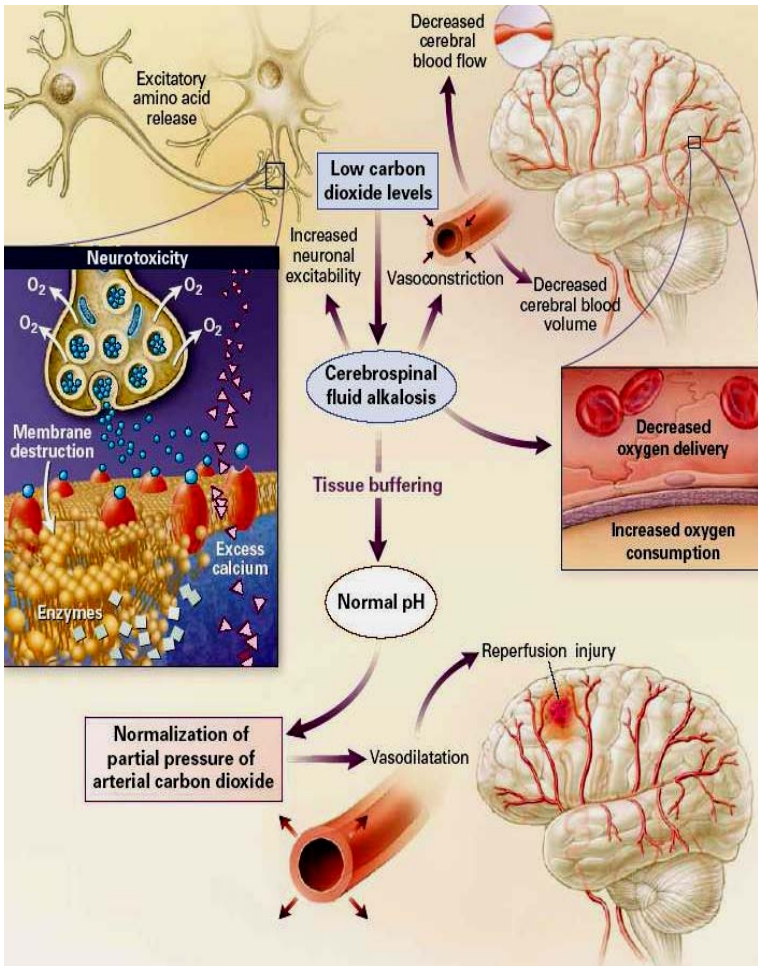


Figure: 8 Negative effects of hypocapnia (Naik, 2007)

2.1.9.2 Conditions that alter carbon dioxide vasoreactivity.

Global CO_2 vasoreactivity is relatively robust and is abolished in terminal conditions and patients with brain damage. However, there are many conditions in which it may be attenuated. Patients presenting with severe carotid stenosis, head injury, subarachnoid haemorrhage (SAH), cardiac failure, or severe hypotension, in which the compensatory cerebral vascular response is already exhausted, may demonstrate a decreased response to changes in CO_2 as compared to healthy individuals. Patients in cardiac with a reduction in left ventricular ejection fraction demonstrate reduced CO_2 vasoreactivity (Georgiadis, Sievert, Cencetti, Unlmann, Krivokuca and Zierz, 2000). Hypercapnia under these

pathological conditions may induce cerebral ischaemia by causing vasodilation of unaffected regions of the brain and vessels. Thus blood flow is diverted away from the maximally dilated, diseased regions. This phenomenon is known as cerebrovascular "steal". Severe hypotension could also cause maximum vasodilation of the cerebral vasculature, resulting in a temporary loss of CO_2 vasoreactivity (Harper and Glass, 1965).

2.1.9.3 Oxygen deficiency

During periods of intense brain activity, the rate of utilization of oxygen by the brain tissue remains within narrow limits i.e., about 3.5 milliliters of oxygen per 100 grams of brain tissue per minute. When blood flow to the brain becomes insufficient to supply the required amount of oxygen, then the oxygen deficiency mechanism immediately causes vasodilation, thereby returning blood flow in the brain and transport of oxygen to the cerebral tissues to near normal (Ganong, 2003). This local blood flow regulatory mechanism is almost exactly the same in the brain as in coronary and skeletal muscle circulation and many other circulatory areas of the body. The response to hypoxaemia is not as quick as the response to changes in pCO_2, because equilibration of CBF takes approximately 6 minutes after the establishment of hypoxaemia (Gary et al, 2003). On the other hand, the effect of hyperoxaemia is less certain, as studies have shown either a slight decrease in CBF velocity or no change at all (Schmetterer, Findl, Strenn, Graselli, Kastner, Elchler and Wolzt, 1997 ; Ellingsen, Hauge, Nicolaysen, Thoresen and Walloe, 1987). Some experiments document that a decrease in cerebral tissue pO_2 below about 30 mmHg (normal value is 35 to 40 mmHg) immediately begins to increase cerebral blood flow (Johnston et al., 2003). This is fortuitous because brain function becomes deranged at lower pO_2 levels, especially at pO_2 levels below 20 mmHg. At these low levels, coma can occur. The oxygen mechanism which

regulates cerebral blood flow is regarded as an important and protective response mechanism against diminished cerebral neuronal activity and, derangement of mental capability (Guyton & Hall, 2000). pO_2 levels of less than 60 mmHg result in a sharp upswing of the pO_2 curve (Figure 9). This results in increased cerebral blood flow.

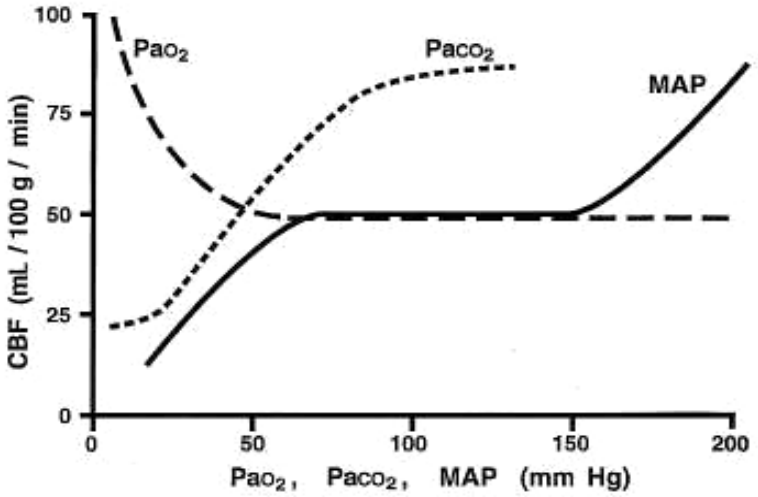


Figure: 9 Change in PO_2 / when PO_2 is less than 60 mmHg, CBF increases rapidly (Guyton 8th Edition, 1991)

2.1.10 CEREBROVASCULAR ANATOMY

2.1.10.1 ARTERIAL SUPPLY

The two internal carotid arteries (80%) and the two vertebral arteries (20%) play a vital role in blood supply to the anterior and posterior parts of the brain respectively. The common carotid arteries originate from the innominate artery on the right side and from the aorta on the left. The internal carotid artery (ICA) supplies blood to the brain and the ipsilateral eye. The ICA consists of four segments: cervical, petrous, cavernous, and supralinoid, describing its course as it enters the cranium. Branches of ICA include, the ophthalmic, posterior

communicating, anterior choroidal, and anterior perforating arteries. They provide most of the blood supply to the cerebrum. Major areas of the brain supplied by the main branches of the ICA have good collateral circulation except for those areas supplied by the middle cerebral artery (MCA). As a result, the MCA territory is prone to ischaemia (Gary, Thibodeau and Patton, 2003).

Posterior blood circulation is comprised of the two vertebral arteries and the basilar artery. The vertebral arteries make up the largest branches of the subclavian artery. Before merging to form the basilar artery, the vertebral arteries give rise to the anterior spinal and posterior inferior cerebellar arteries. Each anterior spinal ramus which originates from the vertebral artery merges with the opposite spinal ramus to form the anterior spinal artery. The posterior inferior cerebellar artery is the largest branch of the vertebral artery, and is responsible for blood supply to the cerebellum and lower brainstem. The basilar artery ascends ventral to the pons and terminates in the pontomesencephalic junction. It also gives rise to the anterior inferior cerebellar, superior cerebellar, and posterior cerebral arteries. The posterior communicating arteries connect the basilar artery to the carotid circulation (Ganong, 2003).

The Circle of Willis (Fig 10) is a representation of the anastomosis of the basal cerebral arteries and the potential collateral circulation. The major function of the circle of Willis is to provide collateral blood flow to that part of the brain with reduced blood flow. In the Circle of Willis the two internal carotids are linked together by the anterior communicating artery while the posterior communicating artery links the internal carotid system with the basilar artery.

These connections make up the collateral circulation. Figure 11 illustrates potential collaterals via the communicating arteries. This is a safety mechanism allowing certain areas of the brain to continue receiving adequate blood supply even when there is an interruption in blood supply somewhere in an arterial system.

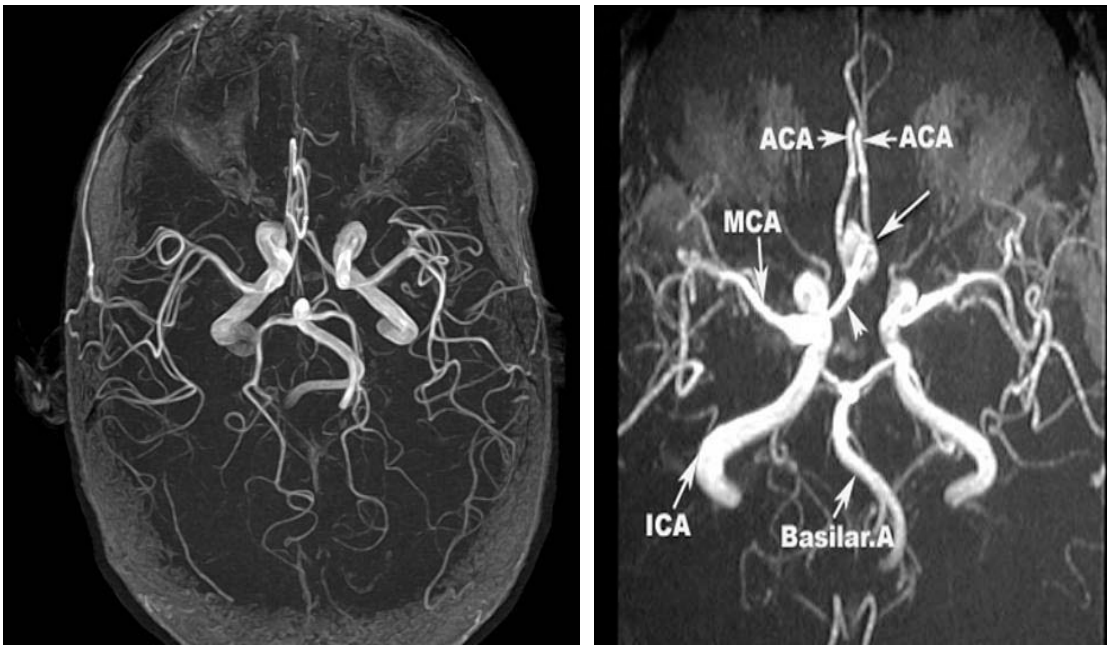


Figure: 10 MR-Angiogram showing The Circle of Willis, potential collaterals via the communicating arteries. All components of a completely intact *COW* or "balanced" Circle of Willis (Diagnostic Imaging Cardiovascular, 2008: p**II**-1-2)

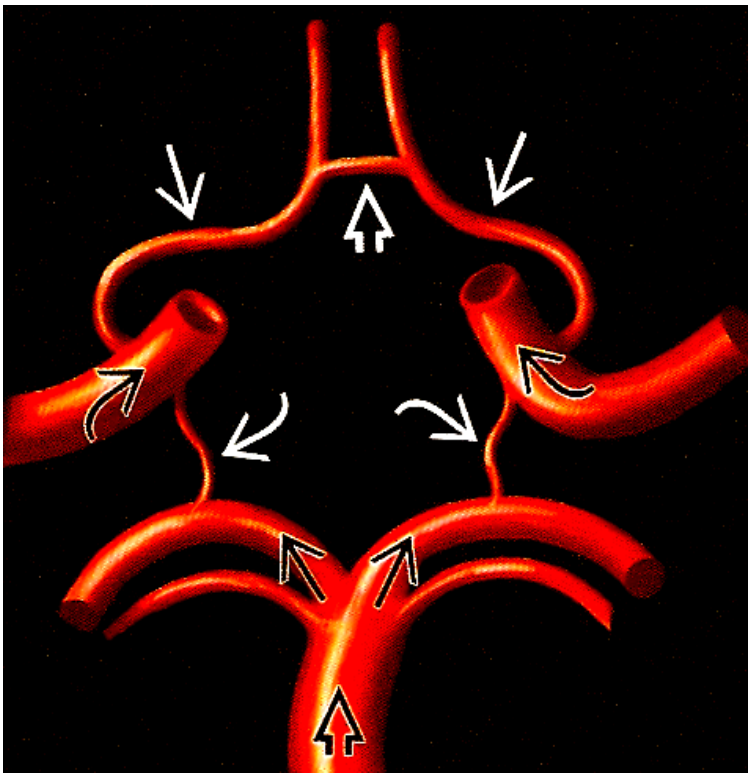


Figure: 11 Graphic illustration of the Circle of Willis, internal carotid arteries, anterior cerebral arteries, anterior communicating arteries, basilar arteries, posterior cerebral arteries and posterior communicating arteries (Diagnostic Imaging Cardiovascular, 2008: p**II**-1-2)

When all arteries are functioning optimally, their blood supplies will not mix where they meet in the Circle because blood pressure within them is equal. If the Circle of Willis constantly maintains blood pressure at fifty percent of its normal level, no infarction or death of tissue will occur in an area where a blockage exists, however collateral circulation is not always sufficient to prevent stroke. Some individuals lack one or more of the communicating arteries in the Circle of Willis. The negative impact of this is that, if an occlusion develops, blood cannot be redistributed from another arterial system and stroke will inevitably occur (McCaffrey, 1999).

2.1.10.2 VENOUS DRAINAGE

The venous system of the brain comprises of both superficial and deep cerebral veins. The superficial veins drain blood from the surface and the cortex of the cerebral hemispheres, whereas the deep veins drain from the deep white matter, the basal ganglia, the diencephalons, the cerebellum, and the brainstem. Large subependymal veins empty into the basal veins which form the great vein of Galen (Figure 12).

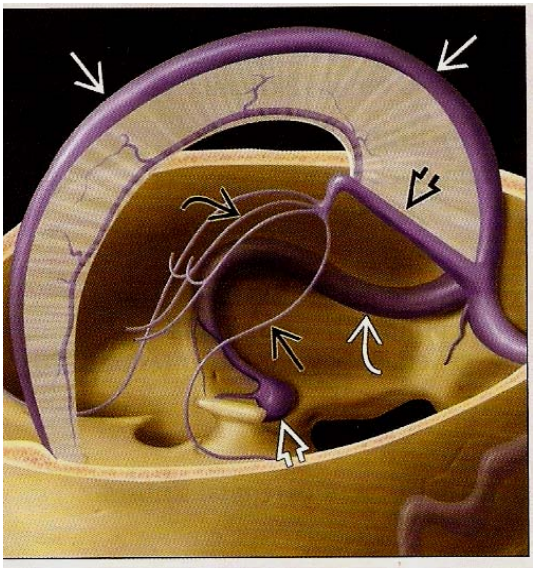


Figure: 12 (Left)

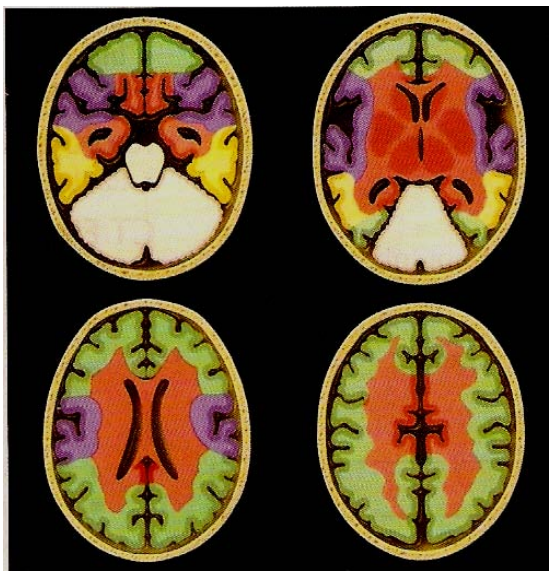


Figure: 12 (Right)

(Left)

Graphic shows cerebral venous anatomy, Superior sagittal sinus, Transverse sinuses, Sigmoid sinus, Internal cerebral veins, Basal veins of Rosenthal, Straight sinuses. Confluence of internal cerebral veins = vein of Galen.

(Right)

Axial graphic shows cerebral venous drainage territories. *Green* = superior sagittal sinus, veins of Trolard, cortical veins. *Yellow* = transverse sinuses, veins of Labbe. *Purple* = cavernous sinuses, superficial middle cerebral vein. *Red* = deep medullary veins, internal cerebral veins, basal veins of Rosenthal, vein of Galen, straight sinuses (Diagnostic Imaging Cardiovascular, 2008: p**II**-1-5)

The superficial and deep veins including the vein of Galen drain into the major dural venous sinuses (Guyton and Hall, 2000). The dural sinuses finally drain into one of the two internal jugular veins (Figure 13).

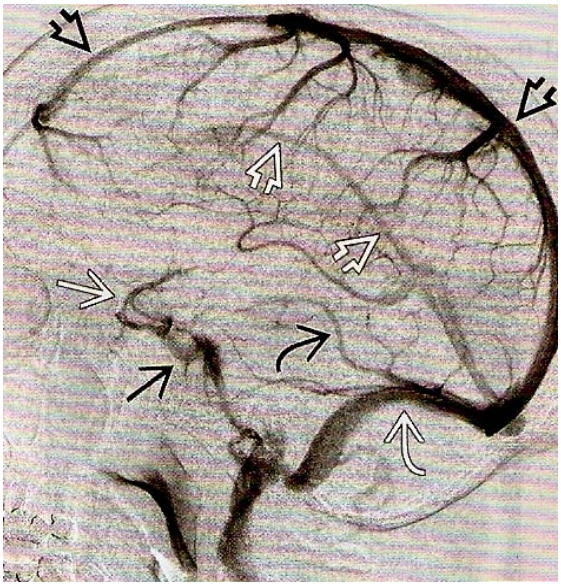


Figure: 13 (Left)

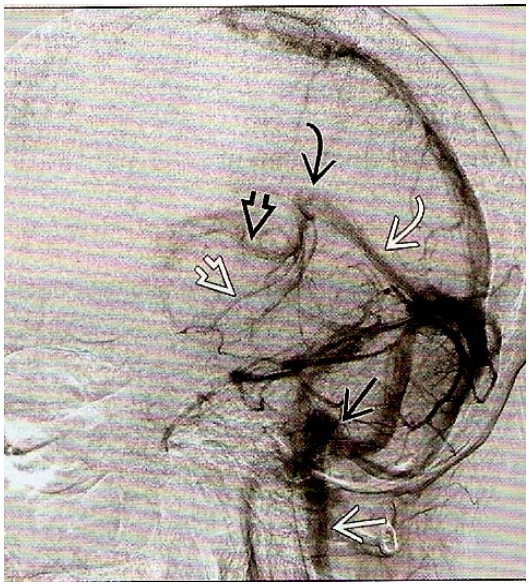


Figure: 13 (Right)

(Left)
Lateral digital subtraction angiogram of right, venous phase shows normal venous anatomy: superior sagittal sinus, inferior sagittal sinuses, veins of Labbe, transverse sinuses, superficial middle cerebral vein, cavernous sinuses.

(Right)
Lateral digital subtraction angiogram of left, venous phase shows normal cerebral deep anatomy: internal cerebral veins, basal veins of Rosenthal, veins of Galen, straight sinuses, sigmoid sinuses, internal jugular veins (Diagnostic Imaging Cardiovascular, 2008: p**II**-1-5)

2.2 LITERATURE REVIEW

2.2.1 HISTORY OF CORNARY ARTERY BYPASS GRAFT SURGERY

Cardiopulmonary bypass (CPB) as a surgical technique was developed and clinically introduced by Dr. John. H Gibbon in 1953. Its application as a circulatory support modality became the mainstay of cardiac surgery, facilitating a variety of complex cardiac procedures (Gibbon, 1954; Murkin, Boyd, Ganapathy, Adams, Peterson, Morgan and Lok, 1999). The overall development of coronary artery bypass grafting with the use of cardiopulmonary bypass and its effect on angina was the product of a series of technical and scientific advances involving surgical, anaesthetic, and perfusion strategies (Selnes et al., 1999). Remarkably, with the exception of newer strategies for myocardial protection, the technical aspects of the procedure have remained unchanged for decades. Independent of cost, complexity and the extensive degree of technical skill associated with cardiopulmonary bypass there has been steadily mounting evidence of adverse neurobehavioral outcomes associated with its usage. Although, the survival rate post cardiac surgery is no longer questionable, subtle signs of central nervous system dysfunction can be observed in otherwise apparently intact patients (Murkin, 1989). The increasing number of patients undergoing cardiac surgery who are of advanced age and who have co-morbid medical conditions underscores the significance of complications for overall patient outcomes.

There is little doubt that the surgery is very effective in reducing angina and in stabilizing ventricular function in most patients. Research conducted 5 years after CABG for severe unstable angina found that 86% of patients were free of the disorder, and of those with angina only 3% had the severe unstable form, 94% of patients remained free of angina

without undergoing additional surgery (Callif, R.M., 1997). Due to recent advances in surgical technique and anaesthesia, CABG is now being carried out in people with co-morbid conditions such as hypertension and diabetes, who may be at a greater risk for complications, as well as in older patients. Although patients in their 70s and 80s tolerate the procedure and have an excellent outcome, the inclusion of patients at higher risk has led investigators to the realisation that serious and potentially fatal neurological consequences may be associated with CABG.

Prior to the advances in extracorporeal circulation technology which is currently implemented worldwide for open heart surgery, anastomosis on coronary circulation was performed on the beating heart with minimal success. This had been attributed largely to poorly evolved surgical techniques. Interest and enthusiasm for the off- pump technique was revived in the mid- 1990s with the introduction of ingenious stabilizers and strategies, the impetus being an attempt to avoid the deleterious side effects of cardiopulmonary bypass, especially in the aged, who bore the brunt of adverse neurological complications ranging from minor cognitive disorders to major stroke (Reddi, Munasur and Kleinloog, 2006). Worldwide, off-pump coronary artery bypass surgery (OPCAB) is a selectively employed technique for myocardial revascularization. Cardiac stabilization and positioning devices, in combination with deep pericardial traction sutures, has further increased the ability to perform multi vessel coronary revascularization during beating heart surgery with avoidance of cardiopulmonary bypass (Murkin, 2002). This approach is meant to obviate the documented deleterious effects of cardiopulmonary bypass. Off-pump surgery techniques avoid blood circulation through a synthetic circuit oxygenator thus reducing activation of the coagulation and inflammatory cascades (Tatoulis, Rice David, Goldblatt and Marasco, 2006;

Paparella, Galeone, Venneri, Coviello, Scrascia, Marraudino, Quaranta, Schinosa and Brister, 2006).

Currently the focus on neurological complications has been magnified due to their association with operative mortality, longer hospitalization, health resource utilization, and impaired quality of life after cardiac surgery (Hogue, Gottesman and Stearns, 2008). Adverse neurological episodes after cardiac surgery are now recognized as a serious and costly healthcare problem mandating urgent attention (Wolman, Nussmeier, Aggarwal, Kanchuger, Roach and Newman, 1999). The exact cause of CPB-related neurologic injury still remains unclear. Intense debates have attributed neurological insult to CPB-related hypoperfusion or microvascular embolization. In addition, extra corporeal circulation is associated with a complex inflammatory cascade, which may contribute to the development of postoperative neurologic morbidity. Considering that CABG represents more than half the workload in adult cardiac surgery worldwide, cerebral protection is an important issue that affects our decision making process and impacts on our daily practice.

2.2.2 NEUROLOGIC OUTCOMES AFTER CORONARY ARTERY SURGERY WITH OR WITHOUT CARDIOPULMONARY BYPASS

Conventional coronary artery bypass grafting (CABG) using the heart-lung machine and cardiac arrest has been the gold standard treatment of ischaemic heart disease for several decades. Worldwide, despite the inexorable rise in the use of angioplasty, many patients still display patterns of coronary artery disease which require them to undergo surgery to improve their longevity. However, the success of CABG has been continuously marred by serious adverse neurological complication, in particular brain damage. The most overt manifestation

of brain damage attributed to the procedure is stroke (Abu Omar et al, 2008). Despite the negative disadvantages of cardiopulmonary bypass, systemic inflammatory syndrome (Sirs) and the generation of microemboli, it is widely used as a large proportion of cardiovascular surgical procedures can only be performed with the use of CPB. In an attempt to ameliorate the potential deleterious effects associated with CPB, over the last decade there has been a resurgence in the interest to perform coronary revascularization without the use of CPB (Stroobant, Nooten, Belleghem and Vingerhoets, 2002).

Over the years there has been intense debate regarding the beneficial effects of off- pump (OPCAB) coronary revascularization as compared to the traditional techniques using the cardiopulmonary bypass circuit and cardioplegic arrest (Silvana, Sharwood and Abramson, 2008). With the advent of a new generation of coronary stabilizers making use of blowers and various manoeuvres used for visualization of posterior and inferior vessels, there has been greater enthusiasm among surgeons to perform OPCAB. The belief that OPCAB results in less adverse neurological events, has resulted in numerous surgeons having opted for the beating heart approach (Stutz, 2003). Majority of the support for this contention is derived from case controlled studies and there is a dearth of robust clinical evidence from randomized controlled trials. Currently, evidence from meta-analysis studies indicate that the rates other than neurological outcomes for perioperative myocardial infarction, reopening for post operative bleeding, renal failure and patient mortality are lower in the OPCAB versus on-pump CABG group (Reston, Tregear and Turkelson, 2003). A recent meta-analysis published by Sedrakyan and colleagues (2007), demonstrated a 50% relative risk reduction of stroke using the OPCAB technique. However, individual trials have failed to demonstrate a significant reduction in stroke after off-pump surgery (Sedrakyan, Wu, Parashar, Bass and Treasure, 2006; Palmer Herbert, Prince, Williams Magee, Brown, Katz, and Mack, 2007).

Bowles and colleagues suggested that avoiding the use of cardiopulmonary bypass (CPB) could lead to reduced cerebral microemboli during coronary revascularization (Wan, Yim and Anthony, 2001). The approach is therefore, indicated in instances where the risk of cerebral and renal compromise is high. However, the occurrence of neurological sequelae associated with OPCAB still ranges between 1.6 and 2% (Reddi, Munasur and Kleinloog, 2006). Haemodynamic instability throughout the positioning, stabilization and interruption of coronary blood flow are important factors that affect the performance of off-pump surgery (Mishra, Shzivastava, Dhara, Bapna, Meharwal and Trehan, 2003). Fluctuations during the intraoperative period, particularly during heart manipulation could result in temporary brain hypoperfusion with neurological sequelae. The extent on cerebral cortical oxygenation also remains unclear (Talpahewa, Ascione, Angelini and Lovell, 2003). Various authors have suggested that the management of patients undergoing OPCAB should be focused on the maintenance of mean arterial pressure, heart rate and cardiac rhythm between stable limits during coronary anastomosis (Denault, 2007; Scarborough, White, Derilus, Mathew, Newman, Sotiris, Hill, Dangas, Boyce, Dullum, Bafi, and Corso, 2003).

With beating heart surgery, avoidance of the embolic potential associated with aortic cannulation, and of the generation of microgaseous and microparticulate emboli from the off pump circuitry, would be expected to significantly decrease cerebral embolic load and improve outcomes (Abu Omar and Taggart, 2009). Further the use of cardiopulmonary bypass has been largely associated with the generation of microemboli which could potentially be avoided by the use of off pump techniques (Brown, Moody, Challa, Stump and Hammon, 2000; Abu- Omar, Balacumaraswami, Pigott, Matthews and Taggart, 2004). Off-pump coronary artery bypass (OPCAB) has been shown to reduce the number of cerebral microemboli generated during coronary surgery, due to the less handling of the often

atheromatous ascending aorta (Marasco, Sharwood, and Abramson, 2008). This reduces the incidence of embolic generation during the time of application and release of the aortic cross clamp or side biting clamp (Abu Omar et al., 2004). In a prospective trial Diegler and colleagues (2000), performed Transcranial Doppler Ultrasonography in forty patients randomized to receive either off-pump or on- pump coronary surgery. Patients in the off - pump group had significantly fewer emboli than patients in the on-pump group. In addition they also assessed early postoperative cognitive function. Of the patients undergoing CABG with CPB, 90% demonstrated some degree of cognitive impairment, whereas cognitive function was preserved after OPCAB (Diegler et al., 2000). If this measure is meaningful, it should translate into improved cognitive outcome.

Neurological complications attributed to extensive atherosclerosis of the ascending aorta, aortic arch and carotid artery, constitute a major cause of morbidity and mortality following CABG. Clevland et al. (2001), in their multi centre study showed that in 1523 patients with known cerebral vascular disease undergoing OPCAB surgery, the incidence of stroke was 2,5%. Another study employed a standardized battery of nine neuropsychological tests perioperatively and 5 days and 3 months postoperatively, in a series of 35 patients undergoing off pump coronary artery bypass surgery, and a demographically similar group of 33 patients undergoing conventional CABG. Cognitive tests included measures of verbal learning and memory, Rey Auditory Verbal Learning Test; visual memory, Benton Visual Retention Test; psychomotor speed and visual concept tracking, trail making tests A and B; manual motor dexterity, Grooved Pegboard; executive functioning, Cowat Word Generation Test; as well as two measures of emotional functioning, State Trait Anxiety Inventory and Geriatric Depression scale. The results showed that there were no clinically apparent strokes in either group. Although, beating heart surgery patients demonstrated a significantly lower

incidence of cognitive dysfunction at 5 days (66% vs 90% respectively, p = 0.025) and 3 months postoperatively (5% vs 50% respectively, p = 0.0011) compared with conventional CABG patients (Murkin, Ganapathy, Adams, Peterson, Morgan and Lok, 1999). Their findings have been consistent with the shorter duration of stay in the intensive care unit, and shorter length of overall hospitalization, despite higher preoperative risk acuity, observed in beating heart versus conventional CABG patients.

For theoretical advantages of avoiding adverse oucomes related to CPB, OPCAB has been generally performed in high risk patients. These risk factors include old age, cerebrovascular disease, chronic obstructive pulmonary disease (COPD), calcification or atheromatous plaque in the ascending aorta, renal failure or advanced heart failure. Large retrospective analyses of surgeon's operative experiences with OPCAB have demonstrated that this procedure is capable of reducing postoperative morbidity and mortality. Using the society of Thoracic Surgeons National Adult Cardiac Surgery Database, Cleveland and colleagues (2001), reviewed the outcomes of 11,717 OPCAB procedures performed at 126 centres from January 1998 to December 1999. They compared the results to 106,423 standard on pump procedures performed during the same time period. The authors found that OPCAB patients had a significant reduction in risk adjusted in hospital mortality (2.3% in off-pump versus 2.9% in the on pump patients) and the rate of major complications (10.6% versus 14.2%). Their review also noted a reduction in neurologic sequelae (Cleveland et al., 2001).

Given the prominent role of cardiopulmonary bypass in causing neurologic injury during CABG, the adoption of OPCAB should result in the improvement of neurological outcome due to both a reduction in the generation of cerebral emboli as well as the avoidance of prolonged periods of cerebral hypoperfusion. However, other investigators believe that the

comparisons of postoperative stroke rate in patients undergoing OPCAB to standard CABG with CPB have failed to demonstrate significant reductions in postoperative stroke rate (Ricci, Karamanoukian, Dancona, Bergsland and Salerno, 2001; Hernandez, Cohn, Baribeau, Tryzelaar, Charlesworth, Clough, Klemperer, Morton, Westbrook, Olmstead and Conner, 2001; Contini, Dimauro, Mazzie, Iaco, Cirmeni, Di Giammarco and Califore, 2000; Kshettry, Flavin, Emery, Demetre, Nicoloff, Arom and Rebecca, 2000). Hernandez et al. (2001), found that the postoperative stroke rate after OPCAB (1.33%) was not significantly different from that after CABG with CPB (1.82%). Conversely, when patients who are at a higher risk for perioperative stroke are considered, literature does indicate a possible reduction in stroke incidence following OPCAB. Ricci and colleagues (2001), reviewed outcomes in 97 OPCAB patients and 72 standard CABG patients who were 70 years of age and older. The investigators found that the incidence of stroke was significantly lower in OPCAB patients than in patients undergoing standard CABG (Ricci et al., 2001). Abraham et al. (2001), showed that in high risk patients (diabetes mellitus, calcified ascending aortas and reoperations), the incidence of stroke was reduced from 3.6% in patients undergoing CPB to 1.2% in patients undergoing off-pump revascularization.

Latest cardiac stabilization and positioning devices, alone or in combination with deep pericardial traction sutures, has greatly increased the ability to perform beating heart surgery to accomplish multi- vessel coronary revascularization without the need for cardiopulmonary bypass. However, positioning the heart for anastomosis of the circumflex (Cx) and the posterior descending artery poses a risk of inducing hypotension, impaired cardiac output, and generalized haemodynamic instability with risk of cerebral compromise (Mishra et al., 2003). Haemodynamic deterioration during coronary anastomosis is a common problem of the procedure. Studies have reported the changes in haemodynamic values during

anastomosis and the recovery of them after the anastomosis by measuring the haemodynamic variables before and after the anastomosis. In a study designed to evaluate the serial haemodynamic changes during coronary artery anastomosis using two deep pericardial stay sutures and the octopus tissue stabilizer on the beating heart, Shinn et al. (2004), concluded that cardiac index (CI) and mixed venous oxygen saturation (SvO_2) decreased significantly during all coronary artery anastomosis immediately after stabilizer application. Considering that OPCAB may be the chosen route for high risk patients, repetitive low cardiac output status may have negative effects on the brain.

By using transoesophageal echocardiography (TOE), in conjunction with continuous cardiac output pulmonary artery and radial artery catheters, Biswas, Clements, Diodata, Hughesa, Chad and Landolfoa, (2001), made a clinical assessment of myocardial performance during myocardial displacement using the Octopus stabilizer for Cx grafting. They demonstrated that reversible left ventricular wall motion abnormalities were more dominant during circumflex (Cx) territory grafting which was also associated with both regional systolic dysfunction and restrictive diastolic filling thus indicating decreased left ventricular compliance. Mathison, Edgerton, Horswell, Akin and Mack, (2000b), demonstrated that the greatest increases in both left (LVEDP) and right ventricular end diastolic pressures (RVEDP) occured during positioning for Cx grafting. Simultaneously, mean arterial pressure (MAP) decreased 22%, stroke volume decreased by 28%, and cardiac output fell by 37%, while left and right atrial pressures (LAP, RAP) increased by 59% and 168% respectively. They also demonstrated that RVEDP increased even with minimal myocardial displacement for left anterior descending artery exposure. They further demonstrated that Cx displacement caused moderate to severe compression of both ventricles. Left ventricular cavity size was

diminished considerably, the left atrium was enlarged, and both the right atrium and ventricle were compressed.

The above clinical studies demonstrate that compromised right ventricular diastolic filling as a result of direct compression, reflected as decreased compliance with increased pressure at decreased volume, appear to be the primary mechanism producing haemodynamic instability during OPCAB surgery. Investigators are certain, that there are haemodynamic changes during OPCAB because of displacement of the heart and the use of the Trendelenburg position obtained for visualisation of posterior and lateral branches. Murkin (2000), reported that manoeuvres such as steep Trendelenburg position have been shown to increase jugular venous pressure, potentially compromising cerebral blood flow through outflow obstruction, independent of whether an otherwise acceptable mean arterial pressure is maintained. Together with a significant decrease in cardiac output, whether due to arrhythmia, dislocation of the heart, subclinical ischaemia, or a combination of these, blood flow to the brain may be significantly compromised (Murkin, 2000 Heart surg forum). In some instances patients may exhibit acute haemodynamic deterioration and instability leading to the emergency need of an intra-aortic balloon pump (IABP) counter-pulsation or CPB support.

In 2008, a meta-analysis to access the significant differences between neurocognitive outcomes in patients undergoing off-pump versus on-pump CABG was carried out by Silvana Marasco and colleagues. A database search for prospective randomised controlled trials in any language was conducted. Eight trials incorporating 892 patients fulfilled their inclusion criteria for reporting neurocognitive outcomes. Data extracted from these trials included various neurocognitive tests, Rey Auditory verbal learning, Grooved pegboard,

Trial A and B and Digit symbol. The results of this meta-analysis showed no significant neurocognitive benefit when comparing off-pump to on-pump surgery (Marasco et al, 2008).

Stroobant and colleagues (2002), examined the frequency of neuropsychological abnormalities in patients undergoing CABG with and without cardiopulmonary bypass at, one day before surgery, 6-7 days after and 6 months after surgery. The authors found, using multivariate analysis that there was no significant differences in neuropsychological performance immediately after surgery. The long term results were more favourable in the off- pump group. However, the preference to operate multiple vessel disease with CPB has to be considered (Stroobant et al, 2002). Erminio Sisillo and colleagues (2007), investigated their data base to identify the differences in the incidence of neurological complications after OPCAB and conventional CABG procedures. Eight thousand and two patients underwent isolated CABG at their institution between January 1998 and January 2005. Off pump coronary artery bypass graft surgery accounted for 1415 of the patient population. The investigators concluded that patients undergoing conventional CABG were not exposed to a greater risk of adverse neurological events when compared to the OPCAB group (Erminio, Marino, Juliano, Beverini, Salvi and Alamanni, 2007).

In 2006, Vedin and associates investigated the impact of cardiopulmonary bypass on the cognitive function of patients after CABG in a prospective randomized trial. Seventy patients between the ages of 50 and 80 years, with stable angina, ejection fraction of > 30% and a lack of tight main stem stenosis were enrolled in the study. Standardized neuropsychological tests were used to evaluate attention, verbal and visuo-spatial short term and working memory, verbal learning, delayed recall, visuo-motor speed and aspects of executive functions. The authors concluded that there were no differences in post operative cognitive

function after on pump compared to off pump coronary artery bypass grafting (Vedin, Nyman, Ericsson, Hylander and Vagge, 2006). In 2007, Hernandez and colleagues conducted a similar study on 201 patients to access neurocognitive outcomes using a 19-test neurocognitive battery at baseline, discharge, and 6 months after surgery. Neurocognitive deficit was defined as a 20% reduction from baseline in 20% of the tests. The authors found no significant difference in the two groups at discharge or at 6 months (Hernandez, Jeremiah, Brown, Donald, Likosky, Clough, Hess, Roth, Ross, Whited, O'Conner and Klemperer, 2007).

Despite the ongoing evolution in CPB management strategies, limited beneficial advances have been made to improve patient neuropsychological outcomes after bypass procedures. The comparison between CABG with and without cardiopulmonary bypass has been arduously documented and subjected to gruelling scrutiny. Previous studies, albeit predominantly retrospective in nature, have questioned the neurological benefit, if any, of performing CABG with or without cardiopulmonary bypass (Hernandez et al, 2007). In a world of evidence-based medicine, demonstrating a difference in neurological outcome between the two groups has become hackneyed and inconclusive (Marasco, Sharwood and Abramson, 2008). The available prospective clinical data are limited to trials both small in patient number and scope. To date there is no evidence from randomized trials to support the hypothesis of reduced stoke in OPCAB patients. The absence of recognized guidelines has meant that the decision to implement CPB has been left to individual surgeons (Keenan, Omar and Taggart, 2005).

2.2.3 CEREBRAL STROKE

Stroke can be defined as the rapid loss of brain function due to disturbances in the blood vessels supplying blood to the brain. It can occur as a result of ischaemia caused by thrombosis or embolism (Figure 14 left), or due to a haemorrhage (Cotran, Ramzi, Kumar, Vinay, Fausto, Nelson, Robbins, Stanley, Abbas and Abdul, 2005; Goldstein, Adams, Alberts, Appel, Brass, Bushnell, Culebras, DeGraba, Gorelick, Guyton, Hart, Howard, Kelly, Nixon and Sacco, 2006). Figure 14 (Right) below illustrates middle cerebral artery thrombosis, embolus with resultant acute ischaemia.

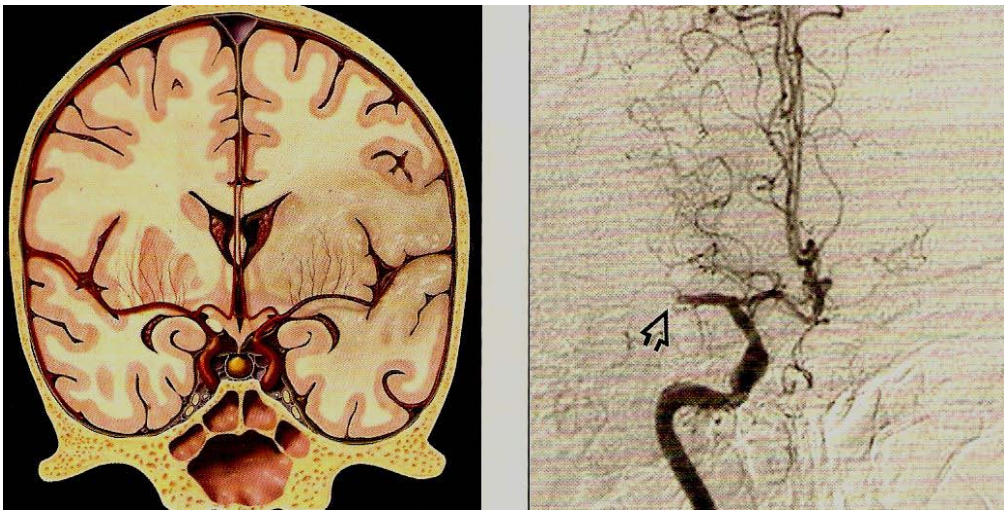


Figure: 14 (Left) Coronal graphic illustrates left (MCA) middle cerebral artery M1 embolus (M1 - horizontal segment: from MCA origin to bi/trifurcation) The proximal occlusion results in complete MCA territory infarction, including deep gray nuclei perfused by lenticulostriate arteries

Figure: 14 (Right) Anteroposterior digital subtraction angiogram (DSA) shows abrupt truncation [⇨] of the M1 segment of the right middle cerebral artery compatible with thrombosis/ embolus with resultant cerebral ischaemia (Diagnostic Imaging Cardiovascular, 2008: p**II**-1-46)

Strokes are often caused by atherosclerotic plaques present in the feeder arteries that supply blood to the brain. Figure 15 illustrated below is a graphic representation of atherosclerotic plaques in the middle cerebral artery with resultant lacunar infarction.

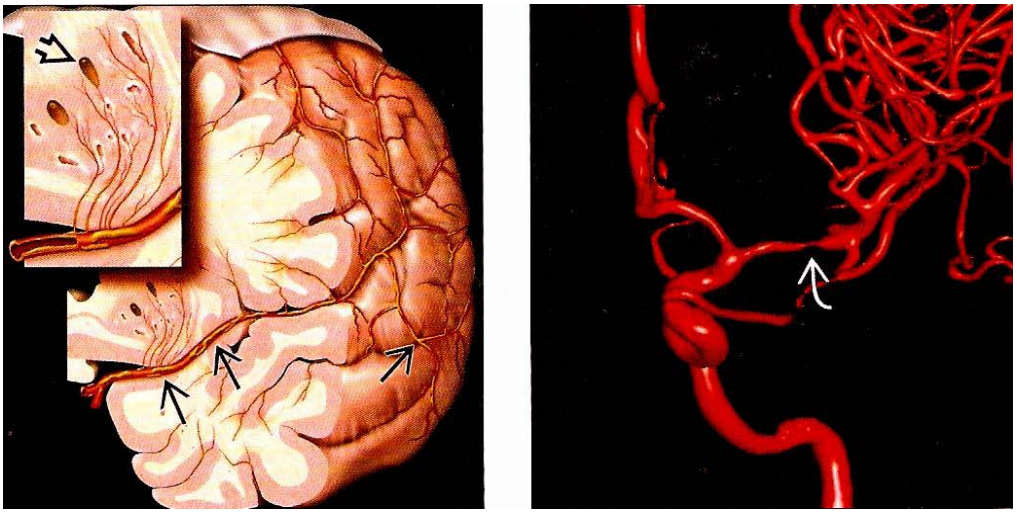


Figure: 15 (Left) Coronal oblique graphic shows atherosclerotic plaques in the left MCA. Diagram also demonstrates lacunar infarction

Figure: 15 (Right) Anteroposterior rotational 3D digital subtraction angiogram shows focal narrowing of the middle cerebral artery (Diagnostic Imaging Cardiovascular, 2008: p**II**-1-82)

Atherosclerotic plaques can activate the clotting mechanism of the blood, causing blood clots that block or obstruct blood flow in the artery, thereby leading to acute loss of brain function in a localized area. In a quarter of patients who develop stroke, high blood pressure causes the blood vessel to burst. Haemorrhage then occurs, compressing the local brain tissue. The subsequent clotting of the blood leads to blockage of blood vessels (Guyton and Hall, 2000). Eighty percent of strokes are due to ischaemia and the remainder are due to haemorrhage.

Ischaemic stroke occurs as a result of decreased or loss of blood supply to parts of the brain, initiating the ischaemic cascade. The function of brain tissue ceases if it is deprived of blood supply and oxygen for more than 60 to 90 seconds and after a few hours it will suffer

irreversible injury possibly resulting in the death of the tissue (infarction). Atherosclerosis causes narrowing of the lumen of blood vessels leading to a reduction in blood flow, by causing the formation of blood clots within the vessel, or by releasing showers of small emboli through the disintergration of atherosclerotic plaques. Embolic infarction occurs when emboli formed elsewhere in the circulatory system, typically in the heart as a consequence of atrial fibrillation, or in the carotid arteries dislodge from their point of origin and enter the cerebral vasculature, lodge and occlude brain blood vessels (Henry, Mohr, Stein and Yatsu, 1986). Figure 16 demonstrates a hyperdense right middle cerebral artery due to thrombus occluding the vessel.

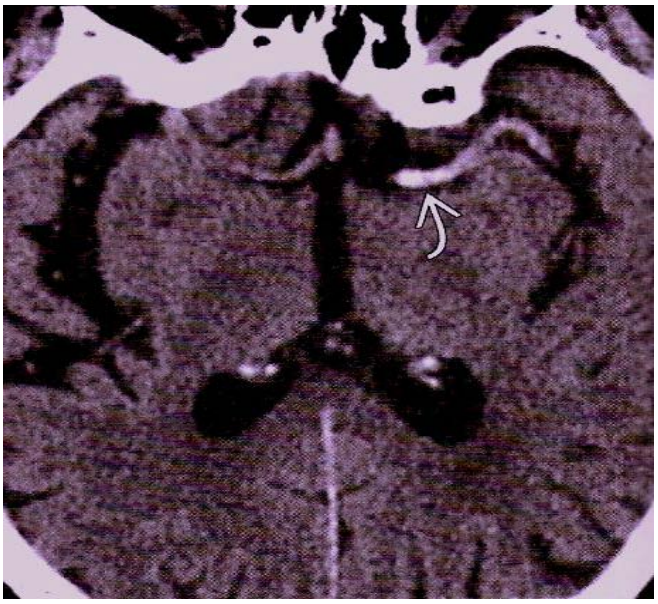


Figure: 16 Axial non enhanced CT demonstrates right MCA ↗ due to thrombus occluding the vessel (Diagnostic Imaging Cardiovascular, 2008: p**II**-1-49)

Many investigators have attempted to identify pathologic changes in the brains of cardiac patients who died postoperatively. In autopsy studies, Brooker and colleagues (1998), found small capillary arterial dilatations containing lipid microemboli in the brain (Brooker, Brown, Moody, Hammon, Reboussin, Deal, Ghazi Birry and Stump, 1998). In another study Emmrich and colleagues (2003), examined the brain of 262 patients who came to autopsy

after cardiac surgery. The authors found that 40% of the CABG patients had large infarcts and 8% showed microinfarcts. In 35% of the autopsy samples brain haemorrhages were noticed (Emmrich, Hahn, Ogunlade, Geiger, Schober and Mohr, 2003).

2.2.3.1 Neurological effect

The neurological effects of a stroke are determined by the brain area being affected. One of the most common types of stroke is the blockage of one of the middle cerebral arteries that supplies the midportion of one brain hemisphere. If the middle cerebral artery is blocked on the left side of the brain, the person is likely to become almost totally demented because of loss of function in Wernicke's speech comprehension area in the left hemisphere. He or she will be unable to speak words because of the loss of Broca's motor area for word formation. Additionally, loss of function of neural motor control areas of the left hemisphere may result in spastic paralysis of most muscles on the opposite side of the body (Weller, 1984; Asao and Hirano, 1981)

Blockage of a posterior cerebral artery causes infarction of the occipital pole of the hemisphere on the same side as the blockage, this causes loss of vision in both eyes in the half of the retina on the same side as the stroke lesion. Strokes that involve the blood supply to both the hindbrain and the midbrain are regarded as devastating because this can block nerve conduction in major pathways between the brain and spinal cord, resulting in incapacitating sensory and motor abnormalities (Guyton and Hall, 2000).

2.2.4 STROKE AFTER CORONARY ARTERY BYPASS GRAFT SURGERY

2.2.4.1 Incidence of stroke after cardiac surgery

Coronary artery bypass grafting maybe associated with adverse neurological sequelae, of which stroke is the most debilitating (Scarbrough et al., 2001). The reported frequency of stroke ranges from 0.8% to 3.2% in retrospective series (McKhann, Grega, Borowicz, Baumgartner and Selnes, 2006) and from 1.5% to 5.2 % in prospective studies (Roach et al., 1996; Stamou, Hill, Dangas, Pfister, Boyce, Dullum, Bafi, and Corso, 2001; Filsoufi, Rahmanian, Castillo, Bonster and Adams, 2008). Despite the various advances in membrane oxygenators and inline filtration, together with improved surgical techniques and cardioplegic solutions, the persistent stroke rate associated with CABG is still prevalent. In the United States alone CABG is regarded as the single largest cause of iatrogenic stroke, with between 5000 and 35000 new strokes occurring as a result of the procedure. (Stamou et al, 2001).

Stroke following CABG is reported to occur more commonly than stroke after other surgical procedures (Limburg, Wijdicks and Li, 1998; Asicone, Barnaby, Reeves, Martin, Chamberlin, Ghosh, Lim and Angelini, 2002). The fatality rate among patients with stroke after CABG is 20%, whereas overall mortality for all CABG patients ranges between 2 to 4% (McKhann, Goldsborough, Borowicz, Mellits, Brookmeyer and Gardner, 1997). In addition to the suffering that patients endure, the economic impact of stroke is substantial. The length of stay in the intensive care unit and in the hospital is significantly longer. Hospital costs are therefore, doubled (Dewey et al, 2003).

In a study conducted by Puskas et al. (2000), 10 860 patients who underwent primary coronary operation were examined at Emory University School of Medicine between 1996 and 1998. One and five year survival rates were 64% and 44% for patients with stroke, and 94% and 81% without stroke, respectively. Among the stroke groups 23% of the patient population died before being discharged from the hospital. The stroke group had a significantly longer stay in hospital, as well as higher costs (Puskas, Daniel, Winston, Wright, Gott, Brown, Craver, Jones, Guyton and Weintraub, 2000). Dacey and colleagues (2005), from the New England Cardiovascular disease study group, compared survival rates in patients with and without stroke. They found that survival rates at 1 year were 83% versus 94.1%, at 5 years 58.7% versus 83.3% and at ten years 26.9% versus 61.9% respectively. Those patients with stroke had a 3- fold greater risk of death during the 10 year follow up (Dacey, Likosky, Leavitt, Lahey, Quinn, Hernandez, Quinton, Desimone, Ross and O' Conner, 2005).

2.2.4.2 Predictors of stroke risk in coronary artery bypass patients

A study conducted by Mckhann et al. (1997), comprised of 456 patients undergoing CABG. Stroke was detected postoperatively by the study team and confirmed by neurologic consultation and computed tomographic scanning. After correlating different risk factors with stroke, the authors deduced that patients at a higher risk of post CABG stroke are dominated by cardiovascular factors such as hypertension, carotid bruit, previous stroke, diabetes, peripheral vascular disease and increasing age. These findings have also been supported by other authors (Herlitz, Wognsen, Haglid, Hartford, Hjalmarson and Karlson, 1998; Ascione et al, 2002; Ancona, Ignacio, Ibarra, Baillot, Matieu, Doyle, Metras, Desaulniers and Dagenais, 2003). Other contributing mechanisms of stroke include

atherosclerotic emboli from the aorta, hypotension from ventricular dysfunction, and reactive thrombocytosis (Hartman, Yao, Bruefach, Barbut, Peterson, Purcell, Charlson, Gold, Thomas and Szatrowski, 1996; Crowley, hannigan and Daly, 1994).

Several studies have tried to identify markers of stroke post CABG. Significant risk factors identified included embolic phenomena, proximal aortic atherosclerosis, intracardiac thrombus, intermittent clamping of the aorta during surgery, preoperative history of endocarditis, alcohol abuse, perioperative dysrhythmia, poorly controlled hypertension and the development of a low output state after cardiopulmonary bypass. (Wolman, Kanchuger, Marschall, Mangano, Newman, Roach, Ley, Aggarwal, Nussmeier and Biosvert, 1999; Houge, Murphy, Schechtman and Davila 1999; Ancona, Ibarra, Baillot, Mathieu, Doyle, Metras, Desaulniers, Dagenais, 2003; Ascione, 2002). Houge et al. (1999), in their study found atrial fibrillation combined with low cardiac output to increase the rate of late postoperative stroke. In a retrospective study, Lahtinen and colleagues attributed 36% of postoperative strokes to atrial fibrillation (Lahtinen, Biancari, Salmela, Mosorin, Satta, Rainio, Rimpilainen and Juvonen, 2004).

Stamou Sotiris and colleagues (2001), investigated the risk factors, prevalence and prognostic implication of postoperative stroke in 16 528 consecutive patients who underwent CABG at the Washington hospital centre between 1989 and 1999. The authors reported that postoperative stroke occurred in 333 patients which constituted 2% of the patient population. These patients were significantly older and more frequently female. Twenty one of the patients with carotid artery disease developed stroke postoperatively. The authors concluded that stroke can be predicted by pre and postoperative clinical factors which include chronic renal insufficiency, recent myocardial infarction, previous cerebrovascular accident, carotid

artery disease, hypertension, diabetes, age > 75years, moderate to severe left ventricular dysfunction, low cardiac output syndrome and atrial fibrillation. Postopertive stroke was also associated with longer postoperative hospital stay (11 ± 4 versus 4 ± 3 days) and higher in hospital mortality (14% versus 2.7%) for patients without stroke (Sotiris et al, 2001). Neuropsychological testing for the assessment of subtle changes was not performed in this trial. Detection of aortic atherosclerosis was done by palpation and not by ultrasonography. The Comorbid conditions listed in the Sotiris trial have also been identified as predictors of postoperative stroke in previous studies (Mooe, Bell, Johnston and Prough, 1999; Anderson, O' Brien, MaWhinney, VillaNueva, Moritz, Sethi, Henderson, Hammermeister, Grover and Shroyer, 1999). Similar findings were also reported by Bucerius et al who did a risk factor analysis of 16,184 patients undergoing coronary artery bypass graft surgery (Bucerius, Gummert, Borger, Walther, Doll, Onnasch, Metz, Falk and Mohr, 2003).

Baker and co investigators (2005), retrospectively analysed a large data base at two south Australian institutions to determine potential risk factors for stroke. A total of 4,380 patients who received CABG on cardiopulmonary bypass between 1992 and 2002 were included in their trial. The authors identified age, diabetes and history of previous stroke to be important factors. They found that the temperature at which cardiopulmonary bypass was conducted had no effect. Therefore, nasopharyngeal temperature on bypass was not identified as a risk factor for stroke (Baker, Hallsworth and Knight, 2005).

In contrast, other studies have reported a significant difference in the risk of stroke between normothermic (3.1%) and hypothermic bypass 1.0% (Mora, Henson, and Weintraub, 1996; Martin, Craver and Gott, 1994). Their diagnosis was confirmed by a neurologist and computed tomographic scans. Twenty five percent of the stroke patients had a previous

history of stroke, as compared to 4.8% of the non stroke patients. Fifty one percent of the stoke patients also had diabetes mellitus. These patients spent a longer time in intensive care and the 30 day mortality was 17.6% as compared to 1.7% of non stroke patients. The impact of stroke on patient outcome is likely to remain substantial in light of the predicted increase in elderly patients, who often suffer from comorbidity predisposing to stroke and will require cardiac surgery (Jones, Weintraub, Craver, Guyton and Cohen, 1991; Peterson, Cowper, Jollis, Bebehuk, Delong, Muhlbaier, Mark and Pryor, 1995).

Figure 17 is a diffusion weighted image of a 73 year old lady presenting with confusion and left arm weakness 2 days after on-pump surgery. Previous history of stroke and cerebrovascular disease is indicative of pathological conditions associated with the cerebrovascular system or the prevalence of carotid bruit (Antunes, Oliveira, and Antunes MJ, 2003).

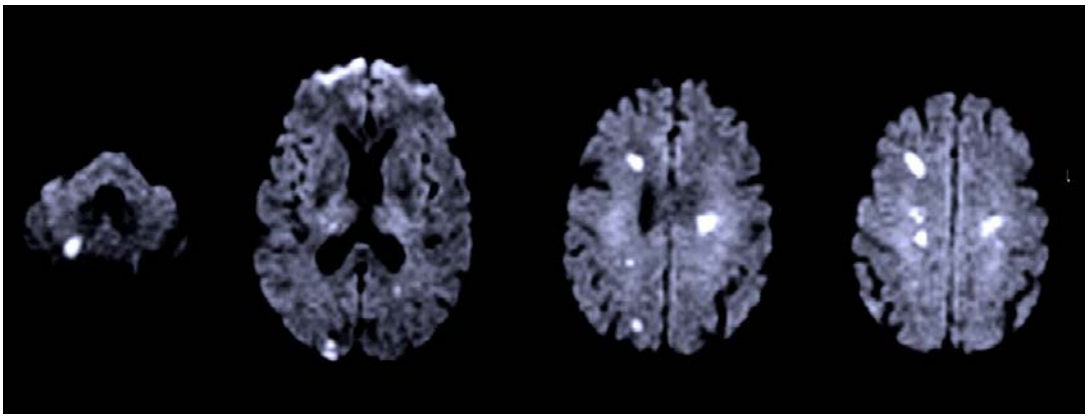


Figure: 17 Diffusion weighted imaging of a 73 year old women with confusion and Left arm weakness 2 days after on pump bypass surgery shows multiple diffusion abnormalities scattered throughout the brain (Sotiris et al, 2001).

2.2.4.3 Stroke: Age related outcome

In a study conducted by Almassi and co-workers (1999), prospective data was collected on 4,941 patients undergoing cardiac surgery. The authors found that patients below 60 years of age had a 1.6% incidence of stroke which increased to 5.25% for patients above 70years (Almassi, Sommers, Moritz, Shroyer, London, Henderson, Sethi, Grover, and Hammermeister, 1999). Figure 18 shows the relationship of increasing age and postoperative stroke rate in their study. Another study reported that the risk of stroke during CABG is a function of patient age. The risk of stroke in patients less than 45 years of age was 0.2 percent which increased to 8% for patients older than 75years. The incidence of severe atherosclerosis in patients between the ages of 75 to 80 years is almost 10% (Gardner, Horneffer, Manolio, Hoff and Pearson, 1986).

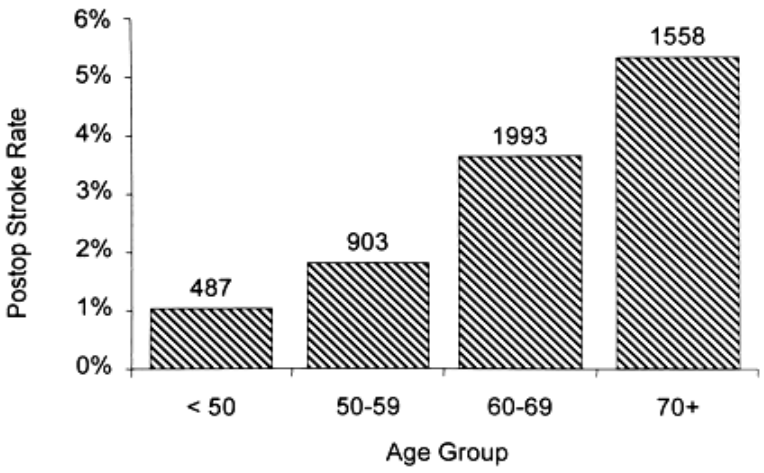


Figure: 18 Relationship between increasing age and postoperative stroke rate (Almassi et al, 1999)

A study also found that patients with a history of hypertension and those with elevated systolic blood pressure above 120 mmHg were categorized as higher risk patients for

perioperative stroke (Almassi et al, 1999). Diagram 19 shows the relationship between the level of systolic pressure and stroke.

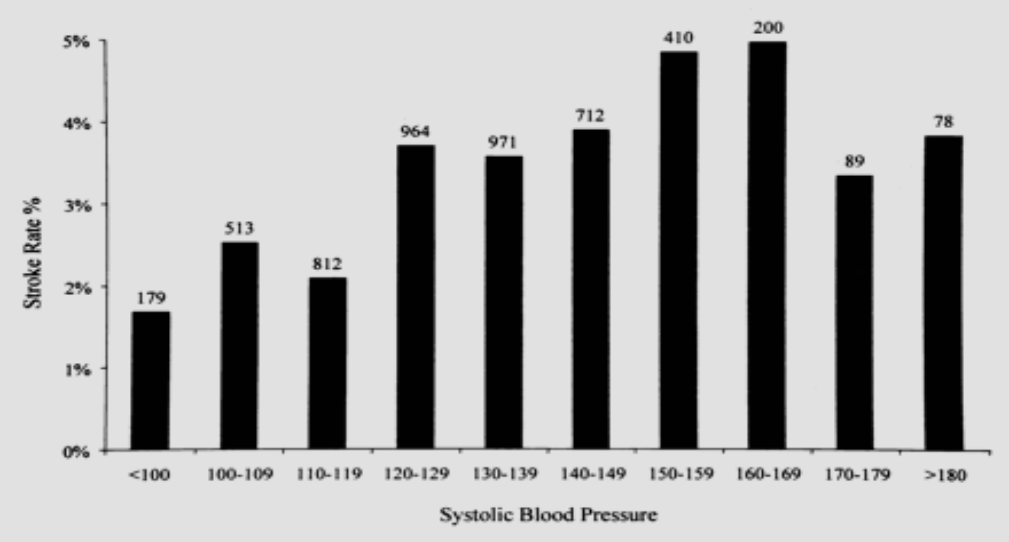


Figure: 19 Relationship between level of systolic blood pressure and stroke (Almassi et al, 1999)

2.2.4.4 Timing of stroke after CABG

In order to provide insight into the aetiology of stroke so that preventative measures could be undertaken, Filsoufi and colleagues (2008), investigated the timing of the event (early ≤ 24 hours versus delayed). The study analyzed the incidence and timing of stroke, the topography and mechanisms of cerebral lesions, independent predictors and late outcome after stroke in patients undergoing coronary artery bypass graft surgery. The investigators retrospectively analyzed prospectively collected data from 2985 patients who had isolated CABG. Off pump CABG was performed according to preference and favoured in elderly patients with significant comorbidities. Patient demographics, risk factors, operative information and postoperative data were analyzed. The logistic European system for cardiac operative risk evaluation (EuroSCORE) was used to determine the risk stratification. Diagnosis was made

by a neurologist and confirmed in most patients by postoperative computed tomography (CT) or magnetic resonance imaging (MRI).

The authors reported a 1.6% (n=48) incidence of stroke and the results were similar between conventional CABG (1.6%) and off pump CABG (1.4%). Early stroke ($\leq$ 24 hours) occurred in 25 patients (52%). Brain imaging was obtained on 44 of the patients, 44 had computed tomography and 3 had magnetic resonance imaging. Results for 33 of the 44 patients were positive showing embolic stroke in 25 patients, watershed in 5 and a mixed pattern in 3 patients. Predictors of stroke include being female, extensive aortic calcification, previous stroke, and congestive heart failure. In hospital mortality rate for stroke was 16.7%. The mortality rate for early stroke was higher at 24% (6 of 25) as compared with 9% (2 of 23) in late stroke. The authors concluded that there is limited information on brain imaging analysis and long term survival after stroke. A larger percentage of the strokes were diagnosed in the first 24 hours after surgery suggesting that intraoperative events are at the origin of neurologic adverse incidents.

Two of the important postoperative complications in stroke patients were respiratory failure requiring prolonged ventilation and systemic infection. This finding is also supported by Likosky and others who found that 42% of strokes were identified within a day after surgery and a further 20% by day 2 (Likosky, Marrin, Caplan, Baribeau, Morton, Weintraub, Hartman, Hernandez, Braff, Charlesworth, Malenka, Ross, and O' Connor, 2003). Preoperative computed tomography is suggested for patients at risk without previous history of stroke (Filsoufi, Rahmanian, Castillo, Bronster and Adams, 2008). Restrepo et al. (2002), suggest that diffusion (DWI) and perfusion (PWI) imaging offer detailed diagnostic advantages over conventional imaging in assessment of patients undergoing CABG

(Restrepo, Wityk, Grega, Borowicz, Barker, Jacobs, Beauchamp, Hillis and McKhann, 2002).

2.2.4.5 Watershed strokes after cardiac surgery

Watershed strokes after cardiac surgery is more prevalent than in any other stroke population. Watershed strokes can be attributed to global hypoperfusion during cardiac arrest or carotid artery stenosis (Gottesman, Sherman, Grega, Yousem, Borowicz, Selnes, Baumgartner and McKhann, 2006). Bilateral watershed infarcts after cardiac surgery are more reliably detected by MRI and diffusion weighted imaging in contrast to clinical diagnosis. Gottesman and colleagues explored the relationship between mean arterial pressure and watershed infarcts in 98 on pump CABG patients. The authors concluded that patients with a decrease in mean arterial of 10mmHg (intraoperative compared with preoperative) were 4.1 times more likely to have bilateral watershed strokes (Gottesman et al, 2006). Figure 20 shows MRI (DWI) images of patients with acute territorial infarct and watershed strokes.

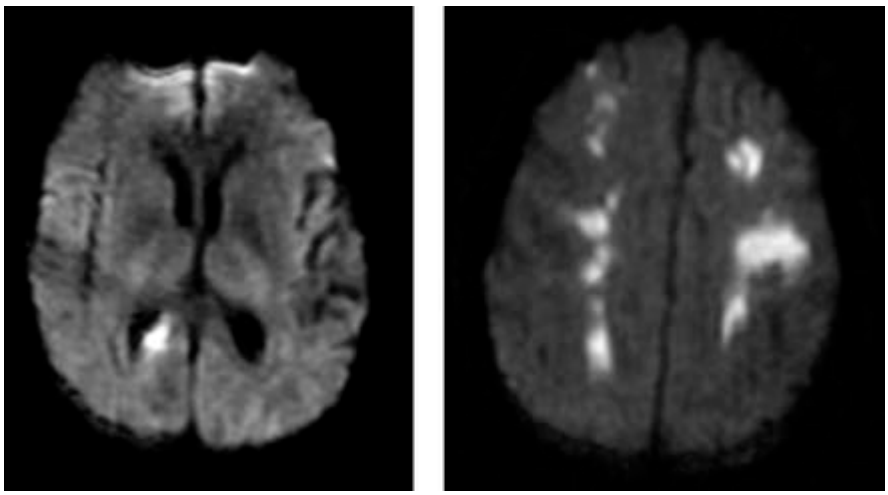


Figure: 20 Two MRI (DWI) images of 2 patients with postoperative infarcts: on **(Left)** Patient with acute territorial infarct **(Right)** Acute bilateral watershed stroke (Gottesman et al, 2006)

2.2.4.6 Epiaortic ultrasonographic scanning and the risk of perioperative stroke

Atherosclerosis of the thoracic aorta has been identified as an important predictor of stroke and cognitive dysfunction after cardiac surgery (Bar-Yosef et al, 2004; Hogue et al, 1999; Arrowsmith, Grocott, Reves and Newman 2000; Blauth et al, 1992). It has become a frequent finding during cardiac surgery as a consequence of the growing population of older patients (Zingone, Rauber, Gatti, Pappalardo, Benussi, Dreas and lattuada, 2006). This population is also at higher risk for age related cerebrovascular disease which may predispose them to severe neurological complications, including stroke in the postoperative period (McKhann, Grega, Borowicz, Baumgartner and Selnes, 2006). Studies suggest that detection of atherosclerotic lesions of the ascending aorta with the use of epiaortic scanning before manipulation and cannulation may reduce the risk of stroke (McKann, Borowicz, Baumgartner and Selnes, 2006; Zingone et al, 2006; van der Linden, Bergman and Hadjinikolaou, 2007; Murkin, 2006).

Surgical manipulation of the aorta during cannulation, aortic cross clamping and proximal anastomosis can cause dislodgement of atherosclerotic plaque with resultant cerebral atheroembolism (Houge, Palin and Arrowsmith, 2006). The jetting effect due to high flow patterns generated at the tip of the CPB aortic cannula may also result in the sand blasting effect facilitating the disruption of atheroma (Scharfschwerdt, Richter, Boehhmer, Detlef and Sievers, 2004). Epiaortic ultrasound is a more sensitive method rather than palpation or transesophageal echocardiography for the detection of atheroma (Davila Roman, Barzilai, and Wareing, 1994). The use of epiaortic scanning together with the " no touch" technique has been shown in observational studies to be associated with a low stroke rate and cognitive dysfunction even in high risk patients (Wareing, Davila, Barzilia, Murphy, and Kouchoukos,

1992; Royse, Ajani, Symes, Maruff, Karagiannis, Gerraty, Grigg and Davis, 2000; Gold, Torres, Maldarelli, Zhuravlev, Condit, and Wasnick, 2004, Hammon, Stump, Butterworth, Moody, Kashemi, Deal, Kincaid, Oaks, and Kon, 2006, Zingone, Rauber, Gatti, Pappalardo, Benussi, Dreas, and Lattuada, 2006).

Figure 21 shows the pathologic specimens of patients who underwent replacement of the ascending aorta. Proposed strategies for the management of atherosclerosis of the ascending aorta include epiaortic scanning, avoidance of partial occlusion cross clamp ("single cross clamp technique), internal mammary artery for proximal bypass graft anastamosis (Y graft), cannulation of the axillary artery, innominate or distal aortic arch, modified aortic cannula with low velocity jetting and incorporated filter (Houge et al, 2006). In a multicentre randomized trial, particulate emboli were captured in 98.6% of cases in which an intraaortic filter was deployed before aortic cross clamp removal (Banbury, Kouchoukos, Allen, Slaughter, Weissman, Berry and Horvath, 2003; Cook, Zehr and Orszulak, 2002). Recently Schmitz and Blackstone showed that intra-aortic filtration may reduce adverse neurologic events in CABG patients by as much as 50% (Schmitz and Blackstone, 2001). These findings have been supported by other investigators who found that patients receiving intra aortic filtration suffered less Type 1 cerebral injury (Greinecker, 2003).

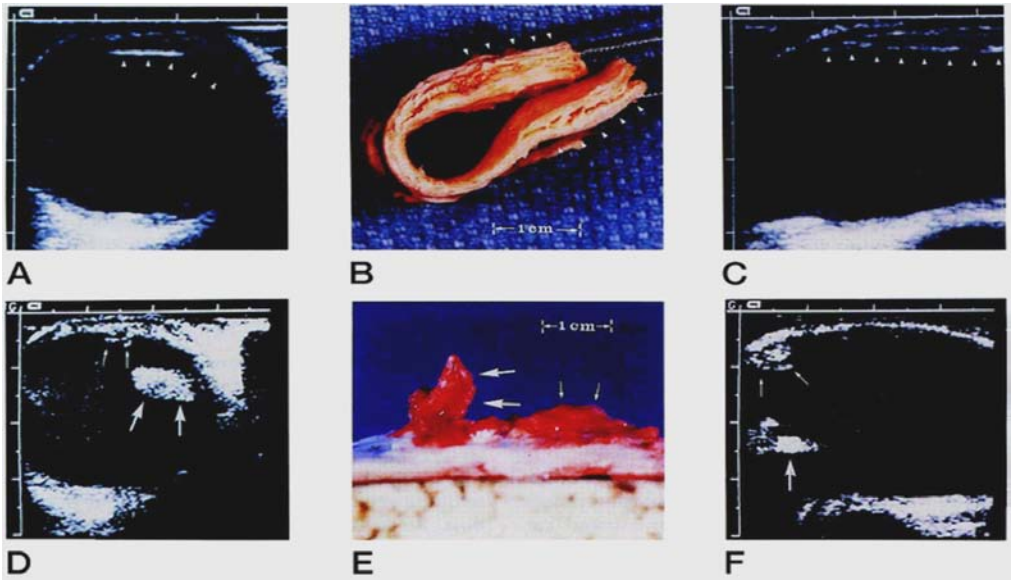


Figure: 21 Epiaortic ultrasound images and pathologic specimen depicting atherosclerosis of the ascending aorta **(Panel A and C)** Ultrasound scans demonstrate circumferential intimal thickening anteriorly **(Panel B and E)** Pathologic specimen confirms the diagnosis **(Panel D and F)** Intimal thickening and large sessile atheroma (David-Roman et al, 2004)

2.2.4.7 Effect of pharmacological agents on the central nervous system

In a study of 810 consecutive candidates who were enrolled for isolated CABG, Aboyans and colleagues (2006), investigated the effect of statins on the incidence of stroke using a specific database. Pravastatin was used in 209 (26%) of patients, simvastatin, 95 patients (12%), atorvastatin, 90 patients (11%), cerivastatin, 53 patients (7%), fluvastatin, 8 patients (1%). Stroke occurred in 11 cases and transient ischaemic attack was noted in four patients during the first month of surgery. In one fatal case atrial fibrillation preceded stroke. Using univariate and multiple regression models to determine predictive factors the authors concluded that preoperative statins were protective. Taking statins at least 4 weeks prior to surgery revealed to be significantly and independently associated with a lower risk of perioperative neurological events (Aboyans, Labrousse, Lacroix, Guilloux, Seifeddine, Sekkal, Guyader, Cornu and Laskar, 2006). These findings have also been supported by other

meta-analyses studies which demonstrated a significant risk reduction in stroke (Dotani, Elnicki, Jain, and Gibson, 2000; Crouse, Byrington, Hoen and Furberg, 1997; Furberg, Adams, Applegate, Byrington, Espeland, Hartwell, Hunningshake, Lefkowitz, Probsfield, Riley and Young, 1994).

There have been a number of different pharmacologic agents demonstrating cerebroprotective efficacy in animal models. However little progress has been made in the area of clinically effective pharmacologic cerebral protection (Murkin, 2001). In a study of 300 CABG patients, Zaidan and colleagues (1991), witnessed a trend towards increased number of strokes with high dose thiopental treated patients (3.3%, 5 of the 149 patients) compared to the placebo group (1.3%, 2 of the 151 patients). They also noticed delayed awakening and higher dose inotropic support in the treatment group (Zaidan, Klochany, Martin and Ziegler, 1991).

In a recent multicentre study assessing aprotinin, patients undergoing CABG were separated into those receiving shed blood (>300mls) and those receiving none. The patients were analyzed for perioperative cerebrovascular accident (CVA). The investigators found that patients with aprotinin administration were associated with a lower incidence of stroke (p = 0.04), lower transfusion requirement (1.1%) and blood loss as compared to the placebo group (2.6%). The return of shed blood in the placebo group increased the risk of CVA more than 3 fold (3.1% vs 0.0%). The findings support the premise that returned shed blood is associated with poor central nervous system outcomes and that aprotinin decreases the risk associated with receiving shed blood (Stump and Murkin, 2000). This finding has been further supported by other meta-analysis studies (Murkin, 2001).

2.2.4.8 Extra and Intracranial atherosclerotic disease

Intrinsic cerebrovascular disease, combined with procedural risks of embolic and hypotensive episodes during cardiac surgery, play a vital role in the genesis of perioperative central nervous system insult (Murkin, 2006; Aboyans, Lacroix, Guilloux, Rolle, Guyader, Cautres, Cornu and Laskar, 2005). In a study of 201 Korean patients presenting for CABG surgery, Yoon and co investigators (2001), found that more than 50% of patients presented with either extracranial (ECAD) or intracranial atherosclerotic disease (ICAD). Thirteen patients presented with both intracranial and extracranial disease. In the same series 25.4% of patients had postoperative neurological injury. The authors concluded that the presence of both ICAD (Figure 22) and ECAD (Figure 23) increase the risk of central nervous injury exponentially (Yoon, Bae, Kang, Lee, Hong, Kim, Park and Roh, 2001, JACC 2011 Vol. 57, No.8:1002-44).

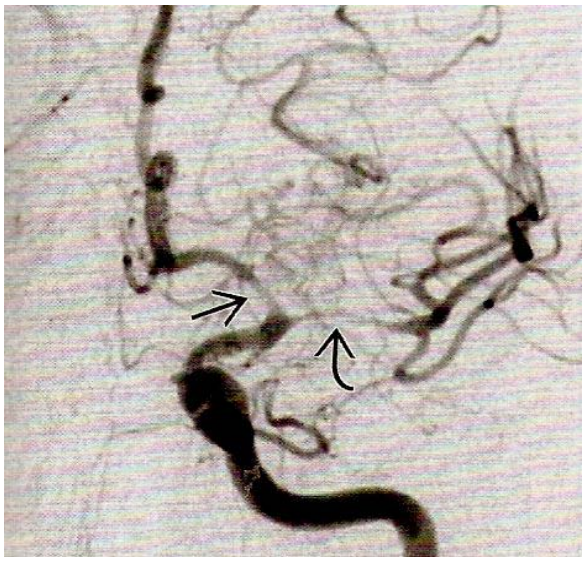
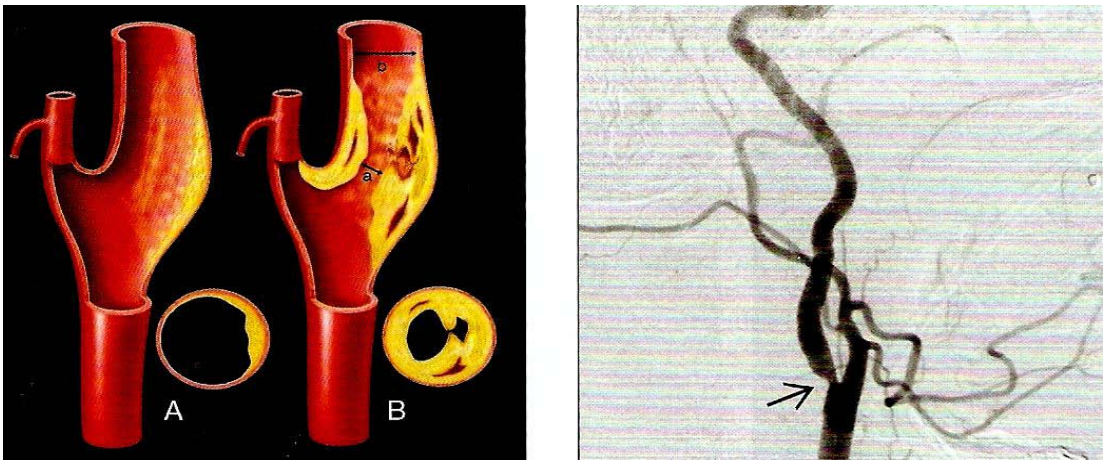


Figure: 22 Anteroposterior digital subtraction angiogram of a left internal carotid artery injection demonstrates severe stenosis of the proximal middle cerebral and mild-moderate stenosis of the proximal anterior cerebral arteries (Diagnostic Imaging Cardiovascular, 2008: p**II**-1-85) Intracranial



(Left) **(Right)**

Figure: 23 (Left) Graphic illustration of (A) mild: "fatty streaks"; slight intimal thickening (B) Severe: Intraplaque hemorrhage ulceration, platelet aggregation **(Right)** Lateral digital subtraction angiogram, common carotid artery injection shows classic example of atherosclerotic stenosis ➔ at the origin of the internal carotid artery (Diagnostic Imaging Cardiovascular, 2008: p**II**-1-78) Extracranial

In another study, 151 patients aged between 41 and 82 years of age were scheduled for CABG. Patients were screened for carotid and intracranial artery disease using magnetic resonance angiography. Cervical carotid artery stenosis of > 50% was identified in 16.6% of patients and intracranial artery stenosis of >50% narrowing was identified in 21.2% of patients. It was estimated that 40% of strokes in these patients could be attributed to ipsilateral carotid artery disease (Naylor, 2004). In 2000, Hirotani and co-workers conducted a study to determine predictors of stroke in 472 patients undergoing CABG. The purpose of the study was to determine the correlation between the presence of carotid or vertebral artery stenosis and postoperative stroke. Patients were screened by duplex scanning for the presence of carotid and vertebral artery occlusion, which was characterized by the degree of wall thickness as none or trivial (<50%), mild (≥50%, <75%), moderate (≥75%, <90%), severe (≥90%, <100%). All subjects underwent computed tomography and were cerebral infarct was observed, magnetic resonance imaging and angiography was performed. The severity of extracranial carotid artery stenosis was found to be a prominent predictor of stroke.

The authors concluded that in order to reduce the rate of stroke, indications for prophylactic carotid endarterectomy (CEA) should be extended to asymptomatic patients with carotid artery stenosis greater than 75% (Hirotani, Kameda, Kumamoto, Shirota and Yamano, 2000).

Various authors have found a correlation between the presence of carotid artery stenosis and postoperative stroke. However, the occurrence of stroke ranges widely probably because the degree of stenosis that was defined differed from 50% to 70% stenosis (Schwartz, Bridgman, Kieffer, Wilcox, McKhann, Tawil and Scott, 1995; Faggioli, Curl and Ricotta, 1990). Cerebrovascular disease is an important factor in the cause of stroke after coronary artery bypass graft surgery (Gold, Charlson, Williams, Szwtrowski, Peterson and Pirraglia, 1995).

2.2.4.9 The effect of single or double aortic clamping on stroke rates

The effect of single (SCT) or double (DCT) aortic cross clamping on the rate of stroke was investigated recently at the Siyami Ersek Thoracic and Cardiovascular Centre. Patients preoperative, perioperative and postoperative data were collected retrospectively and stored in a database. The team evaluated 1100 patients who underwent CABG. In the SCT group (n=550), 7 patients had stroke and in the DCT group (n=550), 9 patients had stroke. Although the number of patients in the SCT group was smaller it was not statistically significant (Ates, Yangel, Gullu, Sensoz, Kizilay and Akcar, 2006). It is believed that performing proximal anastomoses routinely under side biting clamp reduces the ishaeamic heart period and is better for myocardial protection. In contrast other investigators argue that single cross clamping reduces the risk of cerebral embolism whilst manipulating the aorta (Aranki et al, 1994).

Stroke after CABG remains to be a deleterious complication (Ancona et al, 2003). Patients with pre existing risk factors for cerebrovascular disease are high at risk for stroke and can be identified before surgery. Not much is known about the vasculature of the brain prior to surgery. Neurologists can play an active role in identifying those at risk for adverse neurological outcomes (McKhann et al, 2006). Identification of stroke characteristics, associated with adverse outcome can not only aid in prognostication but identify future interventions as more is understood about the mechanisms that result in stroke (Gottesman et al, 2006).

Stroke after cardiac surgery remains a serious and morbid complication associated with a high mortality rate. Several risk factors have been identified as predictors of stroke during CABG. Modification of patient related factors and surgical practice to alter the predictors and added caution to the management of blood pressure as well as maintenance of sinus rhythm postoperatively could reduce the rate of stroke (Almassi et al, 1999). Furthermore the “no touch” technique, the role of aortic atheroma and the innovative steps taken to minimize risk (epiaortic scanning, intra aortic filtration) needs to be evaluated (Sotiris et al, 2001). Women were found to be at higher risk than males for postoperative stroke and in-hospital mortality (Houge et al, 1999). Patients with a previous history of stroke and atherosclerosis of the ascending aorta are at a much higher risk of perioperative stroke (Aboyans et al, 2006).

2.2.5 NEUROCOGNITIVE CHANGES FOLLOWING CORONARY ARTERY BYPASS GRAFT SURGERY

Adverse neurological complications following cardiac surgery have been reported since the dawn of the specialty and represent one of the greatest challenges to coronary artery bypass grafting (Baumgartner, 2007; Knipp, Matatko, Wilhelm, Schlamann, Thielmann, Losch, Diener and Jakob, 2008). Cognitive decline is regarded as the most common cerebral complication after CABG and is often difficult to recognise clinically. According to Selnes et al. (1999), cognitive decline may affect up to 80% of patients at hospital discharge. When compared to patients without any adverse neurological outcomes after coronary revascularization, cognitive deficit is associated with a 10% increase in in-hospital mortality, a twofold increase in length of hospital stay, a fourfold higher rate of discharge to a nursing facility and a longer duration of rehabilitation (Knipp et al, 2008). In South Africa this increases the financial burden on the already strained health care resource.

It is not uncommon to encounter patients after cardiac surgery that are confused or display some sort of memory loss and are unable to complete concentration related activities (Slater, Guarino, Stack, Vinod, Bustami, Brown, Rodriguez, Magovern, Zaubler, Freundlich and Parr, 2009). Impairment to cognition may also include temporary reduction in the ability to form short term or long term memory. The ability to repeat short term memory tasks such as phone numbers may be disrupted. Reductions in the formation of new long term memory may be observed because it requires higher degrees of attention than short term memory tasks (American Family Physician, 2003; ICU Delirium.org). The individual loses the capacity for clear and coherent thought. This is apparent in the lack of any goal directed thinking, the inability to concentrate and incoherent speech. Higher levels of mental skill

required for processing problem solving is also impaired (American Family Physician, 2003; ICU Delirium.org).

Recently recognition of the brain as a potential target of injury during cardiopulmonary bypass (CPB) has been greatly magnified (Mckenzie, Andropoulous, Dibardino and Fraser, 2005). Roach et al. (1996), described coronary artery bypass graft surgery with the use of cardiopulmonary bypass to be associated with significant cerebral morbidity, usually manifested as cognitive decline or stroke. The authors found that the incidence of cognitive decline ranged from about 3% to 50%, depending on patient characteristics, definition of decline, and timing of neuropsychologic assessment (Roach et al, 1996). Van Djik et al. (2000), in their comparable study demonstrated that 23% of patients presented with cognitive decline 2 months after surgery. Although the degree of cognitive decline does not affect many patients in functional terms, a proportion of patients with cognitive decline become sufficiently disabled to affect their routine daily function and work (Roach et al, 1996).

In the prospective study carried out by Roach et al. (1996), 2108 patients were evaluated from 24 United States institutions for two general categories of neurologic outcome: Type I (focal injury, stupor or coma at discharge) and Type II (deterioration in intellectual function, memory deficit, or seizures). The authors observed adverse cerebral outcomes in 129 patients (6.1%). A total of 3.1% had Type I neurologic outcomes (8 died of cerebral injury, 55 had nonfatal strokes, 2 had transient ischaemic attacks, and 1 had stupor), and 3.0% had Type II outcomes (55 had deterioration of intellectual function and 8 had seizures). Patients that presented with adverse cerebral outcomes had higher in-hospital mortality (21% of patients with Type I outcomes died, vs 10% of those with Type II and 2% of those with no adverse cerebral outcomes) (Roach et al, 1996). These documented results highlight the medical

importance of adverse cerebral outcomes after CABG surgery. This includes economic implications as well (Mangano, 1995; Mora Mangano, 1990; Newman, Kirchner, Phillips, Graver, Grocott, Jones, Malk, Reves and Blumenthal, 1996).

2.2.5.1 Cerebral oxygen desaturation as a predictor of cognitive decline and length of hospital stay

A study conducted by Slater et al. (2009), examined the relationship between intraoperative cerebral oxygen saturation using the Invos cerebral oximeter and neurocognitive decline as well as length of hospital stay. 265 patients undergoing coronary artery bypass grafting were enrolled in the study of which 240 met the inclusion criteria. Neurocognitive testing was performed preoperatively, prior to discharge and at 3months. The neurological assessment included the presence or absence of visual disturbance, aphasia, paralysis or weakness and mental status evaluation. Cognitive function was assessed using a battery of standardized neuropsychologic tests. The tests were conducted to evaluate the domains of attention, memory, manual dexterity and frontal eye field dysfunction. Frontal lobe oculomotor activity was measured by saccadic and antisaccadic eye movements. The investigators also used the delirium rating scale (DRS) for assessment of postoperative signs of delirium. Patients were simultaneously evaluated for anxiety and depression as performance of neuropsychologic tests can be influenced by a patient's mood state and anxiety level.

Of the 240 patients enrolled in the study, 143 (60%) developed postoperative cognitive decline and 58 patients (29%) had cognitive decline at 3 months. Of the 58 patients 33 patients had cognitive decline at discharge. Patients with cognitive decline had longer aortic cross clamp and bypass times and a higher score on the delirium rating scale. Patients with prolonged cerebral desaturation had a significantly higher risk of postoperative cognitive

decline. The authors concluded that intraoperative cerebral oxygen desaturation is significantly associated with an increased risk of cognitive decline and prolonged hospital stay. The association between cerebral oxygen desaturation during cardiac surgery and postoperative cognitive dysfunction has also been supported by other studies (Yao, Tseng, Ho, Levin and Illner, 2004; Yao, Levin, Wu, Illner, Yu, Huang and Tseng, 2001).

2.2.5.2 Delirium in the postoperative CABG patient

Patients undergoing cardiac surgery are at increased risk of developing delirium, which predominantly affects elderly cardiac patients. This is associated with longer hospital stay, placement in a care facility and reduced cognitive and functional recovery (Koster, Manp, Hensens, van de Palen, 2009). Delirium can be defined as an acute and relatively sudden decline in attention, focus, perception and cognition. It is commonly associated with a disturbance of consciousness manifested as a reduced clarity of awareness of the surrounding environment. Delirium itself is not a disease, but rather a clinical syndrome which occurs as a result from an underlying disease or problem with mentation.

The components of delirium include the inability to focus attention, confusion, impairment of awareness and temporal orientation. Therefore, it can be regarded as the common manifestation of brain or mental dysfunction (Gunther, Morandi and Ely, 2008). Delirium can be superimposed into a pre-existing dementia. The question often posed when diagnosing delirium is whether the patient has dementia instead. Both delirium and dementia cause disturbances of memory, but the person with dementia does not reflect the disturbance of consciousness as depicted by someone with delirium.

Dementia is insidious in nature and thus progresses slowly, while delirium on the other hand begins with a sudden onset and acute symptoms. A person suffering from dementia appears to be clear headed but can harbour delusions. Since there is no cure for dementia it is vital to prevent it from happening in the first place (Boustani, Peterson, Hanson and Harris, Lohr, 2003; Weller, 1984; Jack de Groot, 1991).

Koster et al. (2009), conducted a study to determine the long term cognitive and functional outcomes of postoperative delirium after cardiac surgery. 112 consecutive patients, aged 45years and older who underwent CABG were enrolled in this prospective observational study. The diagnostic criteria used by the psychiatrist were based on nursing documentation and the diagnostic and statistical manual of mental disorders criteria. These criteria included: disturbance of consciousness with reduced ability to focus, sustain or shift attention; changed cognition or the development of a perceptual disturbance; disturbance which develops over a short period of time and fluctuates over the course of the day; evidence from history, physical examination or laboratory findings that the disturbance is caused by intoxication, medication or a physiological consequence of general condition. A questionnaire was used to evaluate cognitive and functional outcomes 1 to 1.5 years after cardiac surgery.

After discharge 25 patients (24.3%) had memory problems and 24 (23.3%) had concentration problems. Eleven patients were confused at discharge. Twenty nine patients experienced sleep disturbances after discharge. The incidence of sleep disturbance was higher for those patients who experienced delirium. 26.5% of patients were dependant in daily activities after surgery. The common dependency was taking a shower. 36.8% of patients were dependant on a walking stick or a walker. The authors concluded that postoperative delirium after cardiac surgery may be associated with increased mortality, poor

cognitive and functional outcome as well as longer duration of hospital and nursing home placement.

Rockwood and colleagues (1999), observed dementia in older patients without cognitive and functional impairment. The investigators determined that the incidence of dementia was 5.6% yearly over a 3 year period for those without delirium and 18.1% per year for those with delirium. In the study only 21% of the patients with delirium were alive at follow up, compared to 57% without delirium (Rockwood, Cosway, Carver, Jarrett, Stadnyk and Fisk, 1999).

When cognitive deficit becomes permanent, it is referred to as postoperative cognitive dysfunction (POCD), which is a predictor of death, functional capability and rehabilitation (Amador and Goodwin, 2005; Bucerius, Gummer, Borger, Walther, Doll, Falk, Schmitt, and Mohr, 2004; Hanning, 2005; Lewis, Maruff and Silbert, 2005). Prolonged postoperative cognitive dysfunction (POCD) is a frequent consequence after cardiac surgery. However, it also afflicts non cardiac surgery patients. The initial cause of POCD was thought to be cardiopulmonary bypass technique but anaesthesia is also suspected to contribute to POCD. It is characterized by impairment of memory, concentration, language comprehension and social integration which can present days to weeks after surgery and remain as a permanent disorder (Gao, Taha, Gauvin, Othmen, Wang and Blaise, 2005).

Emotional problems are commonly associated with cardiac patients. Wang and colleagues (2008), found that depressive symptoms occurred in 42.7% of patients preoperatively and 23.1% of patients, 6 months after surgery (Wang, Mei, Li, Ji, Sun, Zhu, Chi, Hu, 2008). Depressive symptoms have been confirmed by various other authors in older cardiac patients

(Whooley, de Jonge, Vittinghoff, Otte, Moos, Carney, Ali, Dowray, Na, Feldman, Schiller and Browner, 2008; Detroyer, Dobbels, Verfaillie, Meyfroidt, Sergeant and Milisen, 2008). Murphy and colleagues (2008), concluded that although anxiety and depression resolved for most patients some patients continued to experience worsening depression after cardiac surgery (Murphy, Elliot, Higgins, Le Grande, Worcester, Goble and Tatoulis, 2008).

Koster and colleagues (2008), used the delirium observation screening scale (DOS) listed in table 2 to determine predictors of postoperative delirium. The DOS scale describes behavioural patterns related to delirium. A score of 3 and above indicated delirium whilst a score of 2 required confirmation by the psychiatrist (Koster, Oosterveld, Hensens, Wijma, van der Palen, 2008).

Table: 2 The working method of the delirium observation screening scale (DOS)

The patient:

1. Dozes during conversation or activities
2. Is easy distracted by stimuli from the environment
3. Maintains attention to conversation or action
4. Does not finish question or answer
5. Gives answers which do not fit the question
6. Reacts slowly to instructions
7. Knows which part of the day it is
8. Thinks to be somewhere else
9. Remembers recent events
10. Is picking, disorderly, restless
11. Pulls intravenous tubes, feeding tubes, catheters, ect
12. Is easy or sudden emotional (frightened, angry,irritated
13. Sees persons/ things as somebody/something else

Never = 0 points; sometimes or always = 1 point. A total of 3 or more indicates delirium

Delirium after cardiac surgery and predictive validity of a risk checklist
(Koster et al, 2008)

Although the delirium observation screening scale was used, the authors found EuroSCORE to be the only significant predictor of delirium. In a recently published study by Norkiene and colleagues (2007), a EuroSCORE of 5 or more was associated with postoperative delirium. Considering that the EuroSCORE contains various relevant risk factors for mortality, a positive correlation between postoperative delirium and EuroScore is expected (Norkiene, Ringaitiene, Misiuriene, Samalavicius, Bubulis, Baublys and Uzdavinys, 2007).

Postoperative delirium is a recognised complication after cardiac surgery. Since delirium together with other neurological complications are associated with increased morbidity and resource utilization, independent predictors need to be identified. (Bucerius et al, 2004). In order to identify risk factors for post-cardiac surgery delirium, Bucerius and colleagues evaluated a total of 16,184 consecutive adult patients who underwent heart operations at a single institution. Coronary artery bypass was performed on 8917 of the patient population. The diagnosis of delirium was made by physicians involved in the daily clinical care of patients. Patients with prolonged delirium underwent computed tomography of the brain to look for evidence of stroke. Patients older than 70 years of age constituted 32.5% of the population and 3.6% were older than 80 years of age. The overall prevalence of postoperative delirium in the CABG group was 7.9%. Patients undergoing combined CABG plus valve operations had a higher prevalence of post operative delirium (11.2%). Patients undergoing beating heart surgery presented with the least incidence of post operative delirium (2.3%).

The study identified various risk factors for delirium. A history of cerebrovascular disease was regarded as on of the strongest predictors of delirium in the series (Odds ratio of 2.15). Atrial fibrillation, diabetes mellitus, peripheral vascular disease, preoperative cardiogenic shock, duration of surgery, intra operative haemofiltration, red blood cell transfusion, and age

were also found to be strong predictors of delirium. Atherosclerosis within the cerebrovascular system, in particular the carotid arteries increase the risk of cerebral embolization especially during aortic manipulation. The low prevalence of post operative delirium in the beating heart (BH) is probably due to the avoidance of the deleterious effects of cardiopulmonary bypass (Becerius et al, 2004).

In a study of nine hundred and thirty nine patients conducted by Michael Ho et al. (2004), to determine predictors of cognitive decline following CABG, the investigators found that patients with non-coronary manifestations of atherosclerosis, chronic disabling neurologic illness or limited social support were at risk for cognitive decline (Michael Ho, Arciniegas, Grigsby, McCarthy, McDonald, Moritz, Shroyer, Sethi, Henderson, London, VillaNueva, Grover and Hammermeister, 2004). In a separate study Newman and co-workers found advanced age to be a major risk factor of cognitive decline after CABG (Newman, Blumenthal and Mark, 2004; Edmonds, Cao and Yu, 2002).

2.2.5.3 Magnetic resonance imaging and cognitive decline

The application of magnetic resonance imaging (MRI) to the study of neurological and neuropsychological complications is of particular interest after coronary artery bypass surgery. Cerebral ischaemia has been identified as a crucial pathophysiologic factor for postoperative stroke and may possibly be related to post operative cognitive deficts (Knipp et al, 2008). In this study the authors aimed to characterize long term cognitive performance in a cohort of patients enrolled in a prospective study of cognitive outcomes after on pump CABG. The secondary aim was to elucidate the significance of brain ischaemia, detected by MRI for the development of early and late cognitive changes.

Thirty nine patients scheduled for on pump CABG were enrolled in the study. Preoperative neuropsychologic examination was conducted and a follow up at 3 months and 3 years after surgery was conducted. Cognitive performance was assessed with a battery of 11 standardized psychometric tests assessing 7 cognitive domains. The authors found that baseline to discharge cognitive test scores declined in 7 measures, an improvement was noted at 3 months which declined between 3 months and 3 years. Persistent deterioration in verbal memory relative to baseline was noted. Postoperative cognitive deficits were observed in 56% of patients at discharge, 23% at 3 months, and 31% at 3 years. New ischaemic lesions were noted in 51% of patients on postoperative diffusion weighted imaging. However, a relationship between new lesions and cognitive decline was not established. The authors concluded that long term cognitive performance of CABG patients showed a two stage course with early improvement followed by late decline (Knipp et al, 2008).

2.2.5.4 Presence of coronary collaterals : association with decreased incidence of cognitive decline

Recently Dieleman et al. (2009), evaluated the presence of coronary collaterals and the association with a decreased incidence of cognitive decline after coronary artery bypass surgery. Data of 281 patients undergoing first time CABG surgery were used. The presence of coronary collaterals was determined on the preoperative angiogram using the Rentrop criteria. Cognitive functions, evaluated by a battery of 10 neuropsychological tests were performed 1 day before, 3 months, 12 months and 5 years after the procedure. Cognitive decline was found in 19 patients at 3 months, in 31 patients at 12 months, and in 82 patients at 5 years follow up. The authors concluded that in patients undergoing first time coronary artery bypass grafting, presence of coronary collaterals were associated with decreased risk of cognitive decline at both 3 and 12 months follow up. The authors hypothesised that

patients with collaterals might have improved capacity to maintain adequate cerebral perfusion, resulting in less cognitive decline (Dieleman, Sauer, Klijn, Nathoe, Moons, Kalkman, Kappelle and van Dijk, 2009). In 2004, Nathoe and colleagues, demonstrated that patients with coronary collateral circulation who underwent off-pump CABG had better cardiac outcome, perioperatively and at 1 year following surgery than patients without coronary collaterals (Nathoe, Buskens, Jansen, Suyker, Stella, Lahpor, van Boven, van Dijk, Diephuis, Borst, Moons, Grobbee and de Jaegere, 2004).

2.2.5.5 Neurocognitive outcome after off-pump versus on-pump coronary Revascularization

Recently a meta analysis was conducted to assess whether there were significant differences in neurocognitive outcomes in patients after undergoing on-pump versus off-pump CABG. Eight trials incorporating 892 patients met the inclusion criteria for reporting of neurocognitive outcomes and were included in the meta- analysis. Data from seven studies was sufficient to combine results for five neurocognitive tests (Rey Auditory Verbal Learning, Grooved Pegboard, Trial A and B and Digit symbol). The results of the meta-analysis showed no significant neurocognitive benefits when comparing the off- pump and on- pump CABG groups (Marasco, Sharwood and Abramson, 2008).

Support for this comes from a previous study where the investigators compared changes in cognitive performance from baseline to 3 years in patients undergoing on-pump CABG (n = 152) with those of three control groups: patients with off-pump surgery (n =75); with diagnosed coronary artery disease but no surgery (n = 99) and patients without coronary artery disease risk factors (n = 69). Neuropsychological performance was assessed by testing for language, attention, visuospatial, executive function, verbal and visual memory and

psychomotor and motor speed. The authors found no statistically significant differences in the degree of change between on and off pump groups (Selnes, Maura, Grega, Bailey, Pham, Zeger, Baumgartner and McKhann, 2007; Taggart, Browne, Halligan and Wade, 1999).

Patel and colleagues (2002), examined the database of two institutions to examine and to quantify the independent effects of avoidance of cardiopulmonary bypass and aortic manipulation on neurologic outcomes after CABG. A total of 2,327 patients were identified and divided into 3 groups, on-pump, off-pump with aortic manipulation and off-pump without aortic manipulation. The authors performed a multivariate logistic regression analysis, covariates included in the logistic model included age, sex, redo procedures, diabetes, chronic obstructive pulmonary disease, neurologic disease, peripheral vascular disease, ejection fraction and priority of operation. The authors reported a focal neurological deficit of 1.6% (n = 19) in the on-pump group, 0.4% (n = 2) in the off-pump with aortic manipulation group and 0.5% (n = 3) for the off-pump without aortic manipulation group. The investigators concluded that off-pump surgery with or without aortic manipulation reduces the risk of adverse neurologic events as compared with on-pump surgery (Patel, Deodhar, Antony, Grayson, Pullan, Keenan, Hasan and Fabri, 2002).

2.2.5.6 Percutaneous coronary intervention (PCI) versus CABG

In 2008, Sweet and colleagues, evaluated neuropsychological data gathered from 46 healthy controls, 42 cardiac patients referred for percutaneous coronary intervention (PCI) and 43 cardiac patients referred for coronary artery bypass grafting. Fourteen cognitive tests were utilized at baseline and at 3 time points after surgery (3 weeks, 4 months, 1 year). A greater percentage of CABG (three at 1 year) and PCI (three at 1 year) patients than controls

worsened psychologically in seven tests. The authors found no clear pattern of group differences (Sweet, Finnin, Wolfe, Beaumont, Hahn, Marymont, Sanborn and Rosengart, 2008). The degree of cognitive impairment prior to surgery is an important factor that has been considered in recent studies (Baumgartner, 2007). In another study the investigators found a 50% presence of preoperative silent infarcts in CABG patients with the use of magnetic resonance imaging. This correlated with neurological dysfunction following surgery (Goto, Baba, Yoshitaki, Ura and Sakata, 2000). Various authors suggest that late cognitive changes are related to the presence of preoperative neurological conditions which include cerebrovascular and cardiovascular comorbidities that influence long-term follow up. These causative factors are more likely associated to cognitive changes after CABG rather than exposure to CPB (Baumgartner, 2007; Selnes, Grega, Borowicz, Royall, McKhann and Baumgartner, 2003; Selnes, Grega, Borowicz, Barry, Zeger, Baumgartner and McKhann, 2005; Millar, Ashbury and Murray, 2001).

2.2.5.7 Mechanisms and predictors of postoperative cognitive dysfunction

Neurologic deficit after coronary artery bypass graft surgery is a devastating complication. The reasons cited for these neurological deficits are multifactorial and can be ascribed to cerebral hypoperfusion, age, emboli of air or atheromatus material, haemorrhage, presence of extracranial carotid artery disease, haemodynamic fluctuations, cerebral hyperthermia and metabolic abnormalities (Selnes et al, 2007; Selnes, Pham, Zeger and McKhann, 2006; Slater et al, 2008; Koster et al, 2009; Patel et al 2003; Blauth, 1995; Lazar, Menzion, 1998; Bull, Meumayer, Hunter, Keksz, Sethi, Mclntyre and Bernhard, 1993). In 2004, Ganushchak and co-workers, analysed perfusion records of 1,395 patients who underwent coronary artery bypass grafting. They found that fluctuations in haemodynamic parameters during

cardiopulmonary bypass increased the risk of postoperative neurological complications (Ganushchak, Fransen, Visser, de Jong and Maessen, 2004). Recent findings propose cerebral ischaemia and cerebral oxygen desaturation to be mechanisms of postoperative cognitive dysfunction (Slater et al, 2009). About two decades ago, clinical physiology studies focused on understanding the relationship between cerebral blood flow (CBF) and cerebral oxygen metabolism ($CMRO_2$) during cardiopulmonary bypass (Murkin, Farrar, Tweed, Mckenzie and Guiraudon, 1987). These studies resulted in the widespread generation of hypotheses that related the delivery of cerebral emboli as being proportional to CBF, and highlighted the role of cerebral emboli in the genesis of central nervous system (CNS) injury (Stroobant, Guido van Nooten, Yves van Belleghem and Vingerhoets, 2005; Stroobant and Vingerhoets, 2000).

Cerebral morbidity after CABG surgery has repeatedly been attributed to the use of cardiopulmonary bypass (Roach et al., 1996). Cardiopulmonary bypass increases the permeability of the blood brain barrier (BBB) and generates microemboli which contribute to cognitive decline (Diegeler, Hirsch, Schneider, Schilling, Falk, Rauch and Mohr, 2000; Lloyd, Ascione, Underwood, Gardner, Black and Angelini, 2000; Harris, Bailey, Smith, Taylor, Oatridge and Bydder, 1993). In 1994, Pugsley and colleagues demonstrated that postoperative neuropsychologic deficits were closely related to the number of cerebral microemboli generated following routine CPB (Pugsley et al., 1994). The advent of transcranial Doppler ultrasonography (TCD) has provided a sensitive tool for the detection of emboli generation during CABG. Studies using TCD have reported a positive correlation between the count of high intensity transient signals (HITS) and neurocognitive outcomes (Pugsley et al, 1994; Stump et al 1996).

Recently Stroobant and co investigators (2005), evaluated the effect of on-pump and off-pump CABG on postoperative cognitive impairment and cerebrovascular reactivity, using high intensity transient signals. High intensity transient signals as a measure of embolic load was performed in 32 patients undergoing on-pump surgery and 18 patients in the off-pump group. To measure cognitively induced cerebrovascular reactivity, cerebral blood flow velocity (BFV) was measured preoperatively, early postoperatively and late postoperatively during five cognitive tasks. Seven standardized neuropsycholoical tests were performed at the same time. The authors discovered that the embolic load was much higher in the on-pump group especially during aortic cannulation. No significant correlation was found between the number of HITS and the degree of postoperative neuropsychological impairment. Individual comparisons revealed that 59.4% in the on-pump and 61.1% in the off-pump groups showed evidence of cognitive impairment after coronary artery bypass graft surgery (Stroobant et al, 2005).

2.2.5.8 Gender influence on cognitive function

Women are at higher risk for stroke than men after CABG. Women are widely reported to have higher mortality and morbidity rates after CABG than men (Houge, Barzilai, Pieper, Coombs, DeLong, Kouchoukos and Davilia Roman, 2001). In 2003, Houge and colleagues administered a standard battery of neuropsychological tests to 117 patients (79 men and 38 women) the day before surgery and 4 to 6 weeks after the operation. After adjusting for age, gender, pre-existing medical conditions, level of education, preoperative cognitive results and the duration of CPB, women were associated with poorer performance in visuospatial tasks (Houge, Lille, Hershey, Birge, Nassief, Thomas and Freedland, 2003).

2.2.5.9 Cardiac surgery: Must the brain pay the price?

Mortality attributed primarily to cardiac failure after CPB is acceptable at 0.5% to 5% (Mangano, 1990) despite the ageing population with significant comorbid disease presenting for cardiac surgery (Meharwal and Trehan, 2004; Crosgrove, Loop, Lytle, Baillot, Gill, Golding, Taylor and Goormastic, 1984). However, it has been reported that the incidence of death caused by neurologic deficits has increased from 7.2% to 19.6%, as overall mortality declines (The warm heart investigators, 1994). Therefore, even if cardiac function is improved by surgery, the overall success of an operation may be limited by neurologic or neuropsychologic dysfunction after surgery.

Despite the large volumes of available data, the potential risk and mechanisms of cognitive dysfunction after CABG remain elusive due to discrepancies in patient selection and methods implemented to determine cognitive decline. Establishing the degree of functionally significant vascular disease of the brain prior to CABG should be an essential part of preoperative evaluation, particularly when current advancements in surgical and perfusion techniques are being evaluated (McKhann et al, 2006).

2.2.6 QUALITY OF LIFE AFTER CABG

Indicators of quality of life (QL) after coronary artery bypass is an important patient sensitive tool used to measure the effects of medical treatment. Quality of life outcomes reflect the overall well being and ability of patients to perform daily functions according to their life plans. Some investigators report QL outcomes based on patients satisfaction with surgery, whilst others study specific aspects such as employment status or psychological functioning.

Generally, physical outcomes improve after surgery with a marked decline in complaints of angina and dyspnoea (Newman, Harrison, 2000). One of the most frequently studied social roles following cardiac surgery is employment status. Factors predictive of return to work vary around the world. Various reasons include medical insurance systems, labour market conditions and sick listing traditions among physicians.

In a recent study, Hallberg and colleagues (2009), reported on postoperative continuation of work amongst men and women aged less than sixty who had undergone CABG and were working one year postoperatively. The authors evaluated factors which influenced patients staying on and why patients tend to retire prematurely. The study population comprised of 141 CABG patients, 12 women and 129 men who continued to work one year after surgery. Age, height, postoperative cardiac symptoms, matrimonial status, diabetes mellitus and participation in household work were selected as predictors in the final model. At the ten year follow up, 80% of patients continued to work after coronary artery bypass grafting. The authors found cardiovascular disease to be the single most important factor for premature retirement (Hallberg, Kataja, Tarkk, Palomaki, 2009).

2.2.7 MECHANISMS OF CEREBRAL INJURY FROM CARDIAC SURGERY

Despite continual improvements in surgical and cardiopulmonary bypass techniques, postoperative neurological deterioration remains a frequent problem in patients undergoing cardiac surgery. The exact cause of brain injury during cardiac surgery is almost certainly multifactorial, but mounting evidence suggests that perioperative cerebral injury is believed to result primarily from cerebral embolism or cerebral hypoperfusion. Inflammatory

processes resulting from cardiopulmonary bypass (CPB), organ ischaemia and reperfusion injury further contribute to neurological insult (Houge et al, 2006; Murkin 2002).

2.2.7.1 Cerebral embolism

Microemboli are either gaseous or particulate in composition. Gaseous emboli is said to arise from an open left sided cardiac chamber, air entrained into the CPB circuit, incomplete de-airing, venous cannulation or perfusion interventions (Omar, Pigott, Mathews and Taggart, 2004). Subjects may demonstrate neurocognitive dysfunction and encephalopathy which are believed to result primarily from cerebral microembolism (Arnold, Blauth, Smith, Jagoe, Wootton and Taylor, 1990; Blauth et al., 1995; Hogue et al., 2006; Knipp, Matatko, Schlamann, Massoudy, Forsting, Diener and Wilhelm, 2004; Moody, Brown, Challa, Stump, Reboussin and Leqault, 1995; Pugsley, Klinger, Paschalis, Treasure, Harrison and Newman,1994; Restrepo, Wityk, Grega, Borowicz, Barker, Beauchamp, Hillis and McKhann, 2002; Stump, Rogers, Hammon and Newman, 1996). Macroemboli are typically composed of atheromatous material thought to arise from the atherosclerotic aorta (Houge et al, 2006).

Cerebral macro and micro embolism responsible for the blockage of arterioles have been widely documented using transcranial Doppler (TCD), fluorecein angiography, magnetic resonance imaging and at autopsy (Arrowsmith et al, 2000; Restrepo et al, 2002). Early studies comparing bubble to membrane oxygenators confirmed lower transcranial Doppler embolic signals and improved cognitive outcome with the use of membrane oxygenators and in-line arterial filters (Whitaker, Stygall and Newman, 2002; Pugsley et al, 1994). Figure 24 demonstrates potential embolic material captured by in-line arterial filters during

cardiopulmonary bypass which has prompted concern about the inefficiency of standard filters in the removal of lipid globules associated with cerebral arteriolar emboli (Houge et al, 2006).

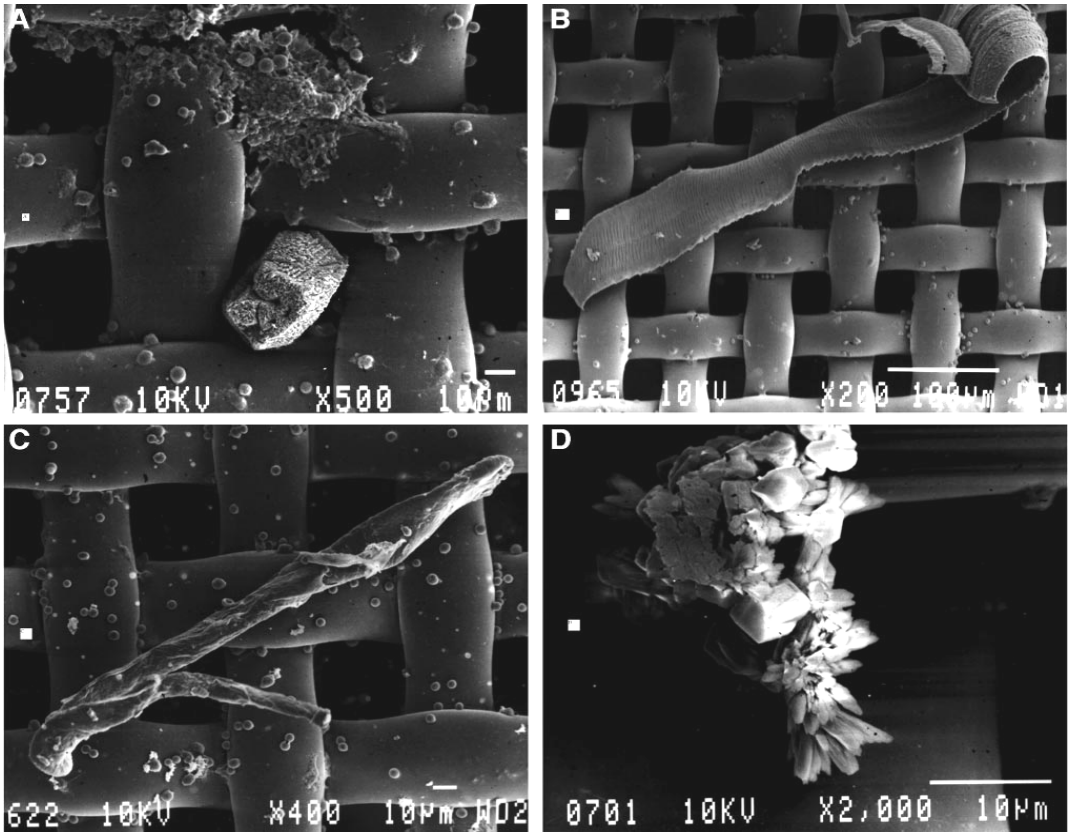


Figure: 24 Scanning electron micrographs of 40-micron arterial line filters after clinically uneventful cardiopulmonary bypass **(A)** A large piece of possibly crystalline material can be seen embedded in the filter mesh. An adherent mass of fibrinous material incorporating erythrocytes can also be seen. **(B)** A particle measuring some 80 x 600um thought to be spallated silicone rubber. **(C)** A particle thought to be an exogenous, organic fibre. **(D)** A complex crystalline deposit. (Houge, et al 2006)

In a randomized clinical trial, Whitaker and colleagues (2004), sought evidence as to whether leucocyte depleting (LD) arterial line filters added a further degree of neuroprotection in patients undergoing elective coronary artery bypass graft surgery. One hundred and ninety two patients scheduled for elective CABG surgery were prospectively randomized to the use of a Pall Leukoguard-6LD filter or either an Avecor Affinity or Pall Autovent-6 control filter. Randomization was achieved with sealed envelopes given to the perfusion department.

Perfusionists then set up the bypass circuit using the appropriate filter. The investigators used intra-operative transcranial Doppler (TCD) to record cerebral blood flow and monitor microembolic events over the right middle cerebral artery. Neuropsychological (NP) assessment was conducted by a single psychologist. A battery of nine NP test were conducted during the preoperative week and at six to eight weeks later during a routine clinic. Evidence of cerebral impairment was obtained by comparing pre and postoperative performance in neuropsychological (NP) tests. The authors concluded that leucocyte depleting filtration reduced the number of microemboli generated and showed a positive trend towards improving NP performance postoperatively (Whitaker, Newman, Stygall, Hope-Wayne, Harrison and Walesby, 2004).

Pugsley et al. (1994), initially demonstrated a correlation between microemboli generated intra-operatively and post-operative NP deficits. The authors found that 8.6% of patients with microemboli counts <200 had deficits compared to 43% of patients with counts >1000. However, the overall number of emboli generated may be attributed to the use of bubble oxygenators (Pugsley, Klinger, Paschalis, Treasure, Harrison and Newman, 1994). Neville et al. (2001), compared 193 patients having CABG to 73 patients having valve replacement surgery. Neuropsychological testing was performed prior to surgery, at 5-7 days and 1 and 6 months post surgery. Carotid Doppler detection of microemboli was also conducted. The authors found that there were more microemboli detected during valve surgery as compared to CABG. There was no significant difference in NP outcome (Neville, Butterworth, James, Hammon and Stump, 2001).

Fearn and colleagues (2001), investigated the influence of cerebral perfusion and embolization during cardiopulmonary bypass on post-operative cognitive function and

recovery. Cerebrovascular reactivity was measured in 70 patients before CABG surgery. Transcranial Doppler of right and left MCAs was used to determine cerebrovascular reactivity to inhaled carbon dioxide preoperatively. The standard technique employed, measures the change in mean MCA blood flow velocity before and after a standard period of carbon dioxide inhalation for each side. Middle cerebral artery (MCA) flow velocity and embolization was recorded by transcranial Doppler throughout the procedure. Regional oxygen saturation was also measured using near infrared spectroscopy (NIRS). In order to measure cognitive function, the investigators used a computerized battery of tests before the operation, at 1 week, 2 months and 6 months after surgery. Elderly patients undergoing urologic surgery served as the control group. The authors found that cerebrovascular reactivity was preoperatively impaired in 49 patients. Median regional cerebral saturation fell by 10%, indicating increased oxygen extraction. Greater than 200 emboli were detected in 40 patients during aortic clamping and release, during initiation of cardiopulmonary bypass and during defibrillation. Cognitive function deteriorated more in patients subjected to CPB than the control group. Emboli was found to be associated with memory loss ($r = 0.3$, $p < .02$ *spearman)* (Fearn, Pole, Wesnes, Faragher, Hooper and McCollum, 2001).

In a separate study carried out to investigate the frequency of cerebral embolization at different stages of coronary artery bypass graft surgery, Fearn and colleagues (2001), used transcranial Doppler to insonate both middle cerebral arteries. The investigators assessed the severity of the ascending aortic atherosclerosis using epicardial ultrasound imaging. Intimal thickness was measured in two places per quadrant and a mean taken. Sixty five patients undergoing CABG were recruited in the study. Embolic signals were recorded during different time periods, placement of aortic purse-string sutures, aortic cannulation for bypass, aortic cannulation for cardioplegia delivery system, application and removal of aortic and

side-clamps, start and end of bypass, manipulation of the heart and defibrillation. The number of embolic signals on TCD in patients with calcification was compared to patients without. The authors found that 56.9% of the patient population had more the 200 emboli entering the middle cerebral artery territories during surgery. Most emboli were generated during the start and end of cardiopulmonary bypass and during defibrillation. Readjustment of the aortic clamp and aortic cannulation accounted for a larger number of emboli which were probably particulate (Fearn, Burgess, Ray, Hooper and McCollum, 2001).

A study conducted by Schmitz and Blackstone (2001), for the International council of emboli management (ICEM) used intraaortic filtration and the Stroke Risk Index developed by the multicentre study of preoperative ischaemia (McSPI). The Stroke Risk Index developed by Wolman et al. (1991), was applied preoperatively to estimate the likelihood that a patient would experience a major perioperative neurological event. 402 patients undergoing isolated CABG and supported by cardiopulmonary bypass were enrolled in the study group. The intraaortic filter was placed in the aorta prior to cross-clamp removal and was removed when the heart was ejecting fully. The location of the filter was distal to the cross clamp, but proximal to the arterial return cannula and innominate artery.

The McSPI Stroke Risk Index consisted of several risk factors: age, unstable angina, history of neurologic disease, prior CABG, history of vascular disease, diabetes and history of pulmonary disease. The investigators observed particulate matter (fibrous atheroma) in over 65% of filters (Figure 25). Six neurologic events were observed which was roughly half of the 13.7 predicted by the Stroke Risk Index ($p = 0.03$). The authors concluded that adverse neurologic episodes associated with coronary artery bypass grafting in which intraaortic filtration was used were fewer based on the Stroke Risk Index (Schmitz and Blackstone,

2001; Wolman, Nussmeier, Aggarwal, Kanchuger, Roach, Newman, Mangano, Marschall, Ley, Boisvert, Ozanne, Herskowitz, Graham and Mangano DT, 1999).

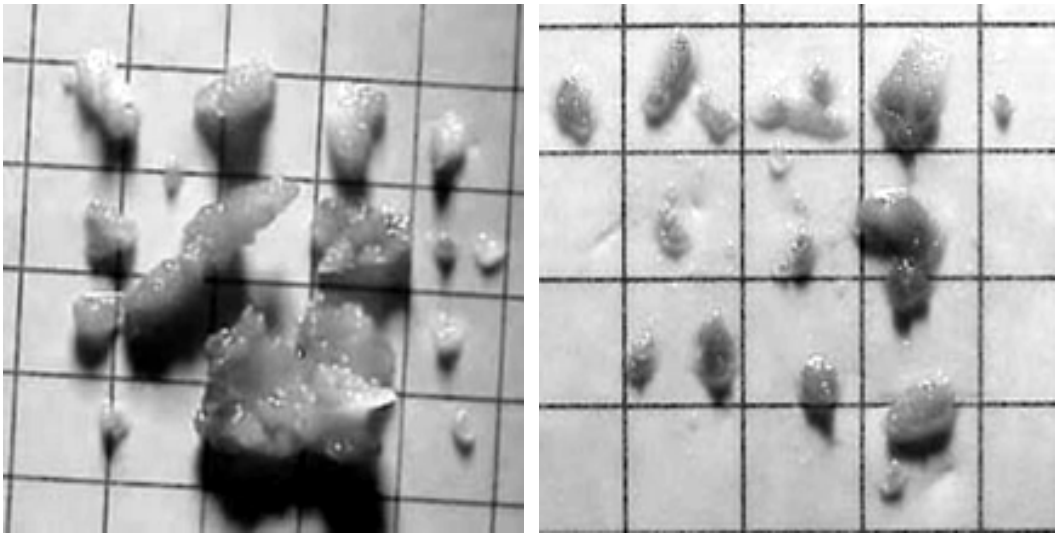


Figure: 25 Gross visual examination at 10x magnification of particulate found in filter mesh from a 67 year old male presenting with myocardial infarction more than 7 days preoperatively, ventricular arrhythmia, obesity, transient ischaemic, renal dysfunction, hypertension and hypercholesterolemia. Aortic assessment was friable, no calcification. Bypass time was 51min; filter dwell time was 30min (Schmitz and Blackstone, 2001).

The retinal and cerebral microembolization study cnducted by Ascione et al. (2005), compared the effects on ophthalmic function of coronary artery bypass grafting with CPB and off-pump (OPCAB) grafting to investigate whether retinal microvascular damage is associated with markers of cerebral injury (S100 protein). It is not uncommon to find patients complaining of postoperative transient loss of vision, poor reading, altered perception of colours and reduced visual acuity (VA). The eye is said to provide a “window” on cerebral circulation and cerebral microvasculature, because the retina is an outgrowth of the embryonic brain and the retinal artery is a branch of the cerebral artery. The investigators used fluorescein angiography and colour fundus to assess retinal microvascular damage. Cerebral injury was assessed using transcranial Doppler ultrasound to detect emboli and serum S100B protein levels. Twenty patients were randomized in the study. The authors

observed retinal microvascular damage in 5 of the 9 CABG-CPB patients and none of the 10 OPCAB patients. Doppler high intensity signals (HITS) were 20.3 times higher in the CABG-CPB group than in the OPCAB group ($p < 0.0001$, 95% confidence interval). Protein S100 levels were also higher in the CABG-CPB group than in the OPCAB group. Figure 26 demonstrates abnormal fluorescein angiography during CABG-CPB surgery.

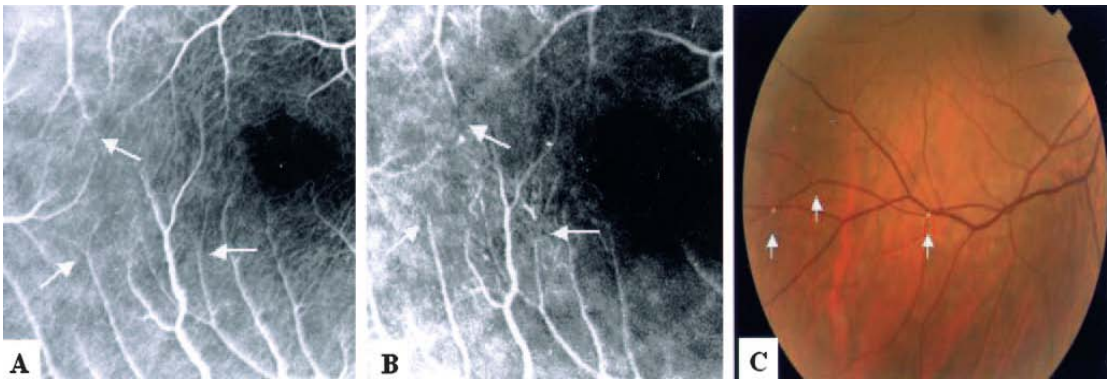


Figure: 26 Example of abnormal fluorescein angiogram during CABG-CPB surgery: **(A)** Before surgery **(B)** After surgery. The arrows indicate multiple sites of postoperative abnormalities which were not present before surgery. **(C)** Colour fundus photograph in the same patient at postoperative day 5, showing a branch of the retinal artery with multiple shiny emboli (arrowheads) (Ascione et al, 2005).

The authors concluded that the associations between retinal microvascular damage, HITS and S100 protein release support the interpretation that coronary artery bypass grafting with the use of cardiopulmonary bypass causes microvascular cerebral damage (Ascione, Ghosh, Reeves, Arnold, Potts, Shah and Angelini, 2005; Grocott, Groughwell, Amory, White, Kirchner and Newman, 1998).

The finding that cerebral microembolization is significantly reduced with avoidance of cardiopulmonary bypass has been supported by various other authors (Abu-Omar, Balacumaraswami, Pigott, Matthews and Taggart, 2004). In contrast Ying-Hua Liu et al. (2009), examined whether avoidance of CPB with off-pump (OPCAB) surgery reduced the

number of cerebral microemboli and the incidence of postoperative cognitive dysfunction (POCD) after CABG surgery in the Chinese population. Two hundred and twenty seven patients were enrolled in the prospective study. Cerebral microemboli were measured continuously with bilateral transcranial Doppler ultrasonography of the middle cerebral arteries. Fifty nine patients underwent CABG with CPB and 168 underwent OPCAB surgery. A battery of seven neuropsychological tests with nine sub subscales was conducted at baseline, 1 week and 3 months after surgery. The median number of cerebral microemboli for patients undergoing CABG-CPB was 430 (range: 155-2088) and 2 (0-66) in OPCAB patients (p <0.001*)*. Non fatal stroke occurred in two patients during hospitalization after surgery, one in the OPCAB group and one in the CABG-CPB group. At 1 week after surgery, POCD occurred in 55.2% of on-pump patients and 47% of off-pump patients (p = 0.283*)*. The overall incidence was 49.1% (110 of 224). At three months after surgery POCD occurred in 6.4% of on-pump patients and 13.1% of off-pump patients (p = 0.214). The overall incidence was 11.2%. The authors concluded that avoidance of CPB resulted in a significant decrease in the number of cerebral microemboli. However, it did not decrease the incidence of POCD at either 1 week or 3 months after CABG (Hua-Liu, Xin-Wang, Huan-Li, Min-Wu, Jin-Shan, Yu Su, Jun Li, Jun Yu, Xia Shi, Ning Huang and Wei Sun, 2009; Martin, Wigginton, Babikian, Pochay, Crittenden and Rudolph, 2009). It is therefore proposed that the quality, but not the number of microemboli, might have an effect on neurological outcome (Newman, Mathew, Grocott, Mackensen, Monk, Bohmer, Blaumenthal, Laskowitz and Mark, 2006).

Several studies have demonstrated that the Doppler microemboli signals detected during surgery impacts on the outcome and length of hospital stay (Georgiadis, Hempel, Baumgartner and Reinhard Zerkowski, 2003). Georgiadis et al. (2003), measured the percentage of embolic signal reduction with the use of arterial filtration and the proportion of

embolic counts reaching the brain, by comparing emboli counts detected before the arterial filter, after the filter and in both middle cerebral arteries. A total of eleven patients were recruited in the study. The investigators found that the arterial filter reduced the number of embolic signals by 58.9% and only 4.4% (2624 of 59132) of the microembolic signals were detected in the middle cerebral arteries.

Fat emboli have been implicated as a cause of cerebral dysfunction after cardiopulmonary bypass. Various materials such as protein debris after denaturation, fat particles, platelet aggregates and atheromatous debris have been identified as possible causes of emboli. Kaza et al. (2003), sought to identify the source of fat emboli during CPB and devise a technique for their elimination. Patients undergoing CPB were prospectively randomized to either cardiotomy suction group (n = 7) or cell saving group (n = 6). Fat emboli were identified using oil red O stain. The emboli were grouped based on the size of their diameter (10-50 μm and > 50 μm particles). As an intervention the investigators added an extra 21 μm filter distal to the cardiotomy reservoir (n = 6), and fat emboli were quantified.

The authors found that patients randomized to the cardiotomy suction group had a significantly higher number of fat emboli at the end of CPB when compared to the cell saver and dual filter groups. The authors concluded that by using the 21 μm arterial filter in series with the cardiotomy reservoir could reduce the amount of fat emboli introduced into systemic circulation and potentially decrease neurocognitive dysfunction associated with cardiopulmonary bypass (Kaza, Cope, Fiser, Long, Kern, Kron and Tribble, 2003; Brooker, Brown, Moody, Hammon, Reboussin, Deal, Ghazi-Birry, and Stump, 1998). Moody et al. (1995), using the staining technique have shown the presence of fat emboli in small capillary

and arterial dilatations in post-mortem studies of the brains of patients who had undergone CPB.

It has been demonstrated that a large majority of cerebral emboli occur during perfusion interventions (during injection of air into the venous side of the cardiopulmonary bypass circuit). In 2001, Borger and colleagues conducted a study to determine whether perfusion interventions were associated with an increased risk of postoperative cognitive impairment. Patients undergoing elective CABG surgery (n = 83) underwent a battery of neuropsychologic tests preoperatively and 3 months postoperatively. Patients were grouped according to the median value of perfusion interventions. Group 1 patients had fewer than 10 interventions and Group 2 patients had more than 10 perfusionist interventions. Both groups were similar for all preoperative, intraoperative and postoperative variables except for longer bypass times in Group 2 patients. Group 2 patients had lower mean scores on 9 of the 10 neuropsychological tests. Rey Auditory, Verbal Learning, Digit Span and Visual Span test were statistically significant. The authors concluded that the introduction of air into the bypass circuit by perfusionists, causing cerebral embolization, may contribute in neurocognitive decline postoperatively (Borger, Peniston, Weisel, Vasiliou, Green and Feindel, 2001). Recently Sauren and colleagues (2007), trailed a new ultrasonic transducer which is capable of diverting emboli into the descending aorta on pigs. The investigators found that the EmBlocker is capable of reducing emboli in the cerebral arteries during extracorporeal circulation and has the potential to lower the risk of postoperative neurological complications (Sauren, Meir, Palmen, Severdija, van der Veen, Mess and Maessen, 2007).

2.2.7.2 Cerebral hypoperfusion

Cerebral hypoperfusion is regarded as a potential and lethal cause of neurologic injury following CABG. Inadequate blood flow to the cerebral parenchyma results in a complex ischaemic cascade, eventually resulting in injury to the brain cells that are under perfused. Prolonged periods of global ischaemia can certainly cause ischaemic damage to watershed areas of the cerebral parenchyma and may therefore result in major stroke. Perioperative episodes of hypotension during cardiac surgery are common and may be attributed to many factors. These common factors include cardiac arrhythmias, impaired left ventricular function, or low systemic vascular resistance. Sustained cerebral hypoperfusion is the primary cause of cerebral injury which may exacerbate injury due to embolism (e.g, delayed embolism "washout," impaired perfusion of ischaemic penumbra, the area at greater risk is the brain tissue surrounding an acute infarct).

In the aging population this form of injury is of importance because even the healthy old brain is fragile (Houge et al, 2008; Caplan, 1998). Twenty seven to forty three percent of patients have been reported to have cerebral oxygen desaturations during CPB. This has been attributed to mismatch of cerebral oxygen delivery and demand (Edmonds, 2002; Croughwell, Newman, Blumenthal, White, Lewis, Frasco and Smith, 1994). In a recent analysis of data of patients who had diffusion – weighted MRI for stroke after cardiac surgery, Gottesman et al. (2007), reported that 68% of patients developed "watershed" strokes occurring at the borderzone between cerebral vascular territories. The authors deduced that a reduction in MAP during CPB of ≥10 mmHg from baseline was associated with a 4.05 times increased odds for bilateral watershed strokes (Gottesman, Hillis, Grega, Borowicz, Selnes, Baumgartner and McKann, 2007). In a separate series of patients, the

authors also found that a decrease in MAP during CPB from baseline was able to predict short-term worsening in cognitive performance (Gottesman et al., 2007).

Cerebral hypoperfusion is of particular importance since it has been identified as a possible source of cerebral injury during “off pump” coronary artery bypass graft surgery. Recent publications indicate that displacement of the heart to gain exposure of lateral or posterior coronary arteries leads to the combination of systemic hypotension and cerebral venous hypertension from traction on the superior vena cava (Fong, Sand and Jacqueline, 2006).

Cerebral hypoperfusion from unrecognised cerebral venous obstruction, inadequate mean arterial pressure, or from hypocapnic alkalosis can be identified by neurological monitoring. Diephuis et al. (2005), in their analysis of jugular oxygen saturations during coronary artery grafting observed that 48% of patients experienced poor global cerebral oxygenation (< 50%) during beating heart surgery in comparison to 27% of patients who were managed with CPB. Patients undergoing beating heart surgery may be exposed to a smaller percentage of micro emboli. However, the risk of cerebral hypoperfusion appears to be much greater than during CPB (Iglesias, Murkin, Hachinski, Silver, Frank, Peterson and Adams, 2002).

In a randomized study targeting a MAP during cardiopulmonary bypass of 50 to 60 mmHg and 80 to 100 mmHg, the authors established that there were fewer combined myocardial infarctions and strokes in the “high” vs “low” MAP group (Gold, Charlson, Williams, Szwtrowski, Peterson and Pirraglia, 1995). Figure 27 shows a diffusion weighted brain magnetic resonance image of a patient with stroke after cardiac surgery. The bright images represent brain injury due to ischaemia. The location of the injury in the end vascular territory of the anterior and middle cerebral arteries and the middle and posterior cerebral

arteries is consistent with a watershed infarction. This is due to cerebral hypoperfusion (Hogue et al, 2008).

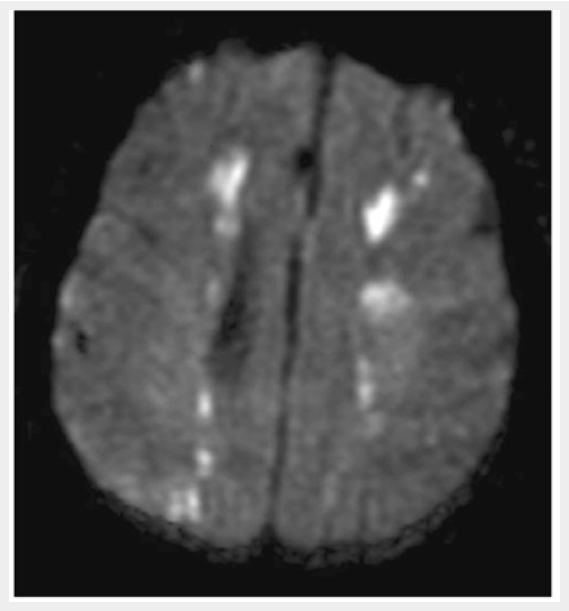


Figure: 27 Magnetic resonance image demonstrating stroke after cardiac surgery (Houge et al, 2008)

Cerebral perfusion pressure is normally 80 to 100 mmHg. The brain, like the heart and kidneys can tolerate swings in blood pressure with minimal change in cerebral blood flow. The cerebral vasculature can adapt rapidly within a time frame of 10-60 seconds to changes in cerebral perfusion pressure, but sudden or abrupt changes in MAP can lead to transient changes even when autoregulation is intact. Autoregulation ensures that as MAP increases there is increased resistance from a reduction in the calibre of the small cerebral arteries and arterioles. Therefore, changes in cerebral perfusion pressure occur as a result of vasodilation due to decreased perfusion pressure or vasoconstriction due to elevations in perfusion pressure (Ganong, 2003).

Cerebral blood flow remains constant between mean arterial blood pressures of 60 mmHg and 160 mmHg as demonstrated in Figure 28. Beyond these limits of autoregulation, CBF is

directly proportional to MAP and can be described as pressure dependant. Elevations in blood pressure above the upper limits of autoregulation can cause rupture of cerebral blood vessels, sometimes resulting in serious brain oedema or cerebral haemorrhage. Patients with impaired CBF-blood pressure due to pre-existing hypertension, cerebral vascular disease or other causes are prone to cerebral hypoperfusion and subsequent ischaemic injury (Houge et al, 2006).

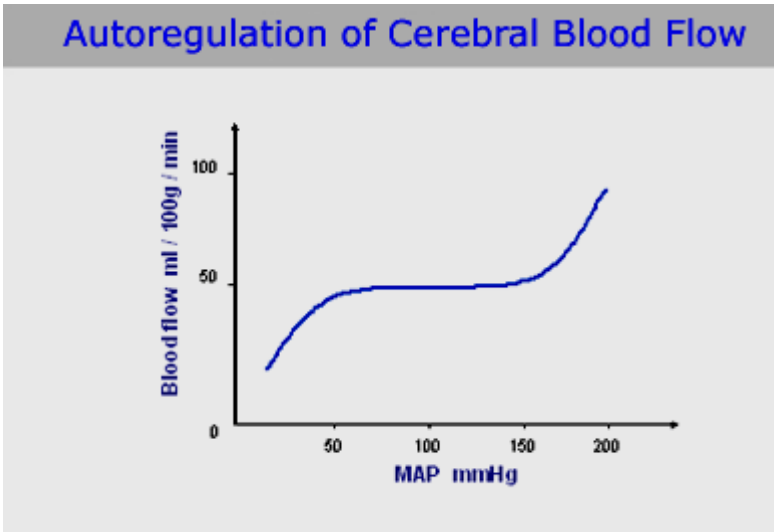


Figure: 28 Cerebral autoregulation curve (Morgan & Mikhail, 2002 p554)

Recently Swaminathan et al. (2007), demonstrated the potential of atheroma disruption due to the sandblasting effect of CPB at the site of the aortic cannula. Patients identified with atherosclerosis of the ascending aorta are more likely to have diffuse atherosclerosis of the cerebral arteries. These patients are of a greater risk and are prone to cerebral insult from hypoperfusion. It is for this reason that avoidance of significant or marked hypotension during and after surgery may be prudent to avoid neurological injury (Swaminathan, Grocott, Mackensen, Podgreanu, Glower and Mathew 2007).

2.2.8 PREDICTORS OF ADVERSE NEUROLOGICAL OUTCOME DURING CORONARY ARTERY BYPASS GRAFT SURGERY

2.2.8.1 Age

Cerebral injury in the aged is an important cause of adverse outcomes after cardiac surgery. In particular, elderly patients with other comorbidities who have the highest postoperative mortality and morbidity rates (Jin and Chung, 2001). The risk and severity of cerebral injury after cardiac operations increases with the use of cardiopulmonary bypass (Zamvar, Williams, Hall, Payne, Cann, Young, Karthilseyan and Dunne, 2002). As a progressively older and sicker population undergoes cardiac surgery the scale of the problem is likely to increase exponentially especially for those older than 75years (Mortasawi, Arnrich, Rosendahl, Frerichs, Albert, Walter, and Ennker, 2002; Tuman, McCarthy, Najafi and Ivankovish, 1992). The surgical population has not only become older, but also has greater prevalence of associated disease, particularly diseases that are known risk factors for cerebrovascular disease. Currently the investigation of neurological and cognitive outcomes after CABG is regarded as the study of a moving target.

Studies have shown that age is a strong predictor of neurological events in patients undergoing CPB. Tuman et al. (1992), prospectively studied 2,000 CABG patients with similar cardiac complications among three age groups. Predictors of postoperative neurologic events included age, preoperative neurologic abnormality, recent myocardial infarction, and duration of CPB. They found a 0.9% incidence of adverse events in patients younger than 65years, a 3.6% incidence in patients aged between 65 and 74 years, and an 8.9% incidence in patients older than 75years (Tuman et al., 1992). Advanced age is one of the most commonly reported independent predictors of postoperative delirium, probably because of its

close association with the atherosclerotic disease process. A study conducted by Bucerius et al. (2000), confirmed that one third of their patient population was older than 70 years of age, and their data confirmed that such patients were at increased risk for delirium.

Similar age related findings were also reported in another study from Johns Hopkins University Hospital in 1985. They retrospectively reviewed the charts of 3,900 CABG patients and showed that 7% of those older than 70 years suffered a perioperative or postoperative stroke (Gardner, Horneffer, Manolio, Pearson, Gott, Baumgartner, Borkon, Watkins and Reitz, 1985). In a study conducted by Almassi and colleagues (1999), prospective data was collected on 4,941 patients undergoing cardiac surgery. The authors found that patients below 60 years of age had a 1.6% incidence of stroke which increased to 5.25% for patients above 70 years (Almassi, Sommers, Moritz, Shroyer, London, Henderson, Sethi, Grover, and Hammermeister, 1999).

Figure 29, demonstrates some of the findings of Tuman et al. (1992), illustrating their finding and showing an association between older age and cerebral dysfunction after CABG surgery. The Figure demonstrates that the cardiovascular outcomes of myocardial infarction and low output state are age independent and are primarily determined by the premorbid status of the patient. The patient who has good ventricular function and undergoes an expeditious operation does well postoperatively; the outcome is a function not of age, but of the premorbid status. On the other hand, the stroke rate increases exponentially with age and is virtually independent of other factors, including the extent of myocardial revascularization.

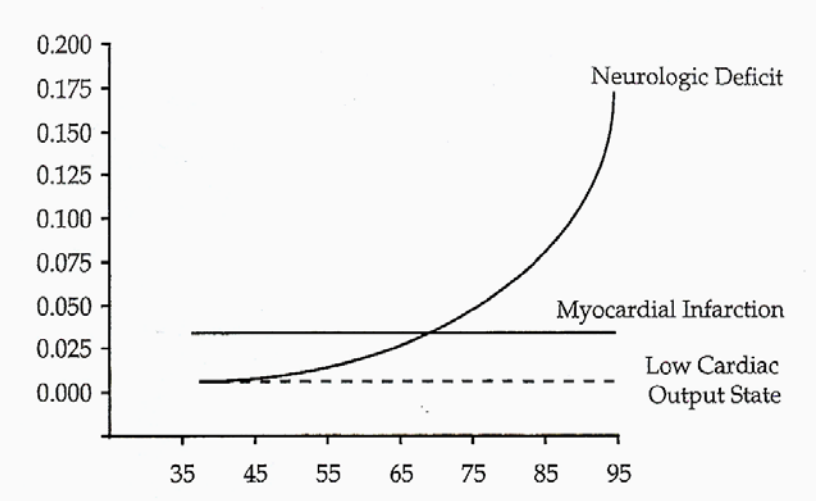


Figure: 29 Effect of advanced age on the predicted probability of neurologic and cardiac morbidity (Tuman et al., 1992)

In a post-mortem study of 221 cardiac surgical patients, Blauth et al. (1992), also found a strong association between age, severity of ascending aorta atherosclerosis, and cerebral atheroemboli. David-Roman et al. (1991) also showed an exponential relationship between age and atherosclerosis of the ascending aorta using epiaortic Doppler scanning.

Mortasawi et al. (2002), studied the role of age as a determinant of mortality in cardiac surgery by calculating the EuroSCORE and the corresponding age adjusted EuroSCORE in 8769 patients who underwent heart surgery. They also collected information on postoperative complications and 30-days mortality. The investigators found that the multimorbidity increased with age and both the EuroSCORE and the age adjusted EuroSCORE values increased significantly with age in the whole group as well as in the group who were alive 30 days after surgery. The incidence of postoperative complications and 30 days mortality increased with age. In the patients who died within 30 days of surgery, the EuroSCORE increased with age. The authors concluded that age is a significant risk predictor in cardiac surgery.

2.2.8.2 Gender

Despite the current advances in cardiac surgical, anaesthetic and perfusion technique, women have an almost twice as high mortality rate than men. The risk profile of female patients differs to that of men and may have a negative impact on surgical outcome (Samalavicius, Misiuriene, Kalinauskas, Norkunas and Baublys, 2009). Cardiovascular disease is the leading cause of death for women in the Western world, accounting for more than 50% of all deaths in the United States (Belo and Mosca, 2004). Women undergoing CABG are more likely to be older, have unstable angina, higher rates of comorbid conditions and smaller coronary arteries which in turn make performing anastomoses difficult and limit graft flow (Houge, Barzilia, Pieper, Coombs, Delong, Kouchoukos and Davila Roman, 2001). In 2004, a study conducted by Humphries and co-workers found that 42% of women were more likely to die within 30 days of CABG (Humphries, Gao, Pu, Litchenstein, and Thompson, 2004).

Samalavicius et al. (2009), conducted a retrospective review of 3177 CABG patients operated on over a 5 year period. Demographic and preoperative risk factors were analysed to evaluate the risk of the procedure. Mortality was the primary outcome but the authors also analysed major morbidity. Overall mortality rate was higher in women than in men (5.2% vs 2.8%, $p < 0.05$). Female patients were older (67.5 ± 8.3 vs 63.1 ± 9.4 years, $p < 0.001$) and had a greater incidence of comorbidities. The internal thoracic artery as a conduit was used less frequently in female patients (62.5% vs 77.8%, $p < 0.01$). Women had a higher rate of low cardiac output syndrome and required a higher rate of blood transfusion (45.2% vs 25.4%, $p < 0.01$) Age, left ventricle ejection fraction and female gender were regarded as significant predictors of postoperative mortality.

Various studies show that the female gender is associated with longer intubation times and postoperative ICU stay (Capdeville, Lee and Taylor, 2001; Butterworth, James, Prielipp, Cerese, Livingston and Burnett, 2000). Houge et al. (2001), conducted a study to evaluate whether women undergoing cardiac surgery were more likely to suffer neurological complications than men. The investigators examined the Society of Thoracic surgery national database and reviewed information on 416 347 patients (32% women) for whom data on neurological outcome were available. The 30 day mortality was higher for women than men (5.7% vs 3.5%). New neurological events after surgery were higher for women than for men (3.8% vs 2.4%) (Houge et al, 2001). Women are at higher risk for postoperative stroke than men (Houge, Lillie, Hershey, Birge, Nassief, Thomas, and Freedland, 2003). Women undergoing CABG are associated with lower functional gains and higher readmission rates than men (Vaccarino, Lin, Mattera, Roumanis, Kasl, Abramson, Krumholz, 2003).

The exact reasons for differences in outcome between men and women are not clear. In most countries women live longer than men who are often addicted to 'risk behaviour' while women are prone to more 'preventitive' behaviour. However, women undergoing CABG show higher operative mortality and morbidity (Peric, Borzanovic, Stolic, Jovanovic, Sovtic, Djikic, Marcetic, Dimkovic, 2010).

Peric et al. (2010), examined the different aspects of quality of life (QOL) of different sex as well as the presumption that sex could be a predictor of QOL after coronary artery bypass grafting. 243 CABG patients were enrolled in the study. The investigators used structured interviews to determine quality of life preoperatively and postoperatively. The authors concluded that when compared to men women have worse preoperative and postoperative

QOL than men. Female sex was a significant predictor of QOL worsening at six months after CABG.

In 2007, Puskas and colleagues conducted a study to determine whether off-pump CABG (OPCAB) altered the gender based disparity. A retrospective review of risk factors and clinical outcomes of 11 413 patients having isolated CABG were examined. Outcomes included in hospital death, stroke, and myocardial infarction or combined adverse cardiac events. Female patients (n = 3248) and those in the OPCAB group (n = 4492) were older, had more comorbidities and were at higher risk than males (n = 8165) and those treated with conventional bypass CABG/CPB. Among the women, OPCAB was associated with a reduction in death (O.R 0.39, p = 0.001), Stroke (O.R 0.43, p =0.002) and major cardiac events (O.R 0.43, p = < 0.001). The investigators found that OPCAB was associated with fewer major cardiac events and benefited women (Puskas, Kilgo, Kutner, Pusca, Lattouf, and Guyton 2007).

In a study targeting the prevalence of stroke after CABG, Tomoko Goto and colleagues (2007), investigated the gender differences in the incidence of craniocervical and ascending aortic atherosclerosis and other risk factors in elderly patients over the age of 60 years. Data was prospectively collected on 720 patients of whom 31.8% were women undergoing CABG surgery. Magnetic resonance imaging and angiography were performed to assess prior cerebral infarctions, carotid artery and intracranial arterial stenoses. The investigators used epiaortic ultrasound to determine atherosclerosis of the ascending aorta and performed neurocognitive tests prior and post surgery. Women were older, had a higher incidence of hypertension and intracranial arterial stenosis. Men had higher rates of hyperlipidemia, peripheral vascular disease, abdominal aortic aneurysm, smoking history, severe carotid

artery stenosis and atherosclerosis of the aorta and were found to be at higher risk for stroke than women (Tomoko Goto, Tomoko Baba, Asuka Ito, Kengo Maekawa, Takaaki Koshiji, 2007).

2.2.8.3 Cerebrovascular disease

Patients with a previous history of stroke or transient ischaemic attack (TIA) are at a higher risk of perioperative stroke. Various risk factors including atheromatous disease of the extracranial cerebral arteries which can result in regional ischaemia during periods of hypoperfusion have been implicated as predictors of adverse neurological outcomes during CABG surgery (Arrowsmith et al, 2000; Ozatik, Gol, Fansa, Uncu, Kucuker, Bayazit, Sener, and Tasdemir, 2005). The problem is further exacerbated with the presence of carotid bruit. A strong correlation between the extent of coronary artery disease and atherosclerosis in the brain has become increasingly recognized. Patients of advanced age with coronary artery disease are more likely to have cerebral vascular disease and are at higher risk of microembolic injury as compared to younger patients (Selnes, 2008). In 2009, Farhoudi and colleagues conducted a study to assess the correlation between postoperative neurological complications and preoperative carotid Doppler and transcranial scanning. Two hundred and one patients undergoing elective, isolated CABG were prospectively studied in the trial. The investigators conducted neurologic examinations, intracranial cerebral artery scanning (TCD) and carotid duplex scanning preoperatively. 131 patients had three coronary vessel disease, 64 had two vessel disease, 5 had one vessel disease and one had diffuse coronary disease. TCD was performed on 183 patients of whom 22 patients presented with abnormalities. 154 patients underwent carotid duplex scanning of whom102 had plaque. 99 patients had stenosis < 50%, 50-74% stenosis in one patient and 75-90% stenosis in 2 cases. The investigators

found that 5 of the 22 patients (22.7%) with intracranial cerebral artery disease (ICAD) showed central nervous system complications (p =0.015). There were significant correlations between the number of involved cerebral arteries and adverse postoperative cerebral events (p = 0.001). The authors concluded that intracranial cerebral artery disease is an independent predictor of CNS complications after CABG (Farhoudi, Parvizi, Bilehjani, Tarzammi, Mehrvar and Safaiyan, 2007; Hirotani et al, 2000).

2.2.8.4 Temperature

Temperature as a physiological variable in cardiac surgery can be manipulated to manage patients according to preoperative risk factors. Systemic and regional hypothermia used for decades during cardiopulmonary bypass has been the mainstay of organ protection (Grogan, Stearns and Houge, 2008; Houge et al 2008). Cerebral metabolic rate decreases by 6 to 7 percent for every one degree drop in temperature (Grigore, Murray, Ramakrishna and Djaiani, 2009). Hypothermia decreases the rate of energy utilization associated with both electrophysiological and basal components as seen in Figure 30.

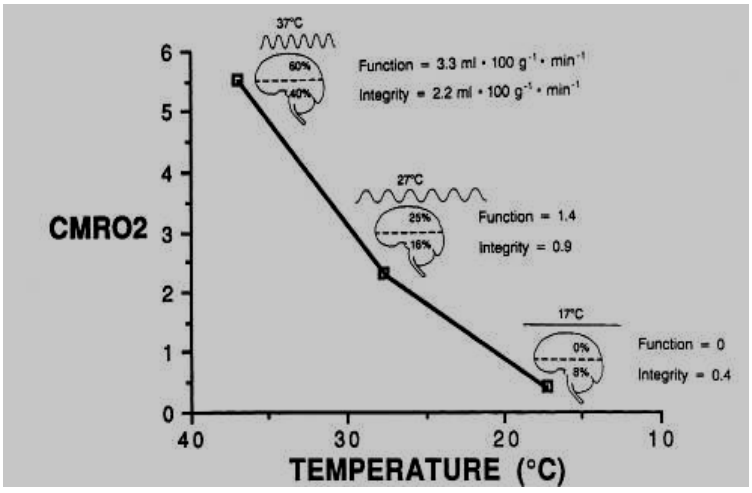


Figure: 30 Effect of temperature on cerebral metabolic rate. (Naik, 2007)

Hypothermia can cause complete suppression of the EEG at temperatures of about 20ºC. Hyperthermia on the other hand has an opposite influence on cerebral physiology (Grigore et al, 2009). Cerebral blood flow and cerebral metabolic rate (CMR) increases at temperatures between the range of 37 and 42 degrees Celsius. However, at temperatures higher than 42 degrees, CMR is dramatically reduced, which is an indication of a threshold for toxic effects of hyperthermia that may occur as a result of protein degradation (Morgan & Mikhail, 2000).

At moderate hypothermia, autoregulation of cerebral blood flow is tightly coupled to cerebral metabolic rate of oxygen consumption. Clinical hypothermia after cardiac arrest has been shown to improve neurological outcome. However, Rees and colleagues (2001), found no differences in risk of stroke between the use of hypothermia and normothermia (OR 0.68, 95% CI, 0.43 to 1.05) (Rees, Stanley, Burke, 2004; Nathan, Wells, Munsor and Wozny, 2001). Nathan et al. (2001), in a study of 223 patients, found that rewarming to a nasopharyngeal temperature of 34ºC from hypothermic CPB temperature of 32ºC results in a lower frequency of neurocognitive dysfunction at 1 week and 3 months after CABG surgery. A distinct disadvantage of hypothermia is the rewarming of the patient at the end of the procedure. Placement of the arterial cannula in the ascending aorta results in the temperature of cerebral blood being close to that of the blood leaving the heat exchanger, thus it is easy to produce cerebral hyperthermia during rewarming (Houge et al, 2008).

Grigore et al. (2002), found that by keeping the gradient between nasopharyngeal and aortic perfusate temperature $\leq$ 2ºC was associated with improved cognitive function compared with conventional rewarming (Grigore, Grocott, Mathew, Bute, Stanley, Butler, Landolfo, Reves, Blumenthal and Newman, 2002). In a separate controlled study by Grigore et al. (2001), where temperature drift and hyperthermia was avoided, hypothermia did not reduce the

frequency of neurocognitive dysfunction after CABG when compared to normothermia (Grigore, Mathew, Grocott, Reves, Blumenthal, White, Smith, Jones, Kirchner, Mark and Newman, 2001).

Aggressive rewarming in order to avoid after drop of temperature may worsen cerebral injury that may result from embolism or infarction (Chauhan, 2009). In contrast concern over risk of postoperative hypothermia as a consequence of inadequate rewarming may result in shivering, arrhythmias, coagulopathy and increased ICU stay. In a recent study conducted by Sahu and colleagues (2009), of 80 patients undergoing CABG with the use of hypothermic CPB, the investigators found that patients rewarmed to 33ºC had less neurocognitive dysfunction and release of S100B protein at 24 hours when compared to patients rewarmed to 37ºC (Sahu, Chauhan, Kiran, Bisoi, Lakshmy, Selvaraj and Nehra, 2009).

Khatri and colleagues (2001), examined the effects of temperature during CABG on quality of life. 209 patients were randomized to normothermic and hypothermic conditions during cardiopulmonary bypass. Physical, psychologic and social measures were taken preoperatively, at 6 weeks and 6 months after surgery. The authors found that hypothermic bypass was associated with higher levels of emotional distress after CABG surgery (Khatri, Babyak, Croughwell, Davis, White, Newman, Reves, Mark and Blumenthal, 2001). Temperature discrepancies among standard monitoring sites in individual patients are often striking, especially between jugular bulb and rectal or bladder temperatures, thus the most accurate monitor of blood temperature may be in the arterial line which can be used as an indicator of cerebral temperature (Nussmeier, 2005; Kaukuntla, Harrington, Bilkoo, Brock, Jones and Bonser, 2004).

Studies related to the effect of temperature on neurological injury during cardiopulmonary bypass have led to various observations and temperature regimens during bypass. For instance, adequate use of hypothermia should be dictated by patients surgical requirement, rewarming should be started early so as to avoid gradients of more than 2ºC between water bath and patient blood temperature. In high risk patients (elderly, diabetics, carotid artery disease and history of neurological injury) rewarming to 33ºC should be considered (Chauhan, 2009).

Fast rewarming rate and uncontrolled cerebral hyperthermia should be avoided during cardiopulmonary bypass and in the postoperative period which can potentially lead to poorer neurological outcome (Grocott, 2009). Monitoring temperature for the prevention of hyperthermia should be advocated to minimize neurological injury especially for patients at higher risk for developing neurologic and neurocognitive complications (Grocott, 2009). Evidence to support the avoidance of hyperthermia comes from Houge et al. (2006), who highlighted worse neurological outcome with hyperthermia. Thus, aggressive rewarming could result in the central nervous system being exposed to the deleterious high temperatures which offset any neuroprotective effects of hypothermia (Grigore, 2009; Cook, 2009). Newer generation conductive and forced air warmers allow for continuous rewarming of patients in the post bypass period without the need for the CPB heat exchanger. This permits patients to be weaned from bypass at lower temperatures confidently knowing that effective rewarming continues after termination of CPB (Grocott, 2009).

2.2.8.5 Acid-Base management - Alpha stat versus pH stat management of blood gases

Nevin and colleagues (1987), highlighted the need for maintaining normocapnia before the onset of cardiopulmonary bypass. The investigators found that at three days after surgery patients who had been inadvertently hyperventilated had a higher incidence of neurological and psychometric deficits than patients who were normocapnic (Nevin, Colchester, Adams, and Pepper, 1987). The solubility of gases in blood increases as temperature decreases. Therefore, the solubility of CO_2 in blood increases resulting in decreased PCO_2 and increased pH. When arterial blood gases are analyzed with temperature correction during hypothermia, patients appear to have respiratory alkalosis, thus the addition of carbon dioxide to normalize PCO_2 and maintain pH at 7.4 is known as pH-stat acid–base management during CPB (Houge et al, 2006). The use of arterial blood gases without correction of temperature is known as α –stat (alpha) management (Arrowsmith et al, 2000). During moderate hypothermic CPB, autoregulation of cerebral blood flow is maintained using α –stat management and lost with pH management.

The inability to regulate cerebral blood flow at lower perfusion pressures, the possibility of 'steal' in patients with cerebrovascular disease and acidosis during rewarming associated with pH management increase the risk of neurological injury (Murkin, 1993). Bashin and colleagues (1990), in a study of 86 CABG patients found no benefit with the use of pH management on either cardiac or neurological outcome (Bashin, Townes, Brenda, Nessly, Micheal, Bledsoe, Hornbein, Davis, Goldstein and Coppel, 1990). Murkin et al. (1995), in a study of 316 patients undergoing CABG with the use of cardiopulmonary bypass found that cognitive dysfunction at 2 months post surgery in patients managed with α- stat was reduced when compared to patients managed with pH stat (27% vs 44%, $p = 0.047$).

Stephan and colleagues (1992), in a prospective randomized trial of 65 CABG at hypothermic (26ºC) CPB, found that pH stat management was associated with cerebral hyperaemia (+ 191% vs -18%) and a higher incidence of neurological dysfunction at 7 days post operatively (p = 0.036) (Stephan, Weyland, Kazmaier, Henze, Menck, Sontag, 1992). Patel et al. (1996), in a study of seventy patients discovered that the frequency of cognitive dysfunction, 6 weeks after CABG surgery was not different between the two management strategies (Patel, Turtle, Chambers, James, Newman and Venn, 1996). Randomized trials of α- stat versus pH stat management of cardiopulmonary bypass during CABG produce conflicting results and provide inadequate data for patients at higher risk for neurological injury (Houge et al, 2006).

Recently, Abdul Aziz and Meduoye (2010), evaluated the results of 16 papers comparing the results of α- stat versus pH stat management. Six of the studies found better cerebrovascular metabolism with alpha-stat managment while three studies found better cerebrovascular metabolism with pH-stat. Four other studies showed no significant difference in the cerebrovascular metabolism between the two management strategies. Comparing the 16 studies based on the age of the patients studied, three out of the four papers demonstrated that the pH-stat method was a better strategy to improve intraoperative and postoperative outcome in paediatric patients. Conversely seven papers suggested that alpha-stat management was associated with better outcome in adult patients. The remaining four papers suggested no significant difference between the pH-stat group and alpha-stat groups.

Nauphal and colleagues (2007), conducted a study to compare the effect of alpha-stat vs. pH-stat strategies for acid-base management on regional cerebral oxygen saturation (rSO_2) in patients undergoing moderate hypothermic haemodilution cardiopulmonary bypass (CPB).

Fourteen patients undergoing elective coronary artery bypass grafting were recruited in the study. Baseline cerebral oximetry readings were taken using the INVOS 5100 cerebral oximeter. The authors found that regional cerebral oxygenation significantly decreased from a pre-bypass value of 75.9 ± 6.7% to 62.9 ± 6.3% during the initial phase of alpha-stat strategy. Shifting to pH-stat strategy resulted in a significant increase of rSO_2 from 62.9 ± 6.3% to 72.1 ± 6.6%. Resuming the alpha-stat strategy resulted in a significant decrease of rSO_2 to 62.9 ± 7.8% which was similar to the rSO_2 value during the initial phase of alpha-stat. The authors concluded that during moderate hypothermic conditions of CPB and haemodilution, regional cerebral oximetry values were significantly higher using pH-stat management rather than alpha-stat management. Cerebral oxygen values during pH-stat management were significantly higher than the baseline values in the awake patient breathing room air, denoting luxury cerebral perfusion. In contrast, the rSO_2 values during alpha-stat was slightly higher than the baseline values suggesting that the alpha-stat strategy avoids luxury perfusion. However, adequate cerebral oxygen supply-demand balance during moderate hypothermia can be maintained (Nauphal, Khatib, Taha, Haroun-Bizri, Alameddine, and Baraka, 2007).

2.2.8.6 Haemoglobin/ Haematocrit targets

Cerebral injury as a result of anaemia may occur due to a reduction in tissue oxygen delivery thereby increasing embolic load due to higher cerebral blood flow rate. The brain compensates for reduced arterial oxygen content by increasing cerebral blood flow and the rate of oxygen extraction (Cook et al., 1998). A study that was conducted on dogs found that the compensatory responses were sufficient to meet cerebral metabolic demand to a haematocrit (Hct) of 15% at a temperature of 28 degrees Celcius (Cook et al., 1998).

A study conducted by Mathew et al. (2004), was interrupted by the data safety monitoring committee due to higher adverse event rates and greater cognitive decline in the low haematocrit group of their randomized trial.

Normally, changes in blood viscosity do not appreciably alter CBF. Haematocrit is the most important determinant of blood viscosity. A decrease in haematocrit results in decreased viscosity and therefore CBF should increase. Unfortunately a reduction in haematocrit also reduces the oxygen carrying capacity of blood and can thus potentially impair oxygen delivery (Tomiyama, Jansen, Brian and Todd, 1999). Elevated haematocrit, as may be seen with marked polycythemia, result in increased blood viscosity and can reduce cerebral blood flow. Studies have suggested that optimal cerebral oxygen delivery may occur at haematocrits between 30% and 34% (Cook, Orszulak and Daly, 1998).

Haemodilution is used during hypothermic CPB to reduce blood viscosity, ensure microcirculatory flow and reduce the need for blood transfusion (Grogan et al, 2008; Sakamoto, Nollert, Zurakowski, Soul, Duebener, Sperling, Nagashima, Taylor, duPlessis and Jonas, 2004). However, this benefit may result in decreased oxygen carrying capacity of diluted blood. Laboratory results contradict this practice suggesting that cerebral microcirculatory flow is impaired during hypothermia at haematocrit levels of 30% (Duebener, Sakamoto, Hatsuoka, Stamm, Zurakowski, Vollmar, Menger, Schafers and Jonas, 2001).

Retrospective analysis suggest that a strong correlation exists between low haematocrit levels and risk adjusted mortality (DeFoe, Ross, Olmstead, Surgenor, Fillinger, Groom, Forest, Pieroni, Warren, Bogosian, Krumholz, Clark, Clough, Weldner, Lahey, Leavitt, Marrin,

Charlesworth, Marshall and O'Conner, 2001; Habib, Zacharias, Schwann, Riordan, Durham, and Shah, 2003; Houge et al, 2006). Habib et al (2003), found that levels less than 22% during cardiopulmonary bypass was independently associated with stroke following CABG. Karkouti and co-workers (2005), discovered that the odds of stroke increased by 10% for every 1% decrease in haematocrit (Karkouti, Djaiani, Borger, Beattie, Fedorko and Wijeysundera, 2005).

In the review of 6980 patients undergoing CABG, DeFoe et al. (2001), reported that low haematocrit levels were related to the need for intraaortic balloon counterpulsation, return to CPB after initial weaning and a higher risk of in hospital mortality. The investigators found no association with stroke. A multicentre study of 5065 CABG patients at 70 worldwide institutions evaluated the impact of preoperative anaemia on patient outcome. The investigators reported that anaemic patients undergoing CABG surgery have an increased risk of postoperative adverse events (Kulier, Levin, Moser, Rumpold-Seitlinger, Tudor, Snyder-Ramos, Moehnle and Mangano, 2007; Bell, Grunwald, Baltz, McDonald, Grover and Shroyer, 2008; Ranucci, Biagioli, Scolletta, Grillone, Cazzaniga, Cattabriga, Isgro and Giomarelli, 2006).

McCusker and colleagues (2006), conducted a study to determine the influence of haematocrit and pump prime on cerebral oxygen saturation. Thirty eight patients were matched on preoperative haematocrit < 40% and > 40% (n = 16). Six patients with blood prime were matched with six crystalloid prime patients. The investigators compared haematocrit and rSO_2 values on CPB. The findings showed that patients in the preoperative haematocrit > 40% group retained higher rSO_2 levels during CPB ($p < 0.01$) and higher levels prior to initiation of CPB. Blood prime increased the percentage rSO_2 values (4.7 ±

11.8% versus –14.2 ± 7.4%). The authors concluded that blood prime is instrumental in preventing cerebral desaturation for high risk patients with low haematocrit (McCusker, Chalafant, de Foe, Gunaydin and Venkataramana, 2006).

Factors influencing blood utilization include old age, female, low preoperative haematocrit, redo operations, patients that have a small body surface area and emergency operations (Bharathi and Scott, 2007). The critical haematocrit is patient specific and is dependant on a number of factors including bypass time and temperature. The lower level of haemoglobin without adverse consequences during coronary artery bypass graft surgery needs to be established (Snyder-Ramos, Mohnle, Weng, Bottiger, Kulier, Levin and Mangano, 2008; Murphy and Angelini, 2006). The adverse effect of blood transfusion is also thought to play a role in neurological injury.

2.2.8.7 Diabetes mellitus and hyperglycaemia

The prevalence of diabetes mellitus in patients undergoing coronary artery bypass grafting is rapidly increasing. These patients are associated with higher perioperative mortality and morbidity resulting in reduced long term survival (Lazar, McDonnell, Chipkin, Furnary, Engelman, Sadhu, Bridges, Haan, Svedeholm, Taegtmeyer and Shemin, 2009). Mounting evidence suggests that maintaining tight glycaemic control in diabetic patients decreases perioperative morbidity and improves short and long term survival. However, the optimal method and guideline to glucose control and level during cardiac surgery needs to be established. Elevated serum glucose levels during cardiac surgery are not unusual, even for non-diabetic patients. This can be attributed to the stress response induced by cardiopulmonary bypass and hypothermia.

Hyperglycaemia (>140mg/dL) also contributes to cerebral injury via several mechanisms. These include cellular acidosis, oxidative stress, increased blood- brain barrier permeability, and brain oedema (Hogue et al., 2006). The benefit of "tight" glycaemic control on neurological outcomes during cardiac surgery is less clear. Hyperglycaemia is commonly prevalent during cardiopulmonary bypass. Peripheral insulin resistance occurs as a result of stress response, increases circulating catecholamines and cortisol, reduction in cellular metabolism due to hypothermia and increased reabsorption of glucose. The exogenous administration of dextrose to cardioplegia and pump prime contribute to hyperglycaemia during CPB (Puskas, Grocott, White, Mathew, Newman and Shar Bar Yosef, 2007).

In an early study conducted by Furnary and coworkers (2003), the investigators examined the effects of glycaemic control during cardiac surgery. The study involved 3,554 CABG patients who were divided into groups based on year of surgery, method of glycaemic control and target glucose level. Patients received subcutaneous insulin administered every 4 hours to maintain serum glucose < 200 mg/dL from 1987 to 1991. A continuous intravenous insulin infusion to target serum glucose between 150 and 200 mg/dL was used from 1991 until 1998. The investigators instituted the Portland protocol from 1998 until 2001, which required a continuous insulin drip to maintain serum glucose between 100 and 150 mg/dL. The investigators found that perioperative mortality decreased by 50% in CABG patients with diabetes after 1992 (4.5% vs 1.9%; $p = 0.0001$) (Furnary, Gao, Grunkemeier, Wu, Zerr, Bookin, Floten and Starr, 2003).

The investigators expanded the series to include an additional 1, 980 patients managed with the Portland protocol from 2001 to 2005. They introduced the 3-blood glucose method to access glycaemic control. The method consisted of the average of all glucose values taken on

the day of surgery and the first and second day postoperatively. An increase in 3-blood glucose (3-BG) was an independent predictor of perioperative mortality (Furnary, Wu, and Bookin, 2004). The importance of tight perioperative glycaemic control was fostered from a trial on 1,548 surgical ICU patients that showed a 34% reduction in mortality (8% vs 4.6%, p =0.04). This was accomplished by maintaining plasma glucose levels between the range of 80 and 110mg/dL with an intensive insulin infusion rather than using insulin therapy when glucose exceeded 215 mg/dL (van den Berghe, Wouters, Weekers, Verwaest, Bruyninckx, Schetz, Vlusselaers, Ferdinande, Lauwers and Bouillon, 2001).

A subsequent trial using a similar protocol on ICU patients found lower morbidity but higher mortality in those patients receiving intensive insulin treatment who required less than three days of ICU stay as compared to the standard treatment group. However, the benefit of intensive insulin infusion on mortality was observed in patients when length of stay was more than three days (van de Berghe, Wilmer, Hermans, Meersseman, Wouters, Ilse Milants, Van Wijngaerden, Bobbaers and Bouillon, 2006). Doenst et al. (2005), conducted a retrospective review of 6,280 cardiac surgical patients to evaluate the effects of hyperglycaemia on clinical outcome. The investigators found that higher glucose levels during surgery was an independent predictor of mortality in patients with and without diabetes (Doenst, Wijeysundera, Karkouti, Zechner, Maganti, Rao and Borger, 2005).

Support for tight glycaemic control is evident from the findings of various other studies (Gandhi, Nuttall, Abel, Mullany, Schaff, Williams, Schrader, Rizza and McMohan, 2005; Fish, Weaver, Moore and Steel, 2003; McAlister, Man, Bistritz, Amad and Tandon, 2003). In a study conducted by Anderson and coworkers, the investigators studied the effect of elevated fasting blood glucose levels in 1,375 CABG patients prior to surgery. Patients with

elevated fasting blood glucose levels had a one year mortality that was twice as great as patients with normal fasting values (Anderson, Brismar, Barr, and Ivert, 2005).

Lazar et al. (2004), presented further evidence to support insulin therapy in CABG patients with diabetes. The investigators used a modified glucose-insulin-potassium solution in the trial of 141 patients undergoing isolated CABG surgery. Patients were prospectively randomized to receive glucose-insulin-potassium to maintain serum glucose levels between the range of 120 and 180 mg/dL or a sliding scale insulin coverage to maintain glucose < 250 mg/dL. The modified glucose-insulin-potassium solution was administered at the onset of induction of anaesthesia and continued for 12 hours postoperatively in ICU. The authors found that these patients achieved better glycaemic control prior to CPB (169 mg/dL vs 209 mg/dl, $p < 0.0001$) and after 12 hours in ICU (134 mg/dL vs 266 mg/dL; $p < 0.0001$). Patients treated with tight glycaemic control reported higher cardiac indices ($p < 0.0001$) and lower requirement of inotropic support (< 0.05) and pacing (< 0.05). The incidence of infection (0% vs 13%; $p = 0.01$) and atrial fibrillation (15% vs 60%; $p = 0.007$) was significantly reduced. Length of hospital stay was shorter (6.5 days vs 9.2 days; $p = 0.0003$) (Lazar, Chipkin, Fitzgerald, Bao, Cabral and Apstein, 2004).

Recently D' Alessandro and co-investigators (2007), correlated the effect of tight glycaemic control with expected EuroScore outcomes in diabetic CABG patients. Three hundred patients receiving tight glycaemic control were matched with three hundred patients without insulin protocols, using propensity based analyses. In the tight glycaemic control group, mortality was significantly lower (1.3% vs 4.3%; $p = 0.01$) and lower in the higher risk cohort (EuroScore > 4; 2.5% vs 8%; $p = 0.03$) (D' Alessandro, Leprince, Golmard, Quattara, Aubert, Pavie, Gandjbakhch and Bonnet, 2007). In contrast, Gandhi and co-workers (2007),

found no difference in outcome in a study of 400 CABG patients randomized to a continuous insulin group and the intermittent bolus of intravenous insulin group. Outcomes measured included incidence of death, sternal wound infections, prolonged ventilation, cardiac arrhythmias, stroke and renal failure within 30 days of surgery. The investigators found no significant difference in length of hospital stay between the groups (Gandhi, Nuttall, Abel, Mullany, Schaff, O' Brien, Johnson, Williams, Cutshall, Mundy, Rizza, McMohan, 2007). Antunes and coworkers (2008), in a study of 4567 CABG patients found diabetes not to be an independent risk factor of in hospital mortality (Antunes, Oliveira and Antunes, 2008).

Butterworth and colleagues (2005), studied the effects of tight glycaemic control in a prospective randomized trial of 381 non diabetic patients undergoing isolated CABG surgery. One group received an insulin infusion when glucose levels exceeded 100 mg/dL and the other received no insulin therapy. The primary outcome was to determine the incidence of new neurologic, neuro-opthalmologic, neurobehavioral deficits or neurologic related death. The investigators found no difference in the incidence of neurologic related complication between the groups. There was no significant difference in operative mortality, inotropic support requirement or length of hospital stay between the groups, although patients in the non treatment group had glucose levels $\geq$ 200 mg/dL (Butterworth, Wagenknecht, Legault, Zaccaro, Kon, Hammon, Rogers, Todd Troost, Stump, Fuberg and Coker, 2005).

Puskas et al. (2007), evaluated the effect of hyperglycaemia which is known to exacerbate other forms of cerebral injury on neurocognitive dysfunction after cardiac surgery (Murkin, 2000). A total of 525 patients having on-pump coronary artery bypass graft surgery underwent cognitive testing at baseline and at 6 weeks postoperatively. The investigators analyzed diabetic and non diabetic patients separately to eliminate confounding effects

between diabetes and hyperglycaemia. The authors concluded that hyperglycaemia had no effect on cognitive function in diabetic patients. However, in non diabetic patients hyperglycaemia was associated with a decrease in cognitive function at 6 weeks postoperatively ($p = 0.0351$) (Puskas et al, 2007).

2.2.8.8 Cerebral perfusion, mode of flow and flow rates

Cerebral perfusion pressure (CPP) is the difference between mean arterial pressure (MAP) and intracranial pressure (ICP) or cerebral venous pressure. Cerebral perfusion pressure = MAP – ICP when cerebral venous pressure is significantly higher than intracranial pressure, perfusion pressure becomes the difference between the measure of mean arterial pressure and cerebral venous pressure. Cerebral perfusion pressure is normally 80 to 100 mmHg. Moderate to severe increases in intracranial pressure can compromise cerebral perfusion and cerebral blood flow although the mean arterial pressure may be normal. Patients with CPP values less than 50 mmHg demonstrate a slowing on the EEG, those with a CPP of 25-40 mmHg typically have a flat EEG. Sustained perfusion pressures less than 25 mmHg result in irreversible brain damage (Morgan & Mikhail, 2000).

The influence of systemic (arterial or pump) blood flow, flow dynamics and CPP on cerebral blood flow and neurological outcomes after coronary surgery has been the subject of recent debate. Systemic flow during CPB is usually determined by the degree of hypothermia and body surface area which is adjusted to obtain adequate tissue perfusion. Non-pulsatile flow is the most widely used method of CPB perfusion, due to past engineering difficulties that have been overcome by computer controlled pumps that allow for pulsatile perfusion (Houge et al, 2006). Non-pulsatile perfusion is said to be associated with diminished endothelial shear stress and

reduced levels of endothelial nitric oxide production resulting in increased vascular resistance (Macha, Yamazaki, Gordon, Watach, Konishi, Billiar, Borovetz, Kormos, Griffith and Hattler, 1996).

In a canine model comparing pusatile and non-pulsatile perfusion, non-pulsatile flow was associated with worse cerebral hyperaemia and lower oxygen consumption (Anstadt, Tedder, Hegde, Tamayo, Crain, Khian, Aleem, White and Lowe, 1993). However, in a prospective study of 316 CABG patients, Murkin and colleagues (1995), randomized patients to either pH stat or alpha stat management of CPB and to pulsatile and non-pulsatile flow. The investigators were unable to demonstrate any influence of pulsatile flow on the incidence of post-operative cognitive dysfunction (Murkin, Martzke, Buchan, Bently and Wong, 1995). It has been well established that low pump flow rates together with arterial hypotension results in decreased cerebral blood flow. Anttila et al. (2005), conducted a study to define a safe minimum flow rate for specific bypass conditions using near infrared spectroscopy and direct observation of cerebral microcirculation on 144 juvenile pigs. The investigators conducted two series of experiments (n = 72 each), piglets were cooled to a temperature of 15º, 25º or 30º on bypass with a haematocrit of 20% or 30%, pH stat management in all followed by 1 or 2 hours of a reduction in flow (10, 25 or 50 ml/kg/min). Animals in series one had a cranial window placed over the parietal cortex to evaluate the microcirculation with intravital microscopy. The investigators labelled plasma with fluorescein isothiocyanate dextran for the assessment of functional capillary density (FCD) and microvascular diameter. In the second series, near-infrared spectroscopy was used to detect tissue oxygenation index (TOI).

The authors found that tissue oxygen index during low flow perfusion and functional capillary density during rewarming and termination from CPB were associated with neurologic insult. Temperature and low flow rate were multivariate predictors of TOI and FCD during rewarming (p =<0.001). The authors concluded that pump flow rates vary according to bypass conditions. Using pH stat and haematocrits of 20% or 30%, flow rates as low as 10ml/kg/min was adequate for 2 hours at a temperature of 15º C. However, under similar conditions at 34º C the flow rate of 10ml/kg/min was likely to be associated with neurological injury (Antitila, Hagino, Zurakowski, Iwata, Duebener, Lidov and Jonas, 2005).

Schwartz and colleagues (1995), measured cerebral blood flow during independent manipulations of arterial blood pressure and pump flow rate in order to determine whether they influence cerebral perfusion during cardiopulmonary bypass. Seven baboons underwent cardiopulmonary bypass and were cooled to 28°C. Arterial pump flow rate and blood pressure was altered in varied sequence to four different conditions: (1) full flow (2.23 ± 0.06 L/min/m^2, mean ± standard deviation) at high pressure (61 ± 2 mm Hg), (2) full flow (2.23 ± 0.06 L/min/m^2) at low pressure (24 ± 3 mm Hg), (3) low flow (0.75 L/min/m^2) at high pressure (62 ± 2 mm Hg), and (4) low flow (0.75 L/min/m^2 at low pressure (23 ± 3 mm Hg). Cerebral blood flow during these haemodynamic conditions was measured by washout of intracarotid xenon. The authors found that cerebral blood flow was greater at higher pressures during CPB, both at low and full flow (Schwartz, Sandhu, Kaplon, Young, Jonassen, Adams, Edwards, Sistino, Kwiatkowski and Michler, 1995).

2.2.8.9 Genetic predisposition

Cardiac patients with similar characteristics, risk factors, medical history and severity of cardiac disease display markedly different neurological and neuropsychological events. Genetic predisposition has been suggested in the susceptibility for cerebral insult from cardiac surgery (Houge et al, 2008). The apolipoprotein E genotype has been shown to increase the risk for Alzheimer's disease and cognitive deficit after cerebral injury (Isoniemi, Tenovuo, Portin, Himanen and Kairisto, 2006). Apolipoprotein E (APOE), a 34 kD glycosylated lipid binding protein which is expressed in three isoforms (ε2, ε3, ε4) functions in the central nervous system to predispose cerebral injury when the lipoprotein is abnormal. Apolipoprotein ε4 increases the risk for cognitive decline. However, data is inconclusive as to its role in cerebral injury (Askar, Cetin, Kumral, Cetin, Acarer, Kasova and Yagdi, 2005; Abildstrome, Christiansen, Siersma and Rasmussen, 2004; Heyer, Wilson, Sahlein, Mocco, Williams, Seiacca, Rampersad, Komotar, Zurica, Benvenisty, Quest, Todd, Solomon and Connolly, 2005).

The impact of genetic variants on stroke risk is not fully established. Grocott et al. (2005), tested the hypothesis that specific genetic polymorphisms are associated with an increased risk of stroke following cardiac surgery. Patients undergoing on-pump cardiac surgery were studied. The investigators isolated DNA from preoperative blood samples and analyzed the samples for 26 different single-nucleotide polymorphisms. The investigators found that the combination of the 2 minor alleles of C-reactive protein (CRP; 3'UTR 1846C/T) and interleukin-6 (IL-6; -174G/C) polymorphisms, occurring in 583 (35.7%) patients, was significantly associated with stroke (odds ratio, 3.3; 95% CI, 1.4 to 8.1; *P*=0.0023). The authors concluded that common genetic variants of CRP (3'UTR 1846C/T) and IL-6 (-

174G/C) were significantly associated with a risk of stroke after cardiac surgery (Grocott, White, Morris, Podgoreanu, Mathew, Nielsen, Schwinn and Newman, 2005).

Recently Mathew and colleagues (2007), conducted a prospective cohort study of 513 patients undergoing on-pump CABG surgery. A panel of 37 single-nucleotide polymorphisms was genotyped using mass spectrometry. The association between single-nucleotide polymorphisms (SNP) and cognitive deficit at 6 weeks postoperatively was evaluated for age, educational level, baseline cognition and population structure. Minor alleles of the C- reactive protein 1059G/C single –nucleotide polymorphism (odds ratio 0.37, 95% confidence interval, 0.16 to 0.78; $p = 0.013$) and the P-selectin allele 1087G/A (odds ratio 0.51, 95% confidence interval, 0.30 to 0.85; $p = 0.011$) were found to be associated with cognitive decline 6 weeks after surgery (Mathew, Podgoreanu, Grocott, White, Morris, Stafford, Mackensen, Rinder, Blumenthal, Schwinn, and Newman, 2007).

2.2.8.10 Atrial fibrillation

Postoperative atrial fibrillation affects more than 30% of cardiac patients, especially in the elderly (Lundqvist, 2006; Houge, Creswell, Gutterman and Fleisher, 2005; Mathew, Fontes, Tudor, James, Duke, Mazer, Barash, Hsu, and Mangano, 2004). Stanely et al. (2002), demonstrated in a study of 380 cardiac patients that those who developed postoperative atrial fibrillation (22%) showed a greater degree of cognitive decline than those who did not ($p = 0.036$). In a study of 2630 patients undergoing CABG surgery, Lahtinen, Biancari, Salmela, Martti, Jari, Satta, Rainio, Rimpilainen, Lepojarvi and Juvonen, (2004), found that atrial fibrillation preceded stroke in 19 of the 52 (36.5%) patients with cerebral ischaemic events.

Filardo and colleagues (2009), recently assessed long term survival in a cohort 6899 CABG patients. The ten-year unadjusted survival rate was 52.3% (48.4%, 56.0%) for patients with new-onset postoperative atrial fibrillation and 69.4% (67.3%, 71.4%) for patients without it. Postoperative atrial fibrillation was significantly associated with increased risk of death and the investigators concluded that the risk of long-term mortality in patients that developed new-onset post-CABG atrial fibrillation was 29% higher than in patients without it (Filardo, Hamilton, Hebeler, Hammon, and Grayburn, 2009).

2.2.9 MONITORING BRAIN OXYGEN SATURATION

It is now well established that manifestations of brain injury may be detected in a disturbingly large number of patients who undergo cardiac surgery. Measurement of the saturation of brain effluent blood gives a global estimate of cerebral oxygenation. Monitoring may provide clinicians with vital information to assist in reducing secondary insults to the brain with potential benefits to a range of patients with actual or potential acute brain injury such as cardiac bypass procedure (Murkin and Arango, 2009; Denault, Deschamps and Murkin, 2007; Macmillen and Andrew, 2000).

The application of specific monitoring to enhance detection of hypoxic conditions associated with neurological injury would allow intervention on individual patients and drive refinements in strategies to further reduce risk. Cerebral desaturation is associated with various adverse systemic outcomes. Therefore, by using the brain as an index organ, interventions to improve cerebral oxygenation can be implemented which would have positive systemic benefits for cardiac surgical patients. Although perioperative events do not completely determine the range of neurodevelopmental outcome, many factors in the

perioperative period present intense pathophysiologic stress. The application of neurologic monitoring during this period can be used as a tool to expose processes associated with central nervous system injury, and therefore, provide a model for exploration of strategies to improve perioperative care (Hoffman, 2006; Murkin, 2007).

Neurologic monitoring in the perioperative period has been extensively reviewed and is widely recommended for high risk patients (Murkinet al, 2009; Denault et al, 2007; Andropoulous, Stayer, Diaz and Ramamoorthy, 2004; Smythe and Samra, 2002). Possible approaches include monitoring of superior vena cava or jugular venous oxygen saturation, regional cerebral oxygen saturation by Near infrared spectroscopy (NIRS), cerebral blood flow velocity by transcranial Doppler, electroencephalography (EEG), and processed EEG.

Near infrared spectroscopy (NIRS) is a technique that has been employed since the mid 1970's and can be used as a non-invasive and continuous monitor of the balance between cerebral oxygen delivery and consumption. The use of NIRS for the assessment of bifrontal regional cortical oxygen saturation has demonstrated a correlation between coronary artery bypass patients having low regional oxygen saturation values and cognitive dysfunction (Yao, Tseng, Ho, Levin and Illner, 2004). Yao et al. (2004), examined preoperative regional oxygen saturation in 156 cardiac surgery patients and found that patients with a baseline regional oxygen saturation of less than 50% had an increased incidence of postoperative neurologic and cognitive deficit as well as prolonged critical care and total hospital stay. This view is supported by Madsen et al. (2000), who defined a normal regional saturation range of between 55% to 78% and observed a marked decrease in patients with chronic heart failure (20% to 58%).

Abnormally high regional oxygen saturation may also signify an underlying problem, for example, in an infarcted region cerebral oxygen saturation may be above normal because of injured or dead neurons which consumes little or no oxygen (Nemoto, Yonas and Kassam, 2000). The abnormal regional oxygen saturation values can be used to alert the operative team to the increased potential for cerebral oxygen imbalance during surgery. The cerebral oximeter has also been reported to detect potential catastrophes of cerebral desaturation because of torsion on the great vessels during manipulation of the heart (Akca and Sessler, 2002; Novitsky, Boswell, 2000).

2.2.9.1 Near- Infrared Spectroscopy (Technology)

Near-infrared spectroscopy (NIRS) is a real time, non invasive measure of tissue perfusion using optical technology. It is a device that can be used as an early warning system of haemodynamic or metabolic compromise, enabling rapid intervention to prevent against potential adverse neurologic outcomes (Vohra, Modi and Ohri, 2009; Kakihana, Matsunaga, Yasuda and Imabayashi, 2008). Near infrared spectroscopy technology (Figure 31) is based on the principle that each tissue substance has a characteristic light absorbance. In the near infrared wavelength range, haemoglobin, and cytochrome aa3 are the main chromophores (light absorbing substances at specific frequency).

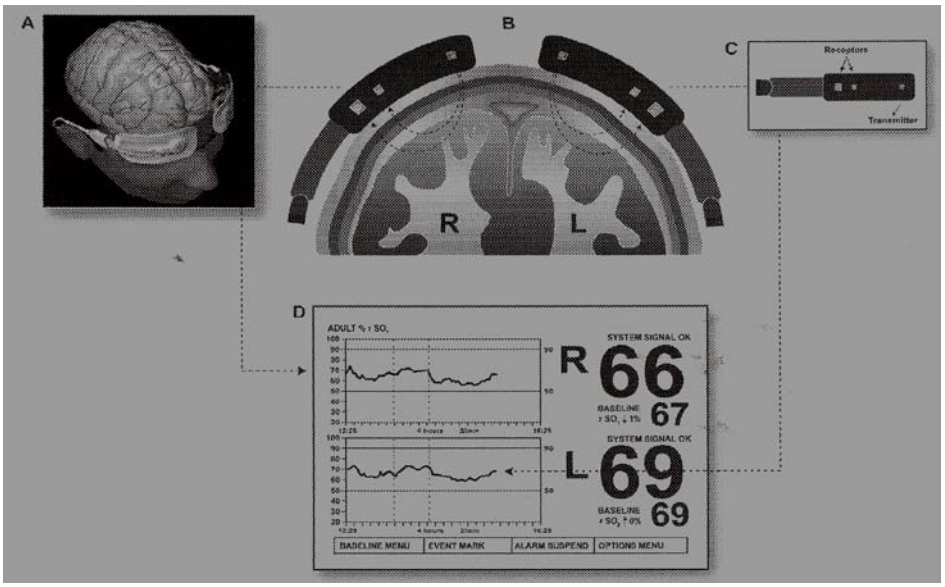


Figure: 31 Operating principles of the use of near- Infrared spectroscopy (Denault et al., 2007) Invos Cerebral Oximeter

(A) Cerebral oxygen sensors are positioned on the patients forehead – Fig 32 (B) Signals generated from left and right hemispheres are transmitted to a display monitor (C) These signals are generated from an optode that has a single transmitter and two receptors. The signals originating from the proximal receptors are subtracted from the distal ones. Therefore, only information from the deeper part of the brain is displayed. (D) The larger numbers displayed on the monitor indicates ongoing cerebral oxygen saturation values and the small number indicates the baseline value obtained at the beginning of the recording from both the right (R) and the left (L) hemispheres- Fig 33

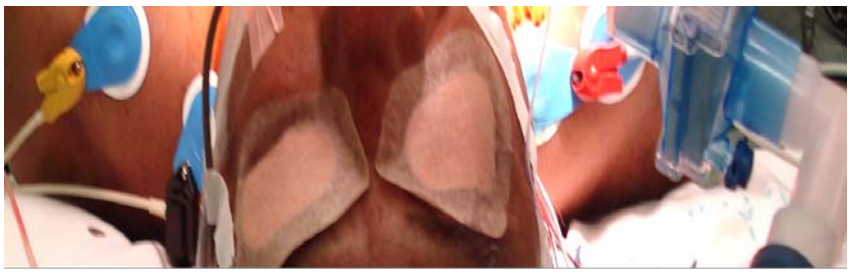


Figure: 32 Cerebral sensors positioned on the forehead (Y. Harilall, 2010)

Figure: 33 Display monitor indicating cerebral oxygen saturation values and baseline values (green) for left (L) and right hemispheres (Y.Harilall, 2010)

The adhesive patches which are attached to the patients forehead contains light sources and receivers, light emitting diodes (LED). They provide two continuous wavelengths of near infrared light at 730 nm and 810 nm. The 730 wavelength measures the oxygenated/ deoxygenated haemoglobin ratio and the 810 wavelenght is the frequency of the isobestic point (crossover point of oxygenated/deoxygenated haemoglobin) and gives an index of total light transmission where the arithmetic difference between reflected signal strength is a measure of total tissue oxygenation (Denault et al., 2007). The key benefit of NIRS derives from the ability to measure cerebral blood oxygenation non-invasively and independent in both hemispheres of the brain. This real time information allows for the detection of cerebral desturation and documentation of trends in oxygenation as they evolve over time (Slater, Guarino, Stack, Vinod, Bustami, Brown, Rodriguez, Magovern, Zaubler, Freundlich and Parr, 2009).

2.2.9.2 Near-Infrared Spectroscopy, Cerebral Oxygenation and Neurological Injury

Cerebral desaturation detected by NIRS generally precedes signs of neuronal dysfunction. In human adults undergoing implantable defibrillator testing, EEG changes during cardiac arrest occured at NIRS rSO_2 of 47% (Levy, Levin and Chance, 1995). In a neonatal piglet model, graded neuronal dysfunction was related to NIRS values observed during progressive hypoxia: lactate accumulated at rSO_2 of 44%; EEG changes occurred at rSO_2 of 42%; the EEG became silent at rSO_2 of 37%, and loss of adenosine triphosphate production resulted in biochemical failure at rSO_2 of 33%. (Kurth, Levy and MaCann, 2002). Thus NIRS can provide a graded signal over a range of hypoxia, resulting in progressive metabolic disturbance, functional deterioration, and actual biochemical failure. Factors related to inadequate oxygen delivery on CPB were recently evaluated using NIRS by Hagino and colleagues (2005), the authors found that the CPB factors of haemoglobin concentration, flow rate, and carbon dioxide tension were determinants of both brain oxygenation by NIRS and histologic injury in a graded hypoxic – ischaemic model (Hagino, Anttila, Zurakowski, Duebener, Lidov and Jonas, 2005).

In 2009, Schon and colleagues conducted a study to determine the usefulness of NIRS monitoring in patients undergoing on-pump coronary artery bypass graft surgery and the relationship between minimal perioperative cerebral oxygen saturation levels and clinically relevant outcomes. A retrospective analysis was conducted on 274 patients monitored with NIRS and 526 patients without the use of NIRS monitoring. The investigators found that monitored patients had more preoperative risk factors, longer duration of surgery, cardiopulmonary bypass and aortic cross clamp times and duration of ICU stay. However, postoperative complications were not different between the groups. Patients with a Euroscore

≤ 8 and intraoperative cerebral saturations (rSO_2) < 50% had postoperative organ complications and longer length of ICU stay. The authors concluded that on pump CABG patients with a high risk profile may benefit from cerebral monitoring and values < 50% are associated with poorer outcome (Schon, Serien, Hanke, Bechiel, Heinze, Groesdonk, Adib, Berger, Eleftheriadis and Heringlake, 2009).

Denault et al. (2007), proposed that an important requirement in the monitoring of cerebral saturation is the elaboration of a clinical algorithm to correct decreases in cerebral saturation values. The authors suggested that the algorithm should be based on optimizing those factors that can affect cerebral oxygen supply and demand such as perfusion pressure, cardiac output, arterial oxygen content, partial pressure of carbon dioxide, and cerebral metabolic rate. In 2009, Murkin and Arrango deduced that a common limitation in studies assessing the impact of cerebral oxygen monitoring is the absence of a defined protocol based on physiologically derived interventions to actively treat cerebral desaturation. In a recent study conducted by Slater and co-workers (2009), 265 patients undergoing CABG utilizing cerebral oximetry were randomized into an active monitoring and an intervention group to improve cerebral oxygen saturation. The investigators found a significant association between prolonged cerebral desaturation and cognitive decline and a three fold increase in hospital stay. However, there was no difference between cerebral desaturation rates between the intervention and control group resulting in the incidence of cognitive decline being similar. The authors ascribed this to poor compliance of the treatment protocol (Slater, Guarino, Stack, Vinod, Bustami, Brown, Rodriguez, Magovern, Zaubler, Freundlich and Parr 2009; Murkin et al, 2007).

Neurocognitive dysfunction after CABG significantly affects patient quality of life, leading to deteriorated health conditions and a lower productive working status for as long as 5 years after the procedure. The societal costs of this type of complication are also significant because patients who develop CABG-associated neurological injury require longer postoperative hospital stay and more extensive rehabilitation. The multiple linkages between hypoxic- ischaemic risk and reduced neurodevelopmental outcome indicate that clinicians have to choose a straightforward perioperative strategy to increase detection, treatment, and prevention of brain hypoxia throughout the period of physiologic risk. The rationale for this type of approach is to further improve outcomes by interrupting the pathway from risk to reversible dysfunction to irreversible injury.

Currently, cerebral oximetry provides the only non-invasive means of continually monitoring brain oxygen imbalances. The overwhelming consensus of published studies suggest that together with an established treatment plan, using cerebral oximetry to enhance detection during cardiac surgery may be associated with a significant reduction in neurocognitive decline. Because the risk associated with cerebral oxygen monitoring is nil, the cost is justifiable and the potential medical and socioeconomic benefits are substantial, therefore the decision to evaluate this technique of monitoring seems uncomplicated (Harvey, Edmonds, Ganzel and Austin, 2004).

2.2.10 BIOCHEMICAL MARKER SERUM S100B PROTEIN AS AN INDICATOR OF NEUROLOGICAL INJURY

Biochemical markers used for the detection and monitoring of organ damage is widespread. Ideally biochemical markers should be organ specific, quantitative and predictable. In 1965, investigators isolated a subcellular fraction from bovine brain, which was thought to contain nervous system specific proteins (Ramlawi, Rudolph, Mieno, Khabbaz, Sodha, Boodhwani, Levkoff, Marcantonio and Sellke, 2006; Hammon and Stump, 2000; Moore, 1965). This fraction was called S100 because the constituents were soluble in 100% saturated ammonium sulphate at neutral pH. S100 is an acidic calcium binding protein (molecular weight 21kDa) (Shaaban Ali, Harmer and Vaughan, 2000). High concentrations are found in glial and Schwann cells. It exists either in the alpha or beta unit configuration. The beta subunit is highly brain specific. S100B is a member of a highly homologous Ca^{2+} binding protein family that possess two EF-hand motifs (Mangano, 2003; Carrier, Denault, Lavoie and Perrault, 2006). The family of S100 proteins consists of 19 members. Most S100 proteins exist as dimers (frequently homodimers) within cells.

Exclusively expressed in vertebrates, S100 is implicated in various intracellular and extracellular regulatory activities. S100B is abundant in the nervous system where it is predominantly expressed in astrocytes, oligodendrocytes and Schwann cells (Einav, Itshayek, Kark, Ovadia, Weiniger and Shoshan, 2008). When secreted by astrocytes, S100B has neurotrophic effects during development and nerve regeneration at physiologic (nanomolar) concentrations. However, high (micromolar) concentrations of S100B have shown to be neurotoxic, participating in the physiology of neurodegenerative disorders. The clinical values have been demonstrated in stroke, cerebral complications association with cardiac arrest and in patients with severe as well as minor head injury (Jonsson, Per Johnsson,

Backstrom, Alling, Dautovic-Bergh and Blomquist, 2004). High concentrations of S100B have been demonstrated in brain injury, ischaemia and hypoxia (Fazio, Bhudia, Marchi, Aumayr and Janigro, 2004).

The use of S100B as marker of neurological injury in the clinical setting is limited by high cost and time requirements for the performance of the enzyme-linked immunosorbent assay (ELISA). S100B can be released in smaller concentrations from the heart or mediastinum and exists in skin, testes, skeletal muscle, adipose tissue and placental tissue. Normal values of S100B in humans are yet to be established and cuttoff values for the diagnosis, quantification and extent of brain injury remain undefined (Shabaan Ali et al, 2000; Wang, Hua Wu, Yuan Fang, Ren Yang and Chih Tseng, 2005). Clinical tools for the early diagnosis of brain injury after CABG are lacking. Therefore, physical examination and intuitive prediction remain the mainstays for both diagnostic and treatment decisions for cardiac patients. The level of S100B at which stroke or cerebral complication can be diagnosed is unknown and its pattern of release give no information about the anatomical distribution of brain injury and functional impact. However, it can be used as a marker and early indicator of brain injury during and after cardiopulmonary bypass (Einav et al, 2008).

In a study conducted by Carrier et al. (2006), the investigators tested the hypothesis that processing pericardial shed blood with a cell saving device would reduce the level of S100B in elderly patients undergoing coronary artery bypass graft surgery. Forty on-pump CABG patients aged 65 years and older were prospectively assigned to processing of pericardial shed blood with a cell saver or to conventional system where cardiotomy blood was collected and reinfused through the arterial circuit. Serum S100B was measured at different time periods (30 minutes, 4 hours, 24 hours and 48 hours after surgery). The investigators found

that serum protein S100B levels averaged 0.06 ug/L ± 0.03 before surgery and 0.51 ± 0.23 ug/L 30 minutes after surgery in the cell saver group compared to 0.076 ± 0.04 before surgery (p = 0.32) and 1.48 ± 0.66 (p = 0.0001) in the conventional group. The authors concluded that S100B levels were significantly higher in the conventional group compared to the cell saver group (Carrier et al, 2006). According to Korfias and co-workers, increases in S100B are dircectly related to the degree of brain injury (Korfias, Stranjalis, Boviatsis, Psachoulia, Jullien, Gregson, Mendelow and Sakas, 2007).

Krnjak et al. (2008), conducted a study to determine whether increased levels of S100B after surgery correlated with the length of hospital stay in patients undergoing coronary artery bypass graft suregry. Thirty two patients were enrolled in the study. Results showed that median S100B concentrations was 0.075 mg/L preoperatively, 0.840 mg/L immediately after the operation, 0.180 mg/L at day 1 and 0.100 mg/L at day 5 postoperatively. The investigators found a positive correlation between length of hospital stay and S100B levels (Krnjak, Trunk, Gersak and Osredkar, 2008).

Jonsson and colleagues (2001), studied the validity of S100B as a predictor of size of brain lesion and median term outcome in patients suffering stroke after cardiac surgery. Twenty patients with clinical signs of postoperative stroke were investigated and S100B measurements were taken at 5, 15 and 48 hours after surgery. Patients were examined using computed tomography and magnetic resonance imaging to confirm diagnosis and size of cerebral infarction. Results showed that S100B blood concentrations taken at 48 hours postoperatively correlated with the size of infracted brain tissue (r = 0.68, p < 0.001). Nine of the twenty patients had levels exceeding 0.5 ug/L and a 2 year mortality of 78% compared to

18% for the patients with concentrations < 0.5 ug/L (Jonsson, Johnsson, Birch-Lensen, Alling, Westaby and Blomquist, 2001).

Wang and co workers (2005), conducted a prospective study to evaluate S100B as an early marker of brain injury in patients undergoing off-pump CABG (n=30) and on-pump CABG (n=60). The investigators sampled blood preoperatively, before CPB, after termination of CPB and 1 day after surgery. Results showed that S100B concentrations peaked in the on-pump group. At day 1 postoperatively, values were similar between the groups and did not return to normal (Wang, Hua-Wu, Yuan-Fang, Ren-Yang and Tseng, 2005).

Ueno and colleagues (2003), conducted serial measurements of serum S100B protein to evaluate the time course of the protein concentration and to determine the clinical relevance of its concentration and subsequent brain injury. Neurologic assessment was conducted on 149 patients undergoing cardiovascular surgery with the use of CPB. Patients were categorized into three groups, (group A) unconsciousness or convulsion, (group B) both unconsciousness and convulsion but no hemiplegia and (group C) unconsciousness and hemiplegia with or without convulsions. S100B was measured at seven time points, before CPB, termination of CPB, and at 5, 12, 24, 48 and 72 hours after CPB. S100B concentrations were higher in groups B and C at 5 hours after cardiopulmonary bypass. At 12 -24 hours concentrations continued to increase up until final measurement at 72 hours. The increase in concentration of S100B was associated with radiological abnormality and brain injury. They concluded that serum S100B protein measurement 12 hours after CPB could be used to predict brain injury (Ueno, Iguro, Yamamoto, Sakata, Kakihana and Nakamura, 2003; Johnsson, Backstrom, Bergh, Jonsson, Luhrs and Alling, 2003).

Johnsson et al. (2003), studied 767 patients who survived more than 30 days after a cardiac operation and found that the probability of death was higher for patients with S100B levels greater than 0.3 ug/L. Elevated S100B concentration 48 hours after surgery implied poor outcome especially in combination with central nervous sytem complication. Microemboli during CABG have been implicated as a possible cause of neurological injury.

Mottallebzadeh et al. (2004), conducted a study to compare the number of HITS (high intensity transient signals) during on and off-pump CABG and determine if S100B levels were related to HITS. Thirty five patients, (n=20) on-pump and (n=15) off-pump were enrolled in the study. Bilateral transcranial Doppler ultrasonography was performed on the middle cerebral artery of patients to detect HITS. S100B concentration was measured preoperatively, end of CPB, completion of anastomoses (off-pump), and 48hours postoperatively. The number of HITS was higher in the on-pump group when compared to the off-pump group (2016 ± 1897 versus 16 ± 21) ($p < 0.0001$). S100B levels in the on-pump group increased from 0.05 ± 0.03 to 0.50 ± 0.28 ug/L ($p < 0.0001$) at termination of bypass. In the off-pump group S100B increased from 0.08 ± 0.05 to 0.35 ± 0.20 ug/L ($p < 0.0001$) at completion of anastomoses. No relationship was found between S100B and HITS in both groups (Motallebzadeh, Kanagasabay, Bland, Kaski and Jahangiri, 2004).

Recently Groom and co-workers (2010), conducted a study to identify the relationship between microemboli leaving the CPB circuit and S100B. Seventy one patients undergoing on pump CABG were enrolled in the study. The investigators monitored microemboli using Power-M-Mode Doppler in the inflow and outflow of the CPB circuit. Blood samples for the measurement of S100B were taken before and within 48 hours of surgery. Majority of the patients had elevated serum levels of S100B (.25 microg/L, median .15 microg/L)

postoperatively. The investigators found a positive correlation between microemboli leaving the CPB circuit and increases in S100B levels postoperatively (Groom, Quinn, Lennon, Welch, Kramer, Ross, Beaulieu, Brown, Malenka, O'Conner and Likosky, 2010). In order to link processes of care with markers of neurological injury, investigators have highlighted the role of biochemical markers of brain injury which would increase the sensitivity and timelines of diagnosing injury (Groom et al, 2010).

It is well established that neurological injury following coronary artery bypass graft surgery significantly affects patient quality of life, leading to deteriorated health conditions and a lower productive working status for as long as 5 years after the procedure. The societal costs of this type of complication are also significant because patients who develop CABG-associated neurological injury require longer postoperative hospital stay and more extensive rehabilitation. The multiple linkages between hypoxic-ischaemic risk and reduced neurodevelopmental outcome indicate that clinicians have to choose a straightforward perioperative strategy to increase detection, treatment, and prevention of brain hypoxia throughout the period of physiologic risk. The rationale for this type of approach is to further improve outcomes by interrupting the pathway from risk to reversible dysfunction to irreversible injury. Currently, cerebral oximetry provides the only non-invasive means of continually monitoring brain oxygen imbalances. The overwhelming consensus of published studies suggest that the establishment of an effective treatment plan together with the use of cerebral oximetry to enhance detection during cardiac surgery may be associated with a significant reduction in neurocognitive decline. Numerous studies have identified possible causes and markers of cerebral injury during cardiopulmonary bypass. However, studies providing definitive measures to deal with cerebral desaturation during cardiopulmonary bypass are lacking. Denault et al. (2007), proposed that an important requirement in the

monitoring of cerebral saturation is the elaboration of a clinical algorithm to correct decreases in cerebral saturation values.

This is the first study conducted to optimize and establish which factors result in an increase in cerebral oxygen saturation during cardiopulmonary bypass. Furthermore the effect of optimizing cerebral oxygen saturation on markers of neurological injury is novel and requires research attention. The findings of this study may result in the formulation of an effective treatment protocol which could be implemented during cardiopulmonary bypass to prevent cerebral desaturation and subsequent neurological injury. Considering the risk associated with cerebral oxygen monitoring is nil, the cost is justifiable and the potential medical and socioeconomic benefits are substantial, the decision to implement this technique of monitoring together with an active treatment protocol seems uncomplicated (Harvey, Edmonds, Ganzel and Austin, 2004).

CHAPTER THREE: METHODS

The aim of the study was to optimize cerebral tissue oxygen saturation using an interventional protocol and to assess the effect on serum S100B protein which is a marker of neurological injury during coronary artery bypass graft surgery. The principal objective was to increase regional cerebral oxygen saturation monitored by Near Infrared Spectroscopy (NIRS) during cardiopulmonary bypass using an interventional protocol. The secondary objectives were to measure and compare the concentration of serum S100B protein which is a marker of brain injury during cardiac surgery both pre and postoperatively between the control and interventional groups in order to formulate an algorithm which could be implemented during cardiopulmonary bypass to increase cerebral oxygen saturation and decrease adverse neurological injury. Another secondary objective was to determine if a correlation existed between central venous oxygen saturation, measured from the CVP and regional cerebral oxygen saturation. The final objective was to establish if central venous oxygen saturation could be used as a marker of brain injury during cardiopulmonary bypass. Central venous lines (CVP) are inserted routinely during cardiac surgery.

The study design was a prospective, quantitative, interventional study to determine whether an increase in low levels of cerebral oxygen saturation, during coronary artery bypass graft surgery resulted in a reduction in S100B concentration. The study included forty (40) patients recruited from Inkosi Albert Luthuli Central Hospital scheduled for elective on-pump coronary artery bypass surgery. Patients were randomized into a control group (n=20) and interventional group (n=20) using a sealed envelope system. The envelope contained specific designation to either group

and were randomly chosen. Blood samples for the analysis of serum S100B protein concentrations were taken both pre and postoperatively.

During cardiopulmonary bypass eight time period measurements of mean arterial pressure (MAP), heart rate, temperature, activated clotting time (ACT), patient oxygen saturation (SpO_2), partial pressure of carbon dioxide (pCO_2), haematocrit, lactate, pH, Haemoglobin (Hb), base excess (BE), potassium (K^+), sodium (Na^+), glucose, calcium (Ca^{2+}), central venous oxygen saturation ($ScvO_2$), cerebral oxygen saturation (rSO_2), fraction of inspired oxygen (FiO_2), sweep rate, flow rate (cardiac index) and percentage isoflurane were taken per patient. In the interventional group the application of an interventional protocol resulted in further data collection of the above listed parameters to determine which interventions instituted during cardiopulmonary bypass resulted in an increase in cerebral oxygen saturation levels from lower levels.

The data collection resulted in a sample size of more than 400 measurements including pre and postoperative concentration of serum S100B protein. Previous studies have shown this sample size to be adequate to compare results of the control group to the interventional group (Groom, et al 2010; Krnjak, et al 2008; Carrier et al, 2006; Micheal, Denault, Lavoie and Perrault, 2006; Kuan, Hsiang, Yu and Chih, 2005; Jens, Hofer, Volkman, Martin, Bardenheuer and Weigand, 2004; Motallebzadeh et al, 2004; Hendrik, Per, Mariiaane, Christer, Stephen, and Blomquist, 2001). The patient number recruited for the study was verified by the biostatistician from the Medical University of KwaZulu Natal (UKZN) and was sufficient to show statistical significance. The plan of the entire research process was set up as in Appendix A and Appendix B.

3.1 SELECTION CRITERIA

Patients enrolled into the study were required to meet the inclusion criteria.

Inclusion criteria

a) Age over 18yrs.

b) Elective on-pump coronary artery bypass graft surgery.

c) Preoperative haematocrit greater than 36% (haemoglobin >12g/dl).

The following patients were excluded from the study:

Exclusion criteria

a) Pregnancy.

b) History of stroke or persistent neurological residue.

c) History of transient ischaemic attack (TIA).

d) Unilateral stenosis of carotid artery greater than 70%, bilateral stenosis of carotid artery greater than 50%.

e) Combined cardiac procedure, ie CABG plus heart valve replacement.

f) Left ventricular ejection fraction less than 40%, Left main stem stenosis more than 70%.

g) Symptomatic chronic pulmonary disease requiring long term medication.

h) Renal insufficiency or anuric renal failure or creatinine above 1.5mg/dl.

i) HIV positive patients.

j) Patients in AF (atrial fibrillation).

k) Patients presenting with left ventricular thrombosis preoperatively.

l) Presence of aortic artheroma detected pre, intra or post operatively.

Before commencement of the actual investigation, ethical approval was obtained from the Durban University of Technology Ethical Committee and permission was also obtained from the Higher Degree's Committee and the Department of Cardiothoracic surgery, IALCH (Appendix C and D). In order to facilitate the study, the research plan was presented to the departments of Cardiothoracic Surgery, Anaesthetics, Cardiovascular Perfusion and Cardiac nursing staff at Inkosi Albert Luthuli Central Hospital.

Patients who met the inclusion criteria were recruited in the cardiac ward. A letter of information and consent form, drawn up by the researcher in both English and Isizulu was presented to all patients participating in the study. Patients were notified as to the purpose and the requirements of the study. Patients were informed that their right to participate in the trial was entirely voluntary and that they were entitled to withdraw at any point without affecting the medical treatment rendered to them. They were also informed that all information used in the trial would remain confidential and that any data reported in scientific journals or published would not include information identifying them as a patient in the study (refer to appendix E and F for consent in English and Isizulu). All patients recruited into the study were under the consultant care of Professor A. Reddi (Head of Department of Cardio-thoracic surgery who confirmed that patients required on-pump coronary artery bypass graft surgery).

Patients, who were willing to participate signed the consent form and were randomized into the control or interventional groups using a sealed envelope system prior to being brought to theatre and surgery. In the interventional group, intraoperative regional cerebral oxygen saturation (rSO_2) monitoring was performed

with active display and administration of treatment intervention protocol. In the control group, regional cerebral oxygen saturation monitoring was not visible to the cardiovascular perfusionist operating the heart lung machine during cardiopulmonary bypass (blinded). Cerebral oxygen monitoring is not routinely monitored in the IALCH unit. Therefore, patients were subjected to the normal routine protocol for CABG surgery which is carried out on a daily basis.

The routine protocol included, induction of patients (anaesthesia), insertion of monitoring lines, harvesting of vein grafts, median sternotomy, cannulation of the heart, conduct of cardiopulmonary bypass, recording, analysis and management of blood gases, cardioplegic arrest of the heart, anastomosis of the distal and proximal grafts, blood salvage using the cell saver and termination of cardiopulmonary bypass.

Blinding the cerebral oxygen monitor from the perfusionist in the control group ensured that the routine conduct of cardiopulmonary bypass was followed without attempting to affect any changes that altered cerebral oxygen saturations displayed on the monitor. Recording of regional cerebral oxygen saturations was conducted by an independent person (another perfusionist) who was not involved in the management of the case so as to ensure that no interventions were carried out on the control group.

Routine patient monitoring was performed by the principle investigator (perfusionist) when the patient arrived in theatre. Arterial blood pressure, non-invasive blood pressure, electrocardiography (ECG), patient oxygen saturation (SpO_2) and central venous pressure (CVP) was routinely measured for all patients. These readings were transduced and displayed on monitors placed in theatre (Appendix G). Insertion of a

radial or femoral arterial line for invasive arterial blood pressure monitoring was routinely performed by the anaesthetist (Appendix G). After induction the anaesthetist inserted central venous lines (CVP) into the internal jugular vein (Figure 34).

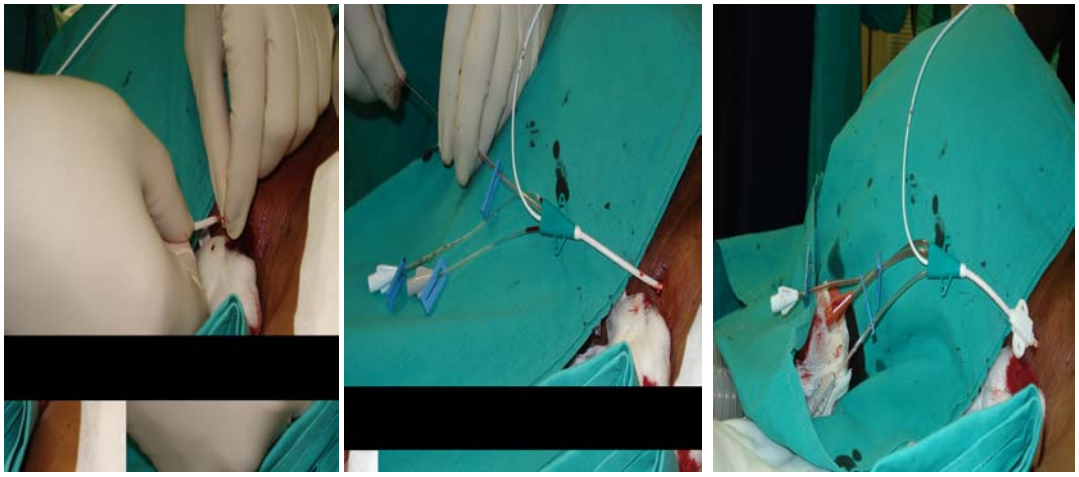


Figure: 34 Insertion of a central venous pressure line with a dedicated transducer line for central venous oxygen saturation monitoring (white cable) Inkosi Albert Luthuli Central Hospital (Y.Harilall, 2010)

Central venous oxygen saturation required for the study was measured from this site using the Edwards transducer CVP set and cardiac output monitor (Vigileo) for continuous oxygen saturation monitoring (Appendix G). Central venous lines are inserted for the administration of drugs and for the measurement of central venous pressure during bypass. Monitoring central venous oxygen saturation is not done routinely. A baseline central venous blood gas together with height, weight and starting haematocrit (Hct) of each patient were taken to perform an in-vivo calibration of the Edwards cardiac output and continuous central venous oxygen saturation monitor (Appendix H).

3.2 Cerebral monitoring

Cerebral monitoring constituted the use of Near infrared spectroscopy monitoring (Invos 5100, Somonetics Corp, Troy MI) monitor. After cleansing of the forehead skin area with alcohol, the adhesive optode pads were placed over each fronto-temporal area as demonstrated in Figure 35.

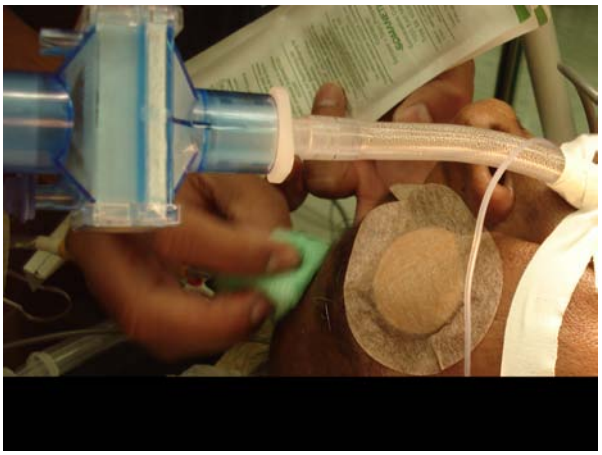


Figure: 35 Cleansing of the forehead with alcohol before placement of the cerebral somasensors (Y.Harilall, 2010)

Two cerebral somasensors were placed on the patient's forehead to measure left and right cerebral saturations (Appendix H). The alcohol prep swabs prevented any grit, dust or sweat from affecting the readings of the electrodes. The sensors were linked by cables to the cerebral monitor which displayed graphic readings of brain oxygen saturations in both hemispheres. Resting baseline values were recorded at least 1min after placement of sensors (Appendix H). In the blinded control group the screen was electronically blinded from the perfusionist doing the case and brain oxygen saturation values were recorded by an independent person.

Near-infrared spectroscopy (NIRS) is a technique that can be used as a non invasive and continuous monitor of the balance between cerebral oxygen delivery and consumption. It is based on the principle that each tissue substance has a characteristic light absorbance. In the near infrared wavelength range, haemoglobin, and cytochrome aa3 are the main chromophores (light absorbing substances at specific frequency). The adhesive patches attached to the forehead contain light sources and receivers, light emitting diodes (LED) providing to continuous wavelengths of near infrared light at 730nm and 810nm. The 730nm wavelength measures the oxygenated /deoxygenated haemoglobin ratio; 810 is the frequency of the isobestic point (crossover point of oxygenated/deoxygenated haemoglobin) and gives an index of total light transmission were the arithmetic difference between reflected signal strength is a measure of total tissue oxygenation.

3.3 Preoperative data collection

The following preoperative data was recorded by the principal investigator.

- Age
- Gender
- Body mass index
- Height
- Weight
- Calculated flow rate (cardiac index)
- Type II Diabetes mellitus (Non insulin)
- Type I Diabetes mellitus (Insulin)
- Baseline rSO_2 (Cerebral oxygen saturation)
- Baseline blood gas
- Activated clotting time (ACT)
- Heart rate
- Mean arterial pressure
- Temperature

3.4 Serum S100B protein sampling

Arterial blood samples were taken from the arterial line preoperatively and postoperatively to determine levels of serum S100B protein (Appendix I). 1-2.5ml of blood was taken by the principle investigator and marked according to a number thus protecting patient identity (PR1 meaning pre bypass and patient number 1). Blood samples were centrifuged at 4000 rpm for 15 minutes in order to separate the serum from other blood components (Figure 36). The serum was pipetted into cryovials and stored in a biofreezer at –20°C until all pre and post patient samples were collected (Appendix I). At the end of the trial the marked frozen samples were analyzed using an ELISA kit to establish the levels of S100B protein. Analysis of serum was done at the department of biotechnology, Durban University of Technology.

Figure: 36 Centrifuging of blood samples at 4000 rpm for 15 minutes IALCH (Y.Harilall, 2010)

3.5 Data collection during cardiopulmonary bypass

During cardiopulmonary bypass eight time period measurements of mean arterial pressure (MAP), heart rate, temperature, activated clotting time (ACT), patient oxygen saturation (SpO_2), partial pressure of carbon dioxide (pCO_2), haematocrit, lactate, pH, haemoglobin (Hb), base excess/ deficit (BE), potassium (K^+), sodium (Na^+), glucose, calcium (Ca^{2+}), central venous saturation ($ScvO_2$), cerebral oxygen saturation (rSO_2), fraction of inspired oxygen (FiO_2), sweep rate, pump flow rate (cardiac index) and percentage isoflurane administered were recorded on a data recording spread sheet for all patients (Figure 37).

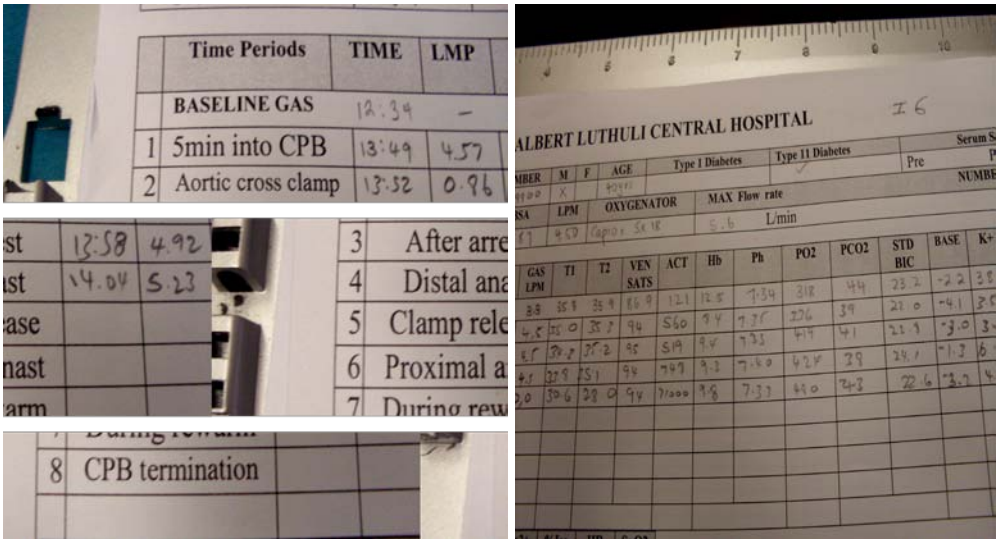


Figure: 37 Time period recording of data measurements in both control and interventional groups. Inkosi Albert Luthuli Central Hospital (Y.Harilall, 2010)

In the interventional group, the implementation of the interventional protocol which resulted in increased cerebral oxygen saturations resulted in further analysis and recording of these measurements to determine which parameters were associated with increased cerebral saturation. Additional data was also recorded by the principal investigator to determine the average number of grafts performed, cardiopulmonary

bypass and cross-clamp times. The additional data was recorded for both control and interventional groups. Cerebral oxygen desaturation during the eight time periods was also recorded to establish a pattern of cerebral desaturation during those time periods.

3.6 Additional data recorded:

- Number of grafts
- Cardiopulmonary bypass time
- Cross clamp time
- Red blood cells given (pack cells)
- Amount of Adrenalin given per patient
- Urine output
- Time period of rSO_2 value < 75% from baseline
- Time period of rSO_2 value < 70% from baseline
- Time period of rSO_2 value < 40% from baseline
- Total cerebral oxygen desaturation time

Table: 3 Sampling sites during CPB (Cardiopulmonary Bypass)

Central venous saturation ($ScvO_2$)	Edwards cardiac output monitor
Cerebral oxygen saturation (rSO_2)	Near-Infrared spectroscopy (NIRS) Somasensors placed on the forehead
Patient oxygen saturation (SpO_2)	Oxygen saturation monitoring using a pulse oximeter placed on the patients finger
Heart rate (HR)	ECG monitor
Mean arterial pressure (MAP)	A. line (Arterial line)
Partial pressure of carbon dioxide ($PaCO_2$)	Blood gas from sampling port of oxygenator
Haematocrit (Hct)	Blood gas from sampling port of oxygenator
Lactate	Blood gas from sampling port of oxygenator
PH	Blood gas from sampling port of oxygenator
Haemoglobin (Hb)	Blood gas from sampling port of oxygenator
Base excess (BE)	Blood gas from sampling port of oxygenator
Pottasium (kcl)	Blood gas from sampling port of oxygenator
Sodium ($Na^{2+)}$	Blood gas from sampling port of oxygenator
Glucose (GM)	Blood gas from sampling port of oxygenator
Calcium (Ca^{2+})	Blood gas from sampling port of oxygenator
FiO_2	Heart lung machine
Sweep rate	Heart lung machine
Cardiac index (Flow rate)	Heart lung machine
Venous saturation	Medtronic Sat/ Hct monitor
Serum S100B protein	Arterial line
Percentage Isoflurane (ISO)	Isoflurane canister on heart lung machine

Blood samples (1ml) are taken routinely during bypass therefore majority of the measurements listed above was derived from a single sample. The only extra blood which was taken from the arterial line was the blood sample of 1-2.5 mls for the measurement of serum S100B pre operatively and once cardiopulmonary bypass was terminated. Blood samples were analysed using the Roche Omni S blood gas analyser. The various sampling sites are pictured under appendix J.

3.7 Interventional Protocol

Prioritized intraoperative management protocol was used to maintain rSO_2 values above 75% of the baseline threshold during cardiopulmonary bypass. Cerebral desaturation was defined as a decrease in oxygen saturation values below 70% of baseline for more than one minute. Interventions commenced within 15 seconds of decrease below 75% of baseline value.

3.7.1 Interventions

1. The position of the patients head was checked to ensure that it was not inadvertently rotated and the face was observed to detect plethora.
2. If pCO_2 was < 35 mmHg during positive pressure ventilation, ventilation was reduced to achieve $pCO_2 \geq 40$ mmHg.
3. Arterial blood gases were used without correction of temperature. This is known as the Alpha stat management of cardiopulmonary bypass.
4. Mean arterial pressure was increased above >60 mmHg by administration of adrenalin (vasoconstrictor).
5. Cardiac index (pump flow rate) was increased eg, from 2.0 L/m^2/min to 2.5 L/m^2/min. The formula used to calculate flow rate was Height X weight of patient / 3600. The square root of the answer was used to determine the body surface area (BSA) of the patient. The BSA was then multiplied by the standard of 2.4 L/min which determined the pump flow rate of each patient. To maximize pump flow rate an index of 3.0 L/min was used.
6. When partial pressure of carbon dioxide (pCO_2) was lower than 40 mmHg, the oxygenator fresh gas sweep rate on the pump was adjusted to achieve pCO_2 values of approximately 40 mmHg.

7. Red blood cells (pack cells) were administered to increase haematocrit (Hct) levels > 20%. This strategy was thought to increase oxygen carrying capacity.
8. Fraction of inspired oxygen (FiO_2) was increased for persistent rSO_2 values below the treatment threshold.
9. Pulsatile flow was used as opposed to laminar flow, to mimic the normal pulsatility of the body.

Optimization of these factors to increase cerebral saturation during cardiopulmonary bypass is not done routinely due to the lack of cerebral oxygen saturation monitoring (NIRS) at Inkosi Albert luthuli Central Hospital. The foundation of the study was to determine which of these factors affect cerebral saturation positively so that an algorithm could be formulated and implemented together with the use of neurological monitoring. The use of NIRS without any interventional protocol would have no impact on patient outcome because the monitor alone can only detect cerebral desaturation.

3.8 Serum S100B Analysis

3.8.1 Introduction

S100B is a member of the highly homologous Ca^{2+} binding proteins family that possess two EF-hand motifs. The family of S100 proteins consists of 19 members. Most S100 proteins exist as dimers (frequently homodimers) within cells. S100 is an acidic calcium binding protein (molecular weight 21kDa) (Shaaban Ali et al, 2000). It has a molecular weight of 11kDa on western blotting and SDS-PAGE. S100 is exclusively expressed in vertebrates and is implicated in various intracellular and extracellular regulatory activities. S100B is found abundantly in the nervous system

where it is predominantly expressed in astrocytes, oligodendrocytes and Schwann cells. High (micromolar) levels of S100B have shown to be neurotoxic, participating in the physiology of neurodegenerative disorders. The clinical values have been demonstrated in stroke, cerebral complications in association with cardiac arrest and in patients with severe as well as minor head injury.

Serum S100B samples were taken from the arterial line pre and postoperatively. 1-2.5ml of blood were taken and marked according to a number (protecting patient identity). The samples were centrifuged in order to separate the serum from other blood components. The serum was stored at –20°C. At the end of the investigation these samples were analysed to determine the S100B protein levels using an ELISA kit S100 (Human) EIA 4555.

The Human S100B ELISA is a HRP labelled antibody based sandwich enzyme immunoassay for the quantitative measurement of human S100B protein in serum, cerebrospinal fluid, heparin plasma and tissue culture medium. It is intended for in-vitro and research use only (Figure 38).

Figure: 38 ELISA kit used for the measurement of S100B
Durban University of Technology (Y.Harilall, 2010)

3.8.2 Features

The various reagents and components supplied with the ELISA kit are listed under (appendix K).

- The total assay time is less than five hours.
- The kit measures S100B protein in serum, heparin plasma or cerebrospinal fluid
- Quality controls are human serum based. Animal serum is used for standard and dilution buffer preparation.
- Standard is recombinant protein based
- Assay format is 96 wells
- Components of the kit were provided ready to use, concentrated or lyophilized

3.8.3 Test principle

In the Human S100B ELISA Standards, Quality Controls and samples are incubated in microplate wells pre-coated with polyclonal anti-cow S100B antibody. After 120 minutes incubation and washing, biotin-labelled monoclonal anti-human S100B antibody is added to the wells and incubated for 60 minutes with captured S100B. After another washing step, streptavidin-HRP conjugate is added. After 30 minutes incubation and the last washing step, the remaining conjugate is allowed to react with the substrate solution. The reaction is stopped by addition of acidic solution and absorbance of the resulting yellow product is measured. The absorbance is proportional to the concentration of S100B. A standard curve is constructed by plotting absorbance values against concentrations of Standards, and concentrations of unknown samples are determined using this standard curve.

3.8.4 Planning and preparation of reagents

A plan outlining the assay procedure and patient serum allocation on the wells was drawn up by the principal investigator as demonstrated in Figure 39. Because pre and post serum sample were analyzed for each patient a plan was required to ensure that correct S100B concentrations were recorded for specific patients according to the numbers allocated e.g. PR 1 and PO 1 (pre sample and post sample).

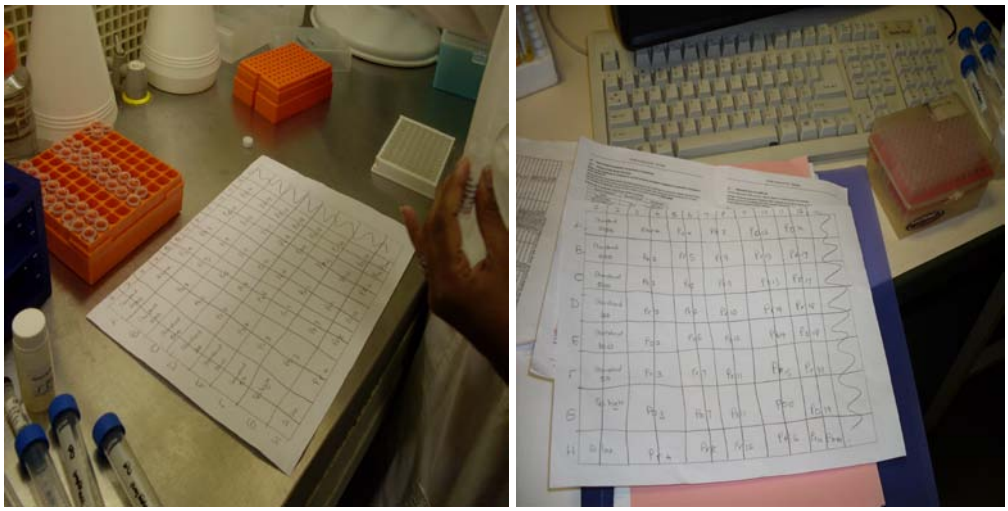


Figure: 39 Plan outlining serum allocation to the 96 well microplate Durban University of technology (Y.Harilall, 2010)

3.8.4.1 Master Standard

The lyophilized Master Standard was first reconstituted according to the certificate of analysis prior to performing the assay procedure. 0.1 ml of distilled water was added to the vial. Thereafter 0.50 ml of the dilution buffer was added to the vial to obtain a concentration of 4000 picograms/ml (Appendix L).

Table: 4 Reconstitution of Master Standard

Volume of standard	Dilution Buffer	Concentration
Stock	-	4000 pg/ml
300 µl of stock	300 µl	2000 pg/ml
300 µl of 2000 pg/ml	300 µl	1000 pg/ml
300 µl of 1000 pg/ml	300 µl	500 pg/ml
300 µl of 500 pg/ml	300 µl	200 pg/ml
300 µl of 200 pg/ml	300 µl	100 pg/ml
300 µl of 100 pg./ml	300 µl	50 pg/ml

Each concentration of the standard was diluted 4x with Dilution Buffer, e.g. 60 µl sample + 180 µl Dilution Buffer was recommended for assaying samples in singlets or in duplicates.

3.8.4.2 Controls (High and Low)

Lyophilized Quality Controls was dissolved with distilled water to the original volume and shaken carefully (not to foam). It was allowed to stand for 25-30 minutes. The solutions were prepared for subsequent dilution. Quality Controls were diluted prior to use 4x (1:4) with Dilution Buffer, e.g. 60 µl sample + 180 µl Dilution Buffer was recommended for assaying samples in singlets or in duplicates. Undiluted Quality Controls were frozen at –20°C until next use.

3.8.4.3 Biotin labelled Antibody Concentrate

1 part of Biotin labelled antibody concentrate (100x) was added to 99 parts of Biotin Ab diluent (Appendix L).

3.8.4.4 Wash solution

The wash solution concentrate was diluted 10 fold in distilled water. 100 mls of wash solution concentrate + 900 mls of distilled water for use of all 96 wells (Appendix L).

3.8.4.5 Sample preparation

Serum samples were diluted 4x (1:4) with the Dilution Buffer prior to being used. e.g. 60 µl sample + 180 µl Dilution Buffer was used for assaying samples in duplicates. Samples were mixed well not allowing any foaming to take place (Figure 40).

Figure: 40 Dilution of serum samples with dilution Buffer (Y.Harilall, 2010)

3.8.5 ASSAY PROCEDURE

Step: 1

100 µl of diluted standards, controls and samples were pipetted in duplicate, into the appropriate wells. 100 µl of dilution buffer was also pipetted as blank in the wells (Appendix M).

Step: 2

The plate was incubated at room temperature (± 25°C) for 120 minutes, shaking at 300 rpm on an orbital microplate shaker (Appendix M).

Step: 3

Thereafter the wells were washed 3-times with wash solution using 0.35 ml of wash solution per well (Appendix N). After the final wash the plate was inverted strongly over a paper towel (Appendix N).

Step: 4

100µl of biotin labelled antibody was added into each well.

Step: 5

The plate was incubated at room temperature for 60 minutes, shaking at 300 rpm on the orbital microplate shaker.

Step: 6

The wells were washed 5-times with the wash solution using 0.35 ml of per well. After the final wash, the plate was inverted strongly against a paper towel.

Step: 7

100 µl of Streptavidin- HRP conjugate was added into each well.

Step: 8

The plate was then incubated at room temperature for 30 minutes, shaking at 300 rpm on the orbital microplate shaker.

Step: 9

The wells were washed 5-times with the wash solution using 0.35 ml of per well. After the final wash, the plate was inverted strongly against a paper towel.

Step: 10

100 µL of substrate solution was added. Exposure of the microtiter plate to direct sunlight was avoided with the use of aluminium foil which was recommended.

Step: 11

The plate was incubated for 20 minutes at room temperature. During this incubation period no shaking was done.

Step: 12

The colour development was stopped by adding 100 µl of stop solution.

Step: 13

The absorbance was established by reading the plate at 450 nm using a microplate reader (DAS Digital Analogic Systems) (Appendix N). The absorbance was read within 5 minutes of adding the stop solution.

3.8.6 Calculations

Most microplate readers perform automatic calculations of analyte concentration. A standard curve was constructed by plotting the absorbance (Y) of standards versus log of the known concentration (X) of standards, using the four parameter function. Figure 41 below shows a typical standard curve for human S100B ELISA. Results were reported as concentration of S100B (pg/ml) in samples. As an alternative method the logit log function can be used to linearize the calibration curve. The logit of absorbance (Y) was plotted versus log of the known concentration (X) of standards. Samples, Quality Controls and Standards were diluted 1:4 prior to analysis, so there was no need to account for this dilution.

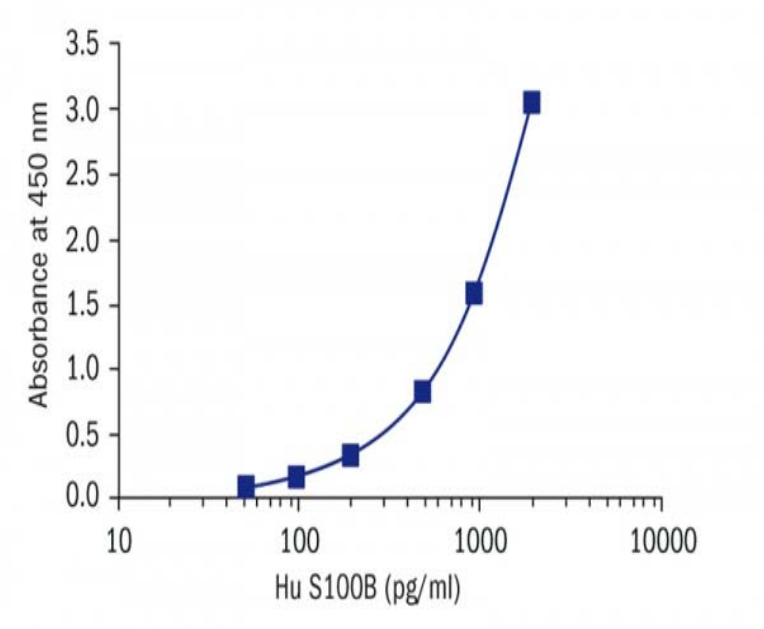


Figure: 41 Human S100B ELISA Standard Curve
ELISA Information Booklet (DRG, 2010)

3.9 STATISTICAL ANALYSIS

The standard curves were plotted and unknown values of S100B concentration were interpolated using Prism 5.03 (trial version © 1992-2010 GraphPad Software Inc.) non linear standard curves module.

SPSS version 15.0 (SPSS Inc., Chicago, Illinois, USA) was used for analysis of data. A p value <0.05 is considered as statistically significant. Clinical data were compared between the intervention and control groups using Mann-Whitney tests for non parametrically distributed dependant variables, t-tests for those which were normally distributed, and Pearson's chi square tests for categorical variables. Participants were randomised into intervention and control groups, and the completeness of the randomization process was checked statistically by comparison of baseline features between the two groups using t-tests in the case of quantitative variables and Pearson's chi square tests or Fisher's exact tests for categorical variables. S100B values were measured quantitatively at two time points and compared between the intervention and control groups using repeated measures ANOVA testing. Profile plots were used to assess the trend of the intervention effects. Within the intervention group the effect of the specific interventions were assessed using Generalized Estimating Equations within the family of Generalized Linear Models. Each intervention received was compared with no intervention within the same participant. This was done separately for each dependant variable specifying a normal distribution with an identity link function.

A statistically significant time*group interaction effect was used to indicate a significant intervention effect. The time*group where the asterisk means multiplied by the interaction effect. Time is the repeated measures of the outcome over time and group is the treatment group to which they were randomised. The interaction between time and group is the differential effect of the intervention compared with control over time (ie the rate of change in the one group compared with the other group), and is known as the treatment effect. If this was significant then it could be established that there is a differential treatment effect and the rate of change of the outcome differs by treatment group. Profile plots were used to assess the direction and trend of the intervention effect. Subgroup analysis on the intervention group allowed comparisons of specific interventions undertaken with cerebral oxygen saturation values and ultimately S100 values to formulate the optimum algorithm using Pearson's chi square tests and Pearson's correlation analysis. Linear regression modelling was used to determine the final algorithm. Linear regression models were also used to determine the predictive value of central venous oxygen saturation for cerebral oxygen saturation whilst controlling for confounding factors. Data collection, recording and analysis using Pearson's, Fisher's and ANOVA testing were done by the principal investigator and statistical analysis was reviewed by a statistician to validate the findings.

CHAPTER FOUR: RESULTS

4.1 Demographics and baseline characteristics:

Forty participants were enrolled into the study and all 40 completed follow up. Their mean age ± standard deviation (SD) was 55.3 ± 9.7 years and ranged from 39 to 72 years. The descriptive statistics for age are shown in Table 5.

Table 5: Summary statistics for age

	Group	N	Mean	Std. Deviation	Std. Error Mean	p value
Age	Intervention	20	53.65	9.767	2.184	0.283
	Control	20	57.00	9.668	2.162	

N	Valid	40
	Missing	0
Mean		55.33
Std. Deviation		9.741
Minimum		39
Maximum		72

Table 6: Gender distribution

Twenty eight of the forty participants were male and 12 were female as shown in Table 6 (p=0.490).

			Group		Total
			Intervention	Control	
Gender	Male	Count	13	15	28
		% within gender	46.4%	53.6%	100.0%
	Female	Count	7	5	12
		% within gender	58.3%	41.7%	100.0%
Total		Count	20	20	40
		% within gender	50.0%	50.0%	100.0%

The summary statistics for height and weight for patients enrolled in the study are shown in Table 7 and 8. The mean height ± SD was 169.5 ± 7.8 and mean weight ± SD was 73.67 ± 7.61.

Table 7: Summary statistics for height

	Group	N	Mean	Std. Deviation	Std. Error Mean	p value
Height	Intervention	20	169.08	8.339	1.865	0.758
	Control	20	169.85	7.407	1.656	

N	Valid	40
	Missing	0
Mean		169.46
Std. Deviation		7.795
Minimum		152
Maximum		185

Table 8: Summary statistics for weight

	Group	N	Mean	Std. Deviation	Std. Error Mean	p value
Weight	Intervention	20	81.545	13.6832	3.0596	0.245
	Control	20	76.760	11.8777	2.6559	

N	Valid	40
	Missing	0
Mean		79.153
Std. Deviation		12.8770
Minimum		56.4
Maximum		110.0

The proportion of patients with and without diabetes did not differ significantly between the treatment groups (p=0.744) as reflected in Table 9.

Table 9: Statistics for diabetes

			Group		Total
			Intervention	Control	
diabetes	0	Count	7	8	15
		% within diabetes	46.7%	53.3%	100.0%
	2	Count	13	12	25
		% within diabetes	52.0%	48.0%	100.0%
Total		Count	20	20	40
		% within diabetes	50.0%	50.0%	100.0%

0- None
1- Type I diabetes
2- Type ii diabetes

Furthermore, the number of grafts performed (Table 10), did not differ significantly between the treatment groups (p=0.809).

Table 10: Statistics for the number of grafts performed

			Group		Total
			Intervention	Control	
grafts	2	Count	5	6	11
		% within grafts	45.5%	54.5%	100.0%
	3	Count	13	13	26
		% within grafts	50.0%	50.0%	100.0%
	4	Count	2	1	3
		% within grafts	66.7%	33.3%	100.0%
Total		Count	20	20	40
		% within grafts	50.0%	50.0%	100.0%

4.2 Comparison of clinical data between intervention and control groups:

There was no difference between the groups in terms of the clinical parameters (Table 11), except for adrenalin quantity where the control value was significantly higher than the intervention value (p=0.043).

Table 11: Statistics of clinical data

	group	N	Mean	Std. Deviation	Std. Error Mean	p value
BSA	Intervention	20	1.947	.1785	.0399	0.323
	Control	20	1.893	.1623	.0363	
Fow rate (LPM)	Intervention	20	4.664	.4338	.0970	0.393
	Control	20	4.553	.3808	.0852	
CPB time (mins)	Intervention	20	133.30	26.864	6.007	0.547
	Control	20	138.20	24.098	5.388	
Cross clamp time (mins)	Intervention	20	80.80	17.781	3.976	0.146
	Control	20	91.85	27.972	6.255	
Adrenalin quant	Intervention	20	15.65	10.975	2.454	0.043
	Control	20	26.00	19.139	4.280	

BSA – body surface area
LMP – liters per minute
CPB – cardiopulmonary bypass time

The median number of packed cells administered per patient in the interventional group was 2 units and 1 unit in the control group (Table 12). Therefore the difference was not statistically significant (p=0.102).

Table 12: Packed cell administration

Median

Group	Pack cells
Intervention	2.00
Control	1.00
Total	1.00
Mann-Whitney U	143.500
Asymp. Sig. (2-tailed)	0.102

4.3 Comparison of S100B values between control and intervention groups

Objective: To compare the level of brain cell injury by measurement of serum S100B pre and post operatively between the control and interventional groups.

Figures 42 and 43 show graphically the interpolation of the unknown concentration values at given absorbences from the standard curve of the control group.

Figure 42: Standard curve of control group

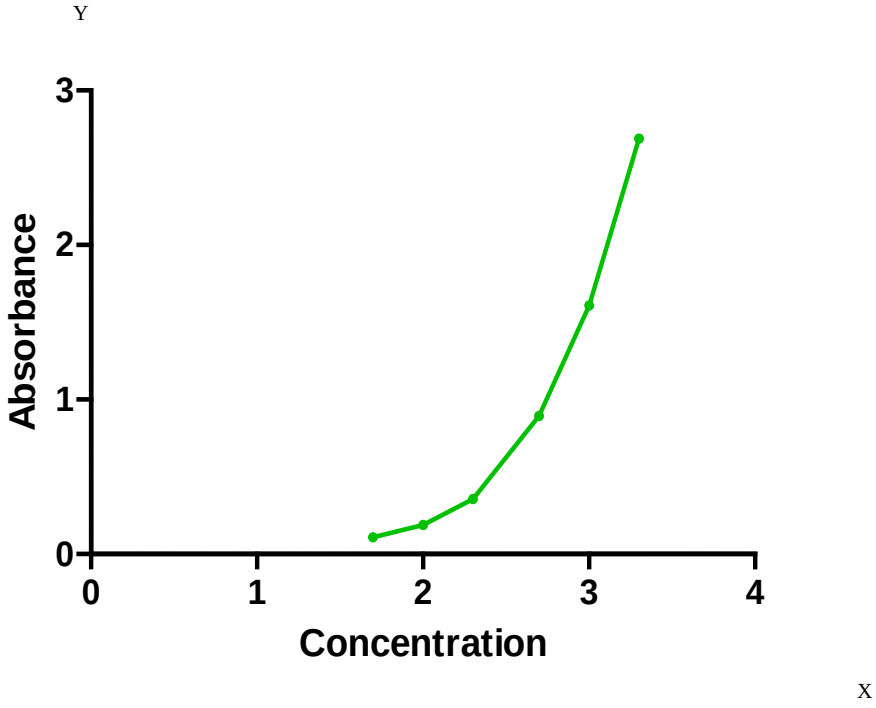
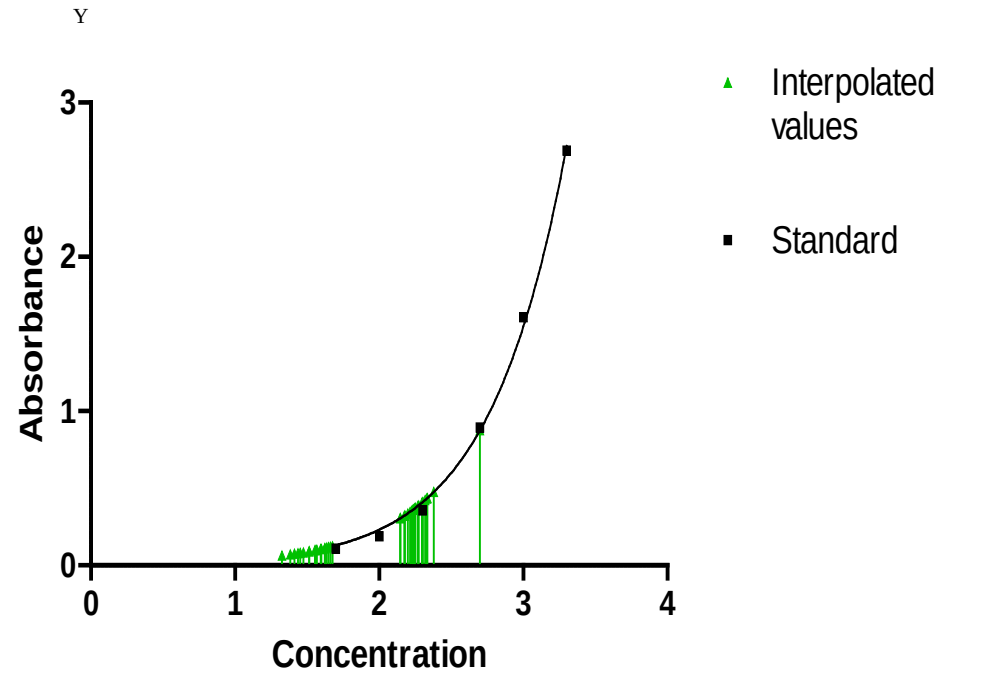


Figure 43: Interpolated values of S100B control group



Figures 44 and 45 show graphically the interpolation of the unknown concentration values at given absorbences from the standard curve of the interventional group.

Figure 44: Standard curve of interventional group

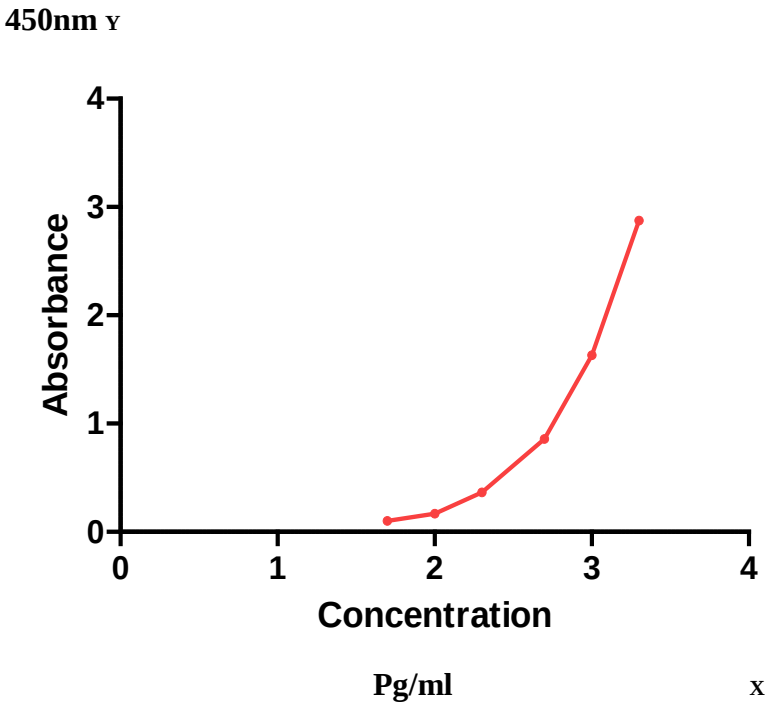
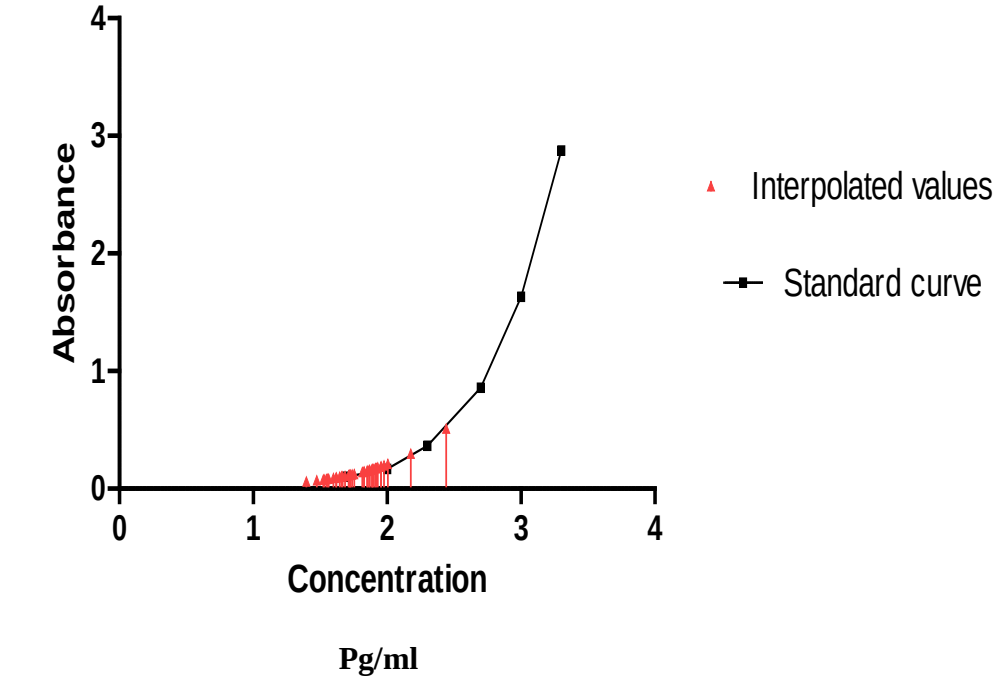


Figure 45: Interpolated values of S100B interventional group



S100B values pre and post intervention were not normally distributed and thus non parametric statistics were used to analyse the data. There was a highly significant difference in the change in S100B concentration pre and post surgery between the two groups. The intervention group showed a small increase of 37.3 (picograms) pg/ml while the control group showed a large increase of 139.3 pg/ml. Therefore, the control group showed a significantly higher increase in S100B concentration over time than the intervention group.

Table 13: Median values of S100B pre and post surgery in both groups

		s100pre			s100post		
		Percentile 25	Median	Percentile 75	Percentile 25	Median	Percentile 75
group	Intervention	35.6	43.0	52.0	71.4	77.7	87.6
	Control	29.1	36.7	42.6	160.8	176.8	199.5

Table 14: Change in S100B values

		Change in S100B		
		Percentile 25	Median	Percentile 75
group	Intervention	33.1	37.3	42.7
	Control	123.8	139.3	159.0

Test Statistics(b)

	Change in S100
Mann-Whitney U	20.000
Wilcoxon W	230.000
Z	-4.869
Asymp. Sig. (2-tailed)	<0.001
Exact Sig. [2*(1-tailed Sig.)]	<0.001(a)

a -Not corrected for ties.
b -Grouping Variable: group

4.4 Analysis of the interventions used

In total 4 different interventions were applied 95 times at 6 different time points in the 20 intervention group patients. The table below shows that intervention 5 was used most often and was applied at time 2 most frequently, followed by time 5.

Table 15: Interventions as per protocol

		Intervention				Total
		4	5	6	7	
time period	1	0	3	0	0	3
	2	4	17	11	1	33
	3	1	0	4	1	6
	4	3	9	11	5	28
	5	2	16	2	3	23
	6	1	0	0	1	2
Total		11	45	28	11	95

All 20 participants received at least 2 interventions, with one participant receiving 8 interventions. The median number of interventions was 5.

4.4.1 Effect of the interventions within the intervention group

There was a highly statistically significant treatment effect of each intervention (4 to 7) compared with no intervention (0) for pump flow rate (LMP). For each intervention the coefficient is positive which means that the value of pump flow rate increased by that amount on average from no intervention (0) to that intervention. The highest effect was found for intervention 5 where the value of LMP increased on average by 2.1 units (Table 16).

Table 16: Generalized estimating equations (GEE) model for pump flow rate (LMP)

Parameter	B	Std. Error	95% Wald Confidence Interval		Hypothesis Test		
			Lower	Upper	Wald chi square	df	P value
(Intercept)	2.001	.0512	1.900	2.101	1528.371	1	.000
[Interv=7]	1.535	.1673	1.207	1.863	84.201	1	.000
[Interv=6]	2.070	.0642	1.945	2.196	1040.792	1	.000
[Interv=5]	2.121	.0682	1.988	2.255	966.390	1	.000
[Interv=4]	1.760	.1876	1.392	2.128	87.965	1	.000
[Interv=0]	0(a)	.	.	.	.	.	.
timeperiod	.440	.0106	.419	.461	1718.575	1	.000
(Scale)	1						

Dependent Variable: LMP
Model: (Intercept), Interv, time period
a -Set to zero because this parameter is redundant.

All interventions except for intervention 7 were significantly effective in increasing the right cerebral oxygen saturation values (rSO_2 R) as reflected in Table 17.

Table 17: GEE model for rSO_2 (Right)

Parameter	B	Std. Error	95% Wald Confidence Interval		Hypothesis Test		
			Lower	Upper	Wald chi square	df	P value
(Intercept)	65.695	2.4637	60.866	70.523	711.025	1	.000
[Interv=7]	1.633	1.1758	-.671	3.938	1.930	1	.165
[Interv=6]	2.773	.3479	2.091	3.455	63.537	1	.000
[Interv=5]	1.918	.2467	1.434	2.401	60.422	1	.000
[Interv=4]	1.696	.3781	.955	2.437	20.124	1	.000
[Interv=0]	0(a)	.	.	.	.	.	.
timeperiod	-1.040	.4201	-1.863	-.217	6.130	1	.013
(Scale)	269.484						

Dependent Variable: rSO_2 right
Model: (Intercept), Interv, time period
a -Set to zero because this parameter is redundant.

All interventions except for intervention 7 were significantly effective in increasing the left cerebral oxygen saturation values ($rSO_{2\ L}$) (Table 18).

Table 18: GEE model for rSO2 (Left)

Parameter	B	Std. Error	95% Wald Confidence Interval		Hypothesis Test		
			Lower	Upper	Wald chi square	df	P value
(Intercept)	65.020	2.3311	60.451	69.589	777.976	1	.000
[Interv=7]	1.481	1.0763	-.629	3.590	1.893	1	.169
[Interv=6]	3.125	.4167	2.309	3.942	56.265	1	.000
[Interv=5]	1.698	.2824	1.144	2.251	36.144	1	.000
[Interv=4]	1.871	.6794	.539	3.202	7.583	1	.006
[Interv=0]	0(a)	.	.	.	.	.	.
timeperiod	-1.296	.3466	-1.976	-.617	13.980	1	.000
(Scale)	262.831						

Dependent Variable: rSO_2 left
Model: (Intercept), Interv, time period
a -Set to zero because this parameter is redundant.

All interventions except for intervention 4 were significantly effective in increasing the pCO_2 values (Table 19).

Table 19: GEE model for PCO_2

Parameter	B	Std. Error	95% Wald Confidence Interval		Hypothesis Test		
			Lower	Upper	Wald chi square	df	P value
(Intercept)	36.212	.5627	35.109	37.315	4140.882	1	.000
[Interv=7]	1.718	.6047	.532	2.903	8.067	1	.005
[Interv=6]	2.118	.3407	1.451	2.786	38.661	1	.000
[Interv=5]	-2.598	.5167	-3.611	-1.585	25.277	1	.000
[Interv=4]	1.126	.6553	-.158	2.411	2.955	1	.086
[Interv=0]	0(a)	.	.	.	.	.	.
timeperiod	.350	.1026	.149	.551	11.628	1	.001
(Scale)	1						

Dependent Variable: pCO_2
Model: (Intercept), Interv, time period
a -Set to zero because this parameter is redundant.

All interventions were significantly effective at lower nasopharyngeal temperature (Table 20).

Table 20: GEE model for Temperature (T1)

Parameter	B	Std. Error	95% Wald Confidence Interval		Hypothesis Test		
			Lower	Upper	Wald chi square	df	P value
(Intercept)	33.598	.2641	33.080	34.115	16184.773	1	.000
[Interv=7]	-2.593	.4918	-3.557	-1.629	27.800	1	.000
[Interv=6]	-2.688	.2372	-3.153	-2.224	128.507	1	.000
[Interv=5]	-1.430	.2516	-1.923	-.937	32.294	1	.000
[Interv=4]	-2.423	.4586	-3.322	-1.524	27.921	1	.000
[Interv=0]	0(a)	.	.	.	.	.	.
timeperiod	-.069	.0505	-.168	.030	1.866	1	.172
(Scale)	6.171						

Dependent Variable: T1
Model: (Intercept), Interv, time period
a-Set to zero because this parameter is redundant.

Interventions 4-7 were significantly effective at lower bladder temperature (Table 21).

Table 21: GEE model for Temperature (T2)

Parameter	B	Std. Error	95% Wald Confidence Interval		Hypothesis Test		
			Lower	Upper	Wald chi square	df	P value
(Intercept)	34.500	.2622	33.986	35.014	17307.957	1	.000
[Interv=7]	-2.623	.4352	-3.475	-1.770	36.318	1	.000
[Interv=6]	-2.452	.2294	-2.902	-2.003	114.344	1	.000
[Interv=5]	-1.235	.2268	-1.679	-.790	29.653	1	.000
[Interv=4]	-2.641	.3345	-3.297	-1.985	62.337	1	.000
[Interv=0]	0(a)	.	.	.	.	.	.
timeperiod	-.290	.0495	-.387	-.193	34.315	1	.000
(Scale)	5.024						

Dependent Variable: T2
Model: (Intercept), Interv, time period
a -Set to zero because this parameter is redundant.

All interventions were also significantly effective at lower haematocrit (Hct) as can be seen in Table 22.

Table 22: GEE model for Hct

Parameter	B	Std. Error	95% Wald Confidence Interval		Hypothesis Test		
			Lower	Upper	Wald chi square	df	P value
(Intercept)	30.845	.8113	29.255	32.435	1445.673	1	.000
[Interv=7]	-1.485	.4237	-2.315	-.655	12.286	1	.000
[Interv=6]	-4.413	.3957	-5.188	-3.637	124.376	1	.000
[Interv=5]	-3.471	.3159	-4.090	-2.852	120.762	1	.000
[Interv=4]	-4.746	.5960	-5.914	-3.578	63.407	1	.000
[Interv=0]	0(a)	.	.	.	.	.	.
timeperiod	-1.011	.1443	-1.294	-.729	49.116	1	.000
(Scale)	20.764						

Dependent Variable: Hct
Model: (Intercept), Interv, timeperiod
a -Set to zero because this parameter is redundant.

4.5 Factors affecting cerebral oxygen saturation and correlation analysis between cerebral and central venous oxygen saturations

A backwards elimination technique was used to determine which of the covariates were significantly predictive of rSO_2. Initially all covariates were entered into the model and then they were eliminated one by one until a final model with only significant covariates was obtained. Central venous oxygen saturation was forced to remain in the model regardless of statistical significance.

The factors which significantly predicted rSO_2 right whilst controlling for time and central venous oxygen saturation, were partial pressure of carbon dioxide (pCO_2), temperature, pump flow rate (LMP), mean arterial pressure (MAP), haemoglobin (Hb), percentage isoflurane, heart rate (HR) and patient oxygen saturation (SpO_2). Central venous oxygen saturation was not significantly related to rSO_2 right (Table 23).

Table 23: Factors affecting cerebral oxygen saturation (Right)

Parameter	B	Std. Error	95% Wald Confidence Interval		Hypothesis Test		
			Lower	Upper	Wald chi square	df	P value
(Intercept)	-354.207	132.8652	-614.618	-93.796	7.107	1	.008
Timeperiod	.718	.2204	.286	1.150	10.612	1	.001
Vensats	.093	.0794	-.063	.248	1.359	1	.244
PCO2	.418	.0683	.284	.552	37.400	1	.000
Temp	1.694	.1646	1.371	2.016	105.934	1	.000
LMP	.779	.2453	.298	1.259	10.078	1	.002
ARTP	.053	.0225	.009	.097	5.563	1	.018
Hb	1.312	.2867	.750	1.874	20.949	1	.000
Iso	-.602	.2155	-1.024	-.179	7.796	1	.005
HR	-.024	.0100	-.044	-.005	5.847	1	.016
Sp02	2.250	1.1385	.018	4.481	3.905	1	.048
(Scale)	49.307						

Dependent Variable: rSO_2 Right
Model: (Intercept), time period, Ven sats, PCO_2, Temp, Pump flow rate, MAP, Hb, Iso, HR, $Sp0_2$

The factors which significantly predicted left cerebral oxygen saturation whilst controlling for time and central venous oxygen saturation were, partial pressure of carbon dioxide (pCO_2), mean arterial pressure (MAP), haematocrit (Hct), temperature. Central venous oxygen saturation was not significantly associated with rSO_2 left (Table 24).

Table 24: Factors affecting cerebral oxygen saturation (Left) rSO_2

Parameter	B	Std. Error	95% Wald Confidence Interval		Hypothesis Test		
			Lower	Upper	Wald chi square	df	P value
(Intercept)	-38.347	11.7695	-61.415	-15.280	10.616	1	.001
timeperiod	.696	.2212	.263	1.130	9.904	1	.002
Vensats	.044	.0876	-.127	.216	.256	1	.613
PCO2	.565	.0750	.418	.712	56.622	1	.000
ARTP	.106	.0121	.082	.129	76.669	1	.000
Hct	.270	.0775	.118	.422	12.131	1	.000
Temp	1.213	.1477	.924	1.503	67.497	1	.000
(Scale)	50.204						

Dependent Variable: rSO_2 left
Model: (Intercept), timeperiod, Vensats, PCO_2, ARTP, Hct, T2, $FI0_2$, PO_2

4.6 The intervention effect (Intervention vs control)

There was a highly significant difference between the intervention and control groups in terms of cerebral desaturation time (p<0.001). The mean for the control group was higher than for that of the intervention group (Table 25).

Table 25: Cerebral desaturation time (minutes)

	group	N	Mean	Std. Deviation	Std. Error Mean	P value
Desaturation time	Intervention	20	24.70	11.819	2.643	<0.001
	control	20	63.85	23.424	5.238	

Repeated measures ANOVA testing was performed in order to compare the effect over time between the intervention and control groups.

There was a statistically significant intervention effect for cerebral oxygen saturation (p=0.024) (Table 26). The values in the intervention group were increased compared with those in the control group (Figure 46 and 47).

Table 26: Intervention effect for cerebral oxygen saturation

Effect	**Statistic**	**P value**
Time	Wilk's Lambda = 0.042	<0.001
Time*group	Wilk's Lambda =0.593	0.024
Group	F=3.154	0.084

Figure 46: Profile plot of rSO_2 right by time and intervention group

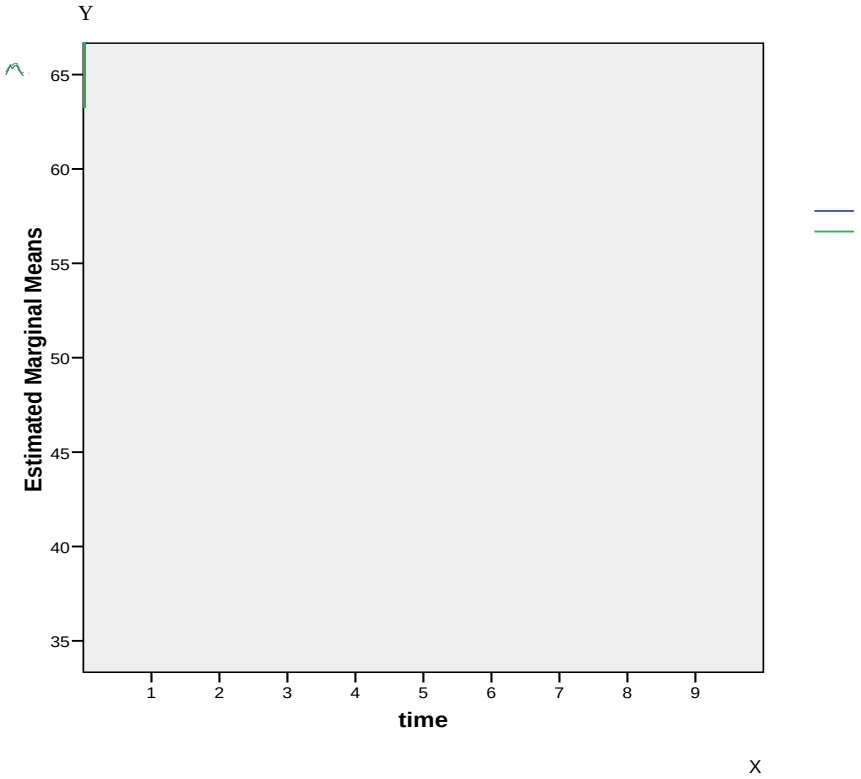
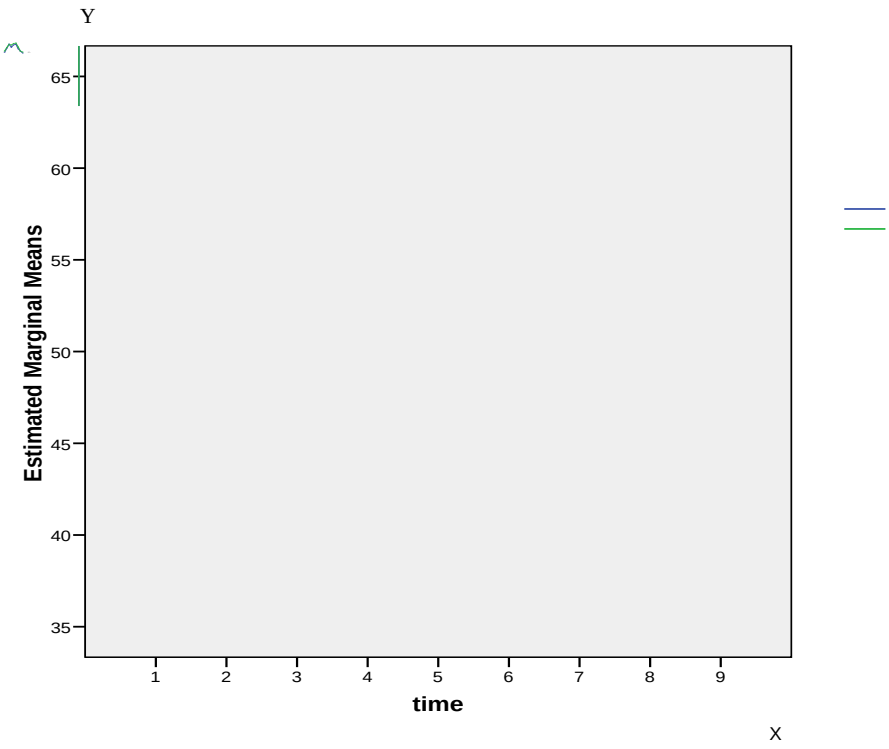


Figure 47: Profile plot of rSO_2 left by time and intervention group



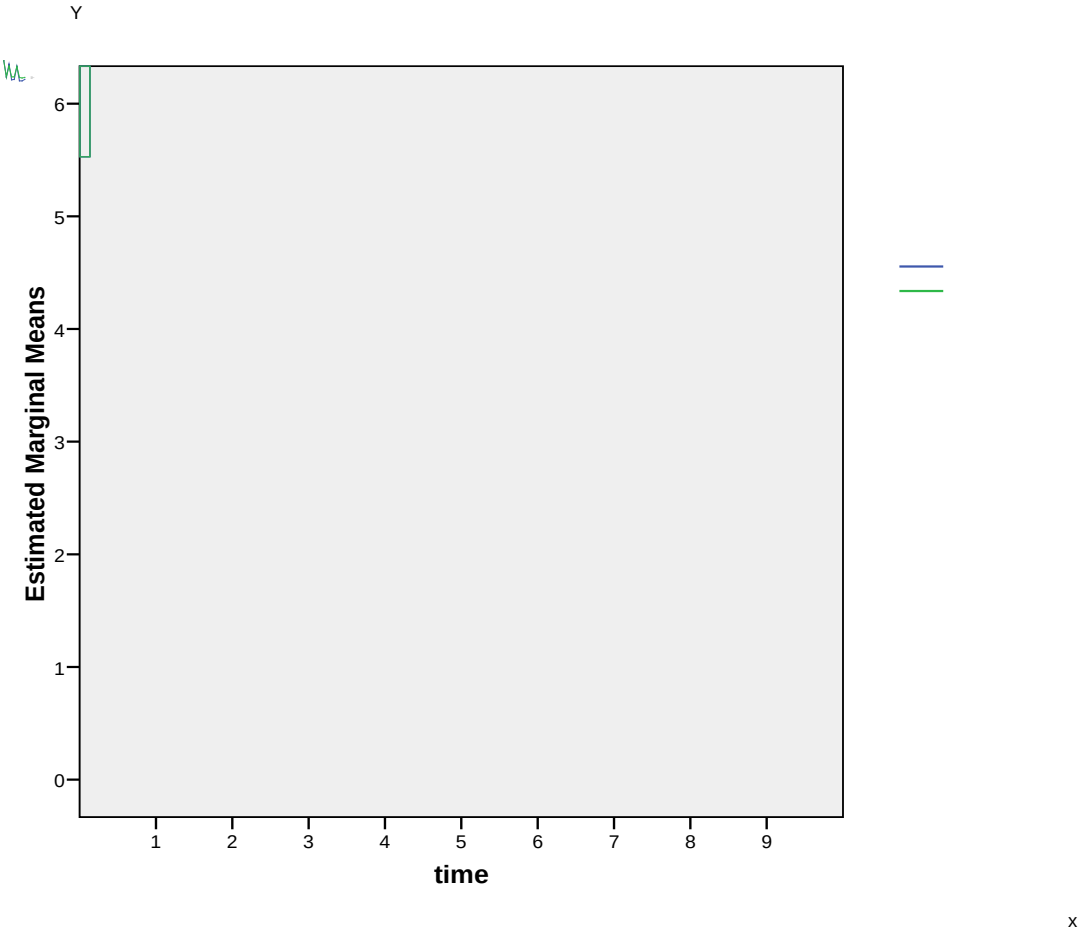
4.6.1 Pump flow rate

As indicated in Table 27, there was a statistically significant intervention effect for pump flow rate (p<0.001). Figure 48 shows the increase in pump flow rate in the interventional group as compared to the control group.

Table 27: Intervention effect for pump flow rate

Effect	Statistic	P value
Time	Wilk's Lambda =0.004	<0.001
Time*group	Wilk's Lambda =0.223	<0.001
Group	F=15.887	<0.001

Figure 48: Profile plot of Pump flow rate (LMP) by time and intervention group



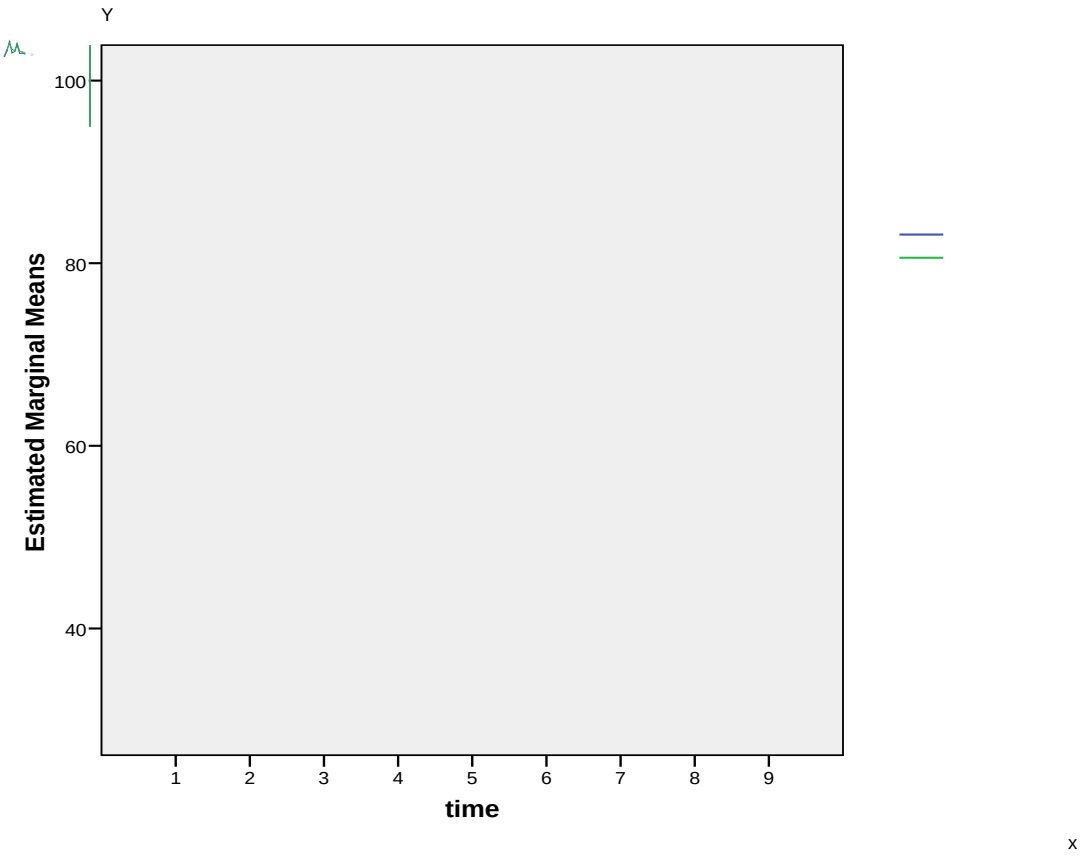
4.6.2 Mean arterial pressure

Table 28 shows that there was a statistically significant intervention effect for increasing mean arterial pressure (p=0.011). Figure 49 shows increased mean arterial pressure in the interventional group as compared to the control group.

Table 28: Intervention effect for mean arterial pressure

Effect	Statistic	P value
Time	Wilk's Lambda = 0.088	<0.001
Time*group	Wilk's Lambda =0.557	0.011
Group	F=6.890	0.012

Figure 49: Profile plot of Mean arterial pressure by time and intervention group



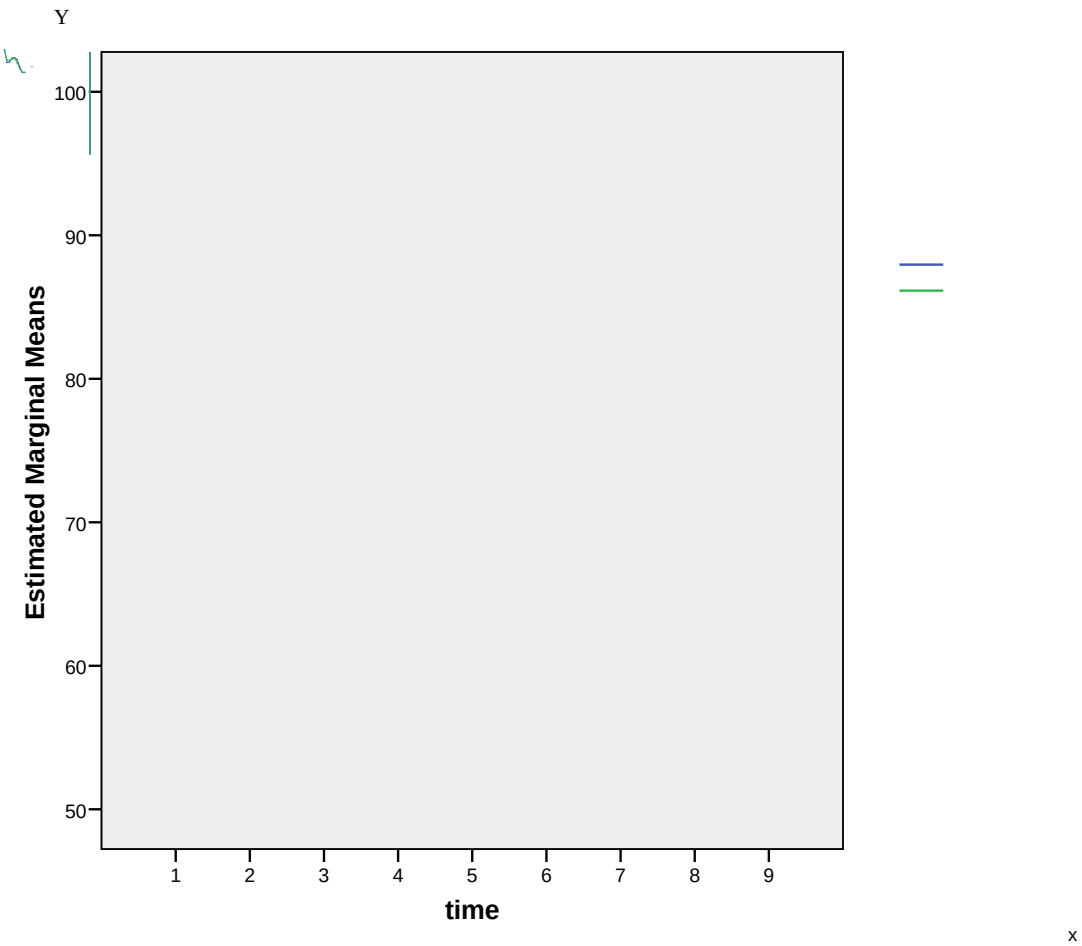
4.6.3 FiO_2 (fraction inspired oxygen)

There was a statistically significant intervention effect for FiO_2 (Table 29). However, the profile plot shows that the two groups started and ended at the same point (Figure 50).

Table 29: Intervention effect for FiO_2

Effect	Statistic	P value
Time	Wilk's Lambda =0.006	<0.001
Time*group	Wilk's Lambda = 0.483	0.002
Group	F=0.985	0.327

Figure 50: Profile plot of FiO_2 by time and intervention group



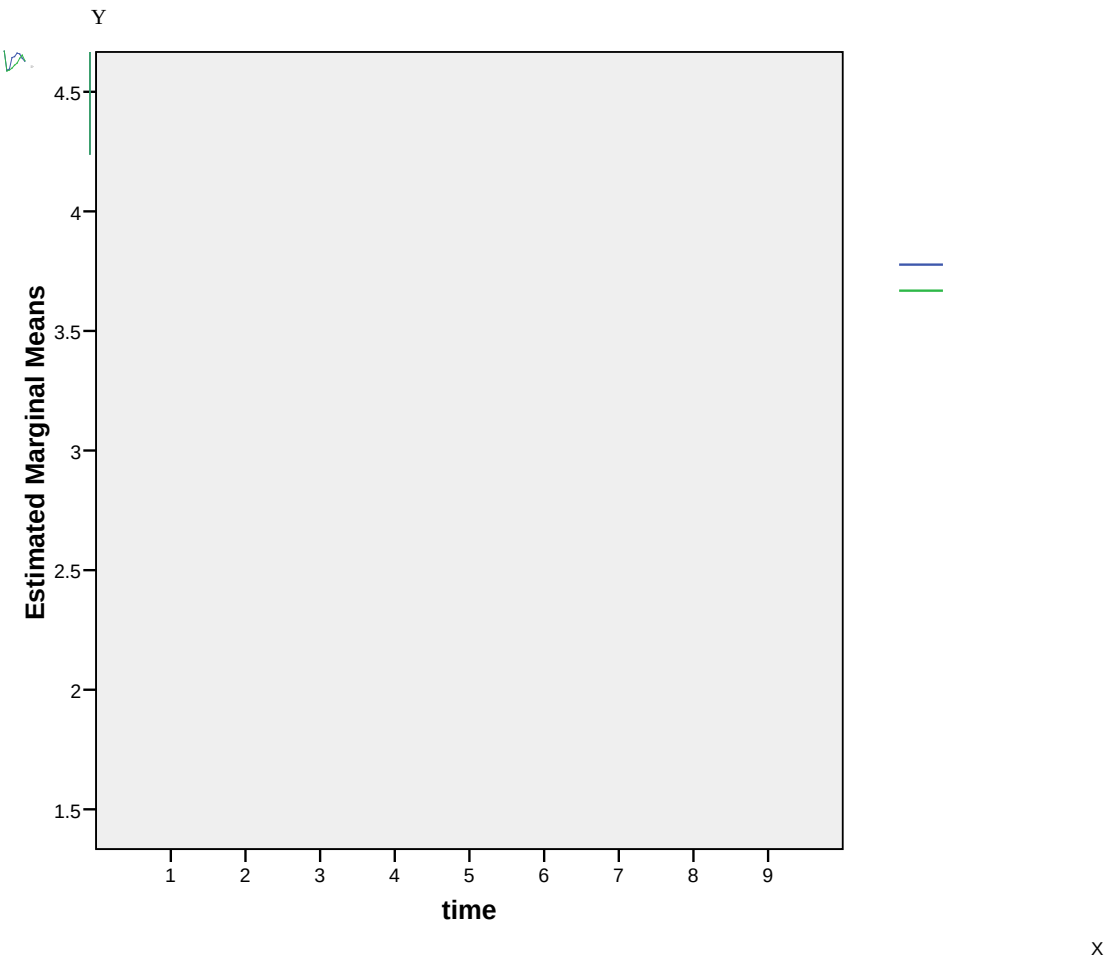
4.6.4 Fresh gas flow on pump (GAS LPM)

There was a highly significant intervention effect for fresh gas flow (p<0.001) (Table 30). Figure 51 shows the change in fresh gas flow between the control and interventional groups.

Table 30: Intervention effect for fresh gas flow

Effect	Statistic	P value
Time	Wilk's Lambda =0.090	<0.001
Time*group	Wilk's Lambda =0.248	<0.001
Group	F=15.512	<0.001

Figure 51: Profile plot of Fresh Gas Flow by time and intervention group



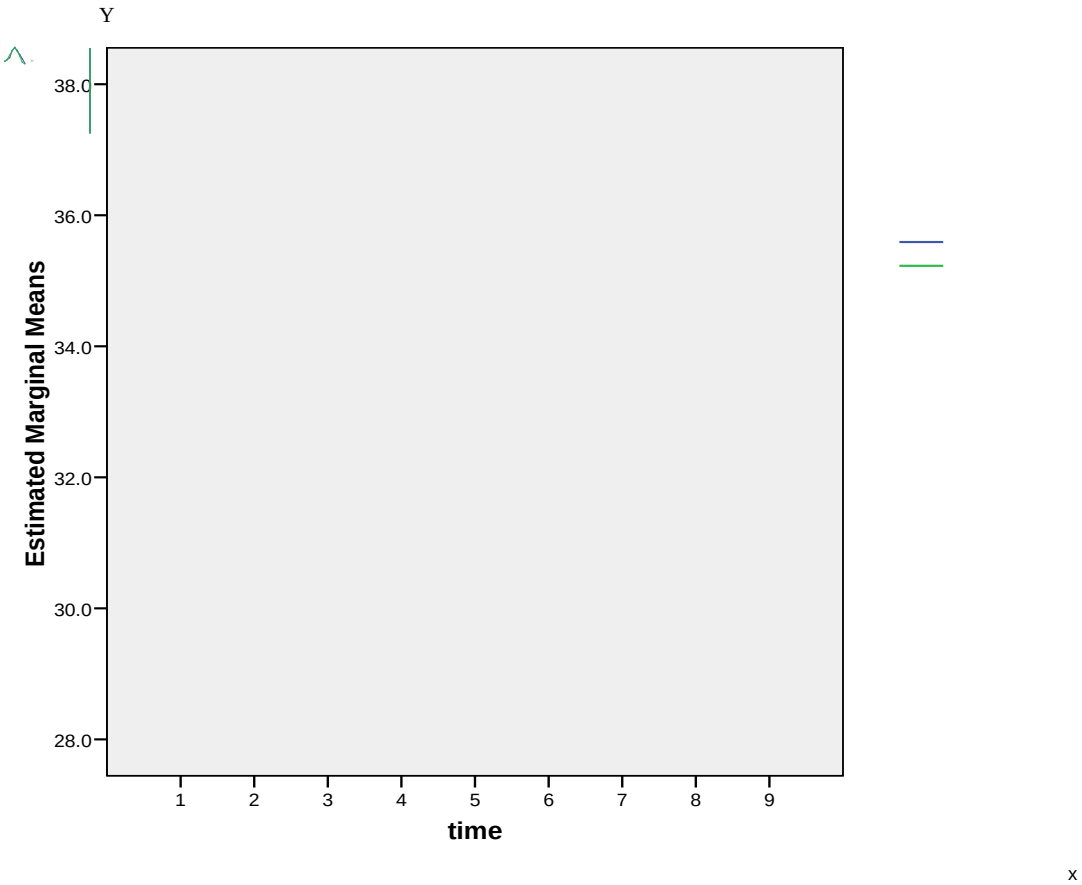
4.6.5 Temperature (T1) Nasopharyngeal

There was a highly significant intervention effect for nasopharyngeal temperature (p<0.001) (Table 31). However, both groups started and ended off at similar values (Figure 52).

Table 31: Intervention effect for temperature (T1)

Effect	Statistic	P value
Time	Wilk's Lambda =0.016	<0.001
Time*group	Wilk's Lambda = 0.399	<0.001
Group	F= 0.780	0.383

Figure 52: Profile plot of Temperature (T1) by time and intervention group



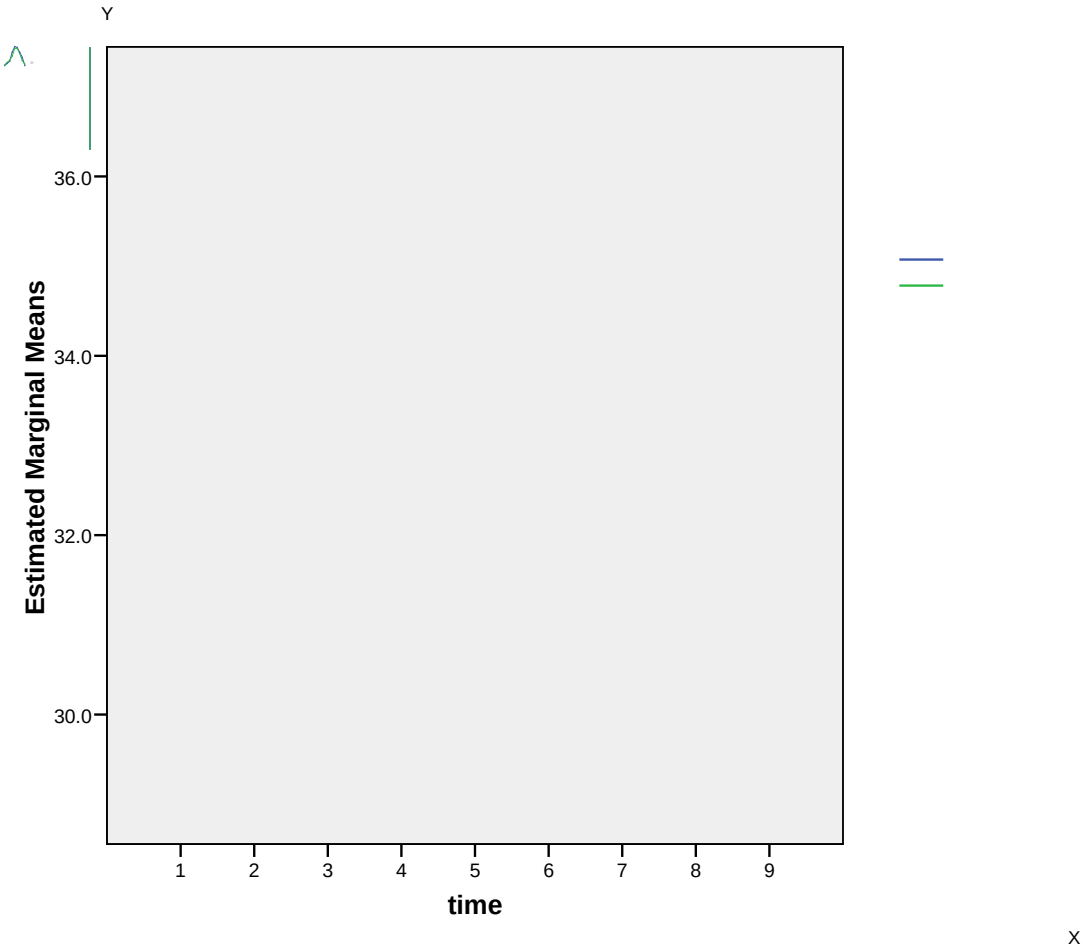
4.6.6 Temperature (T2) Bladder

There was a highly significant intervention effect for bladder temperature (p<0.001) (Table 32). However, both groups started and ended off at similar values (Figure 53).

Table 32: Intervention effect for temperature (T2)

Effect	Statistic	P value
Time	Wilk's Lambda =0.022	<0.001
Time*group	Wilk's Lambda =0.376	<0.001
Group	F=2.682	0.110

Figure 53: Profile plot of Temperature (T2) by time and intervention group



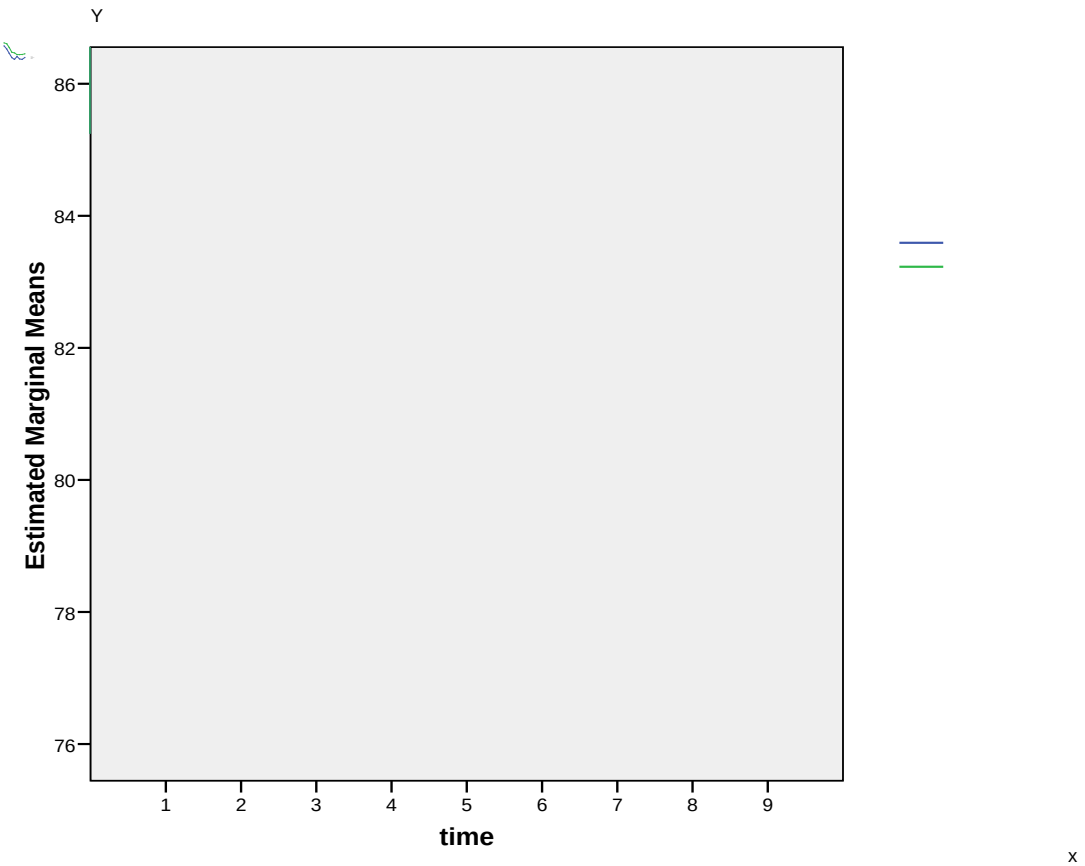
4.6.7 Central venous oxygen saturation

There was no effect of the intervention on central venous oxygen saturation when compared with the control group (p=0.845) (Table 33). The profile plot shows that the two group profiles were almost parallel over time (Figure 54).

Table 33: Intervention effect for central venous oxygen saturation

Effect	Statistic	P value
Time	Wilk's Lambda =0.444	0.001
Time*group	Wilk's Lambda = 0.885	0.845
Group	F= 2.454	0.126

Figure 54: Profile plot of Central venous oxygen saturation by time and intervention group



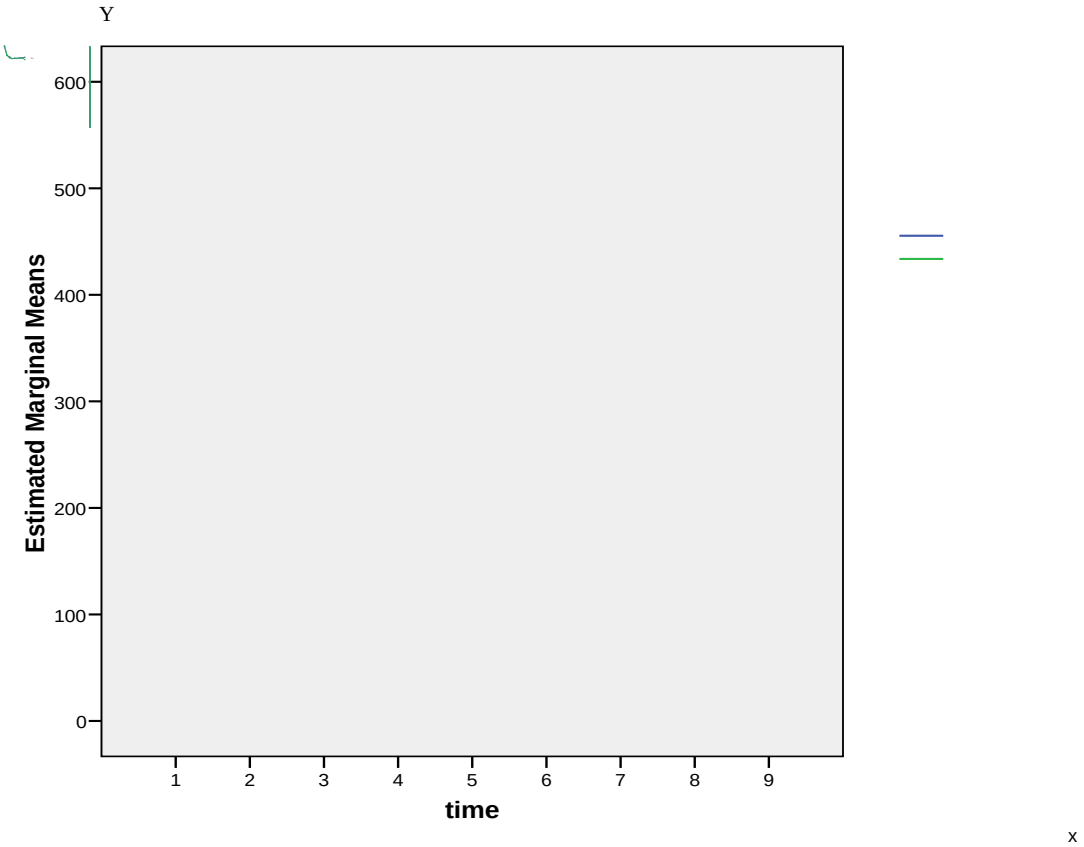
4.6.8 Partial pressure of oxygen (pO_2)

There was no effect of the intervention on partial pressure of oxygen when compared with the control group (p=0.062) (Table 34). The profile plot shows that the two group profiles were almost parallel over time except at the last time point (Figure 55).

Table 34: Intervention effect for partial pressure of oxygen

Effect	**Statistic**	**P value**
Time	Wilk's Lambda =0.013	<0.001
Time*group	Wilk's Lambda = 0.644	0.062
Group	F= 0.537	0.468

Figure 55: Profile plot of pO_2 by time and intervention group



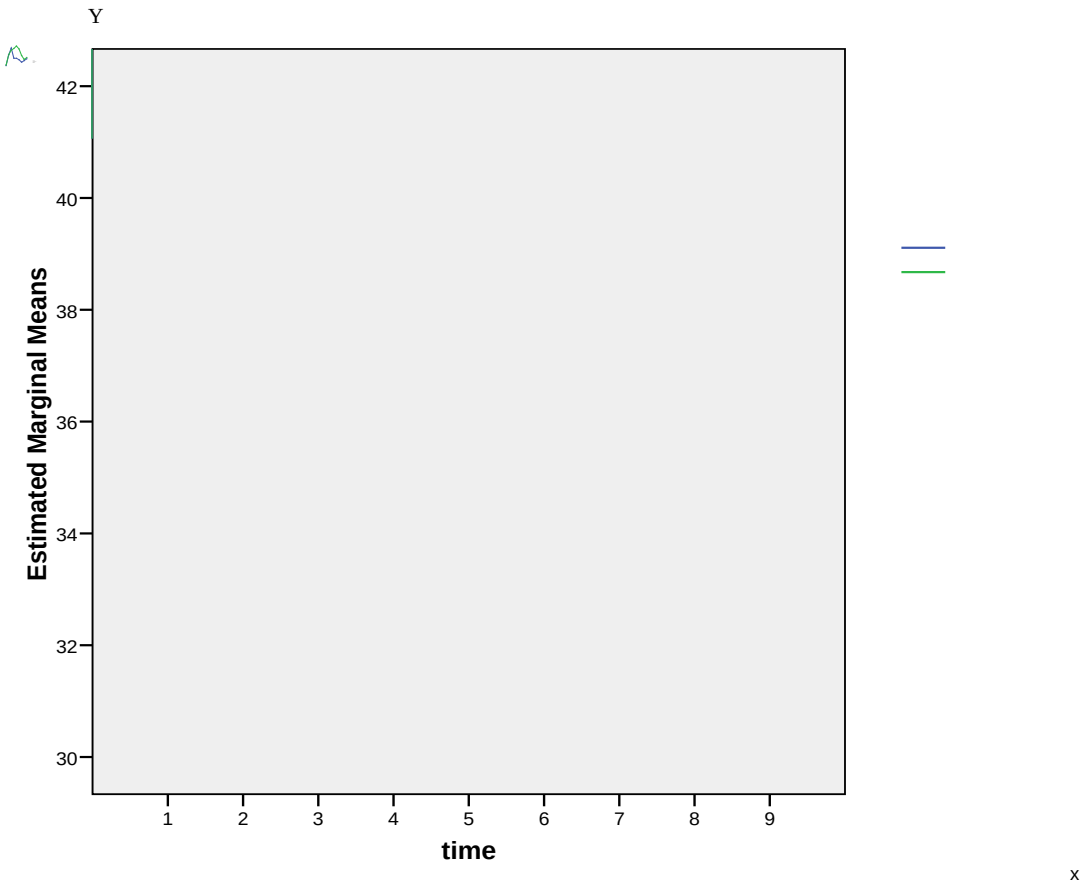
4.6.9 Partial pressure of carbon dioxide (pCO_2)

There was a highly significant intervention effect for partial pressure of carbon dioxide (p<0.001) (Table 35). The profile plot shows that the values in the intervention group increased relative to the control group after the third time point (Figure 56).

Table 35: Intervention effect for partial pressure of carbon dioxide

Effect	Statistic	P value
Time	Wilk's Lambda =0.123	<0.001
Time*group	Wilk's Lambda = 0.396	<0.001
Group	F= 34.9	<0.001

Figure 56: Profile plot of pCO_2 by time and intervention group



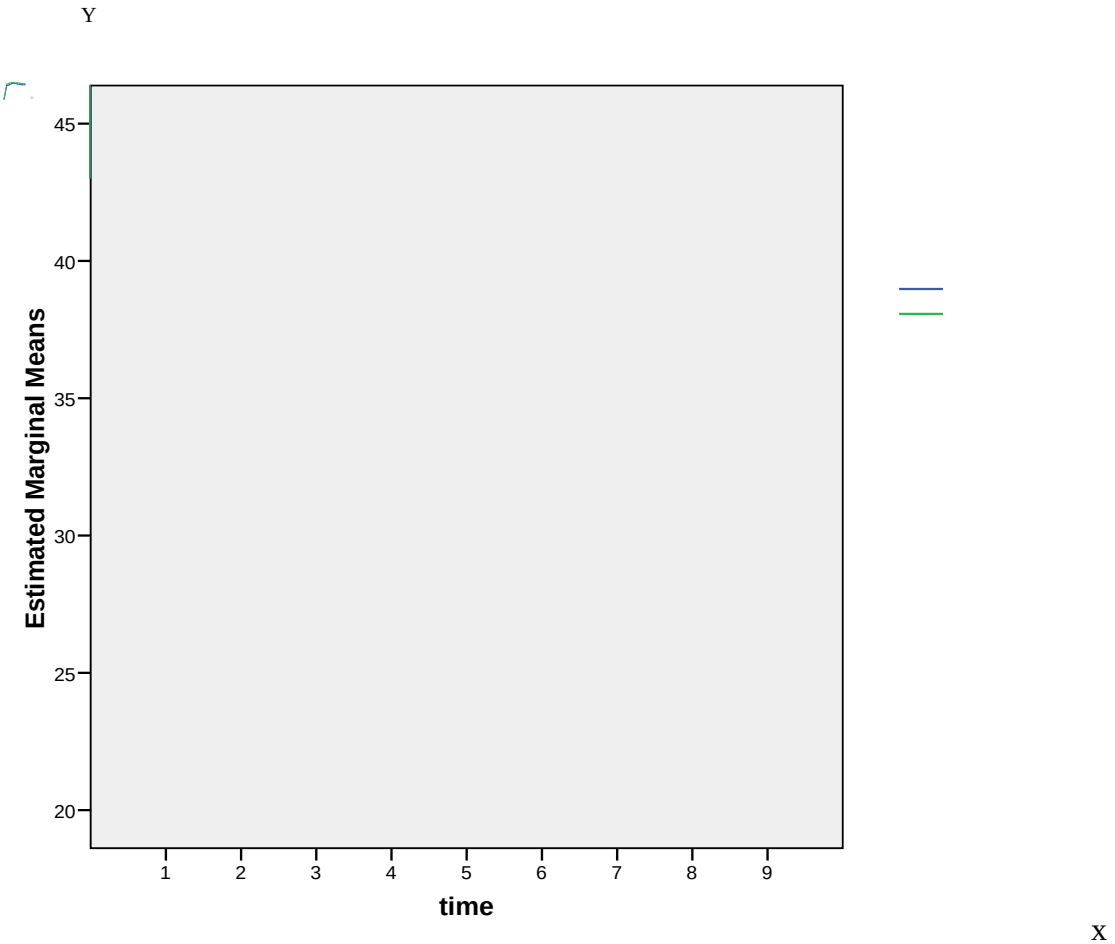
4.6.10 Haematocrit (Hct)

There was no evidence of an intervention effect for Hct (p=0.897) (Table 36). The profile shows that the values were similar for both groups (Figure 57).

Table 36: Intervention effect for haematocrit

Effect	Statistic	P value
Time	Wilk's Lambda =0.032	<0.001
Time*group	Wilk's Lambda = 0.901	0.897
Group	F= 4.287	0.045

Figure 57: Profile plot of Hct by time and intervention group



CHAPTER FIVE: DISCUSSION

Neurological injury after cardiac surgery is a serious and costly healthcare problem. The application of neurological monitoring during cardiac surgery may enhance the detection of hypoxic conditions associated with neurological injury. This may provide clinicians with vital information to assist in reducing secondary insults to the brain from cardiac surgery (Harilall, Adam, Biccard and Reddi, 2011). However, the evaluation of new monitoring devices requires the determination of its reliability, accuracy and clinical utility whereby patient outcomes can be improved by analysis of data provided by the monitor (Kim, Ward, Cartwright, Kalano, Chlebowski and Henson, 2000). The Invos cerebral oximeter is a new monitor which provides an estimation of regional oxygenation in the cerebral microvasculature. Early studies in cardiac surgery demonstrated a significant correlation between low cerebral oximetry readings and poorer outcomes (Edmonds, Sehic, Pollock and Ganzel, 1998; Yao, Tseng, Boyd, Shukla and Hartman, 1999). The common limitation in studies assessing the impact of cerebral oxygen monitoring is the absence of a defined protocol based on physiologically derived interventions to actively treat cerebral desaturation (Murkin et al, 2009).

In this cohort of patients undergoing coronary artery bypass grafting with the use of cardiopulmonary bypass, the prospective investigation was to determine if cerebral tissue oxygen saturation could be optimized using an interventional protocol. The secondary aim was to compare the levels of serum S100B protein concentration which is a marker of neurological injury during cardiac surgery between a control group with no intervention and the interventional group with active treatment.

The common interventions applied to increase cerebral oxygen saturation from lower levels would result in the formulation of an algorithm which could be implemented during cardiopulmonary bypass to increase cerebral oxygen saturation and reduce adverse neurological injury after coronary artery bypass graft surgery. This is the first study analysing the effect of optimizing cerebral oxygen saturation on markers of neurological injury in patients under going on-pump coronary artery bypass graft surgery.

The results of the study show that there was a highly significant difference in the change in S100B concentrations pre and post surgery between the intervention and control groups. The intervention group showed a smaller increase in S100B concentration of 37.3 picograms per millilitre (pg/ml) while the control group showed a larger increase of 139.3 pg/ml. Therefore the control group showed a significantly higher increase in S100B concentration over time than the intervention group ($P < 0.001$). The median concentration of S100B for the interventional and control groups prior to surgery were 43 pg/ml and 36.7 pg/ml respectively which increased to 77.7 pg/ml in the interventional group and 176.8 pg/ml in the control group post coronary artery bypass graft surgery. These findings demonstrate the advantageous effect of optimizing cerebral oxygen saturation using an interventional protocol on markers of neurological injury.

The clinical values of S100B have been demonstrated in stroke, cerebral complications associated with cardiac arrest and in patients with severe as well as minor head injury (Jonsson, Per Johnsson, Backstrom, Alling, Dautovic-Bergh and Blomquist, 2004). High concentrations of S100B have been demonstrated in brain

injury, ischaemia and hypoxia (Fazio, Bhudia, Marchi, Aumayr and Janigro, 2004). A prospective study to evaluate S100B as an early marker of brain injury in patients undergoing off-pump CABG (n=30) and on-pump CABG (n=60) showed that S100B concentrations peaked in the on-pump group (Wang et al, 2005).

Studies conducted to determine whether increased levels of S100B after surgery correlated with the length of hospital stay in patients undergoing coronary artery bypass graft surgery showed that the median S100B concentration was 0.075 mg/L preoperatively and 0.840 mg/L immediately after the operation. The investigators found a positive correlation between length of hospital stay and S100B levels (Krnjak et al, 2008). A study of 767 patients who survived more than 30 days post cardiac surgery revealed that the probability of death was higher for patients with S100B levels greater than 0.3 ug/L (Johnsson et al, 2003).

The use of S100B as marker of neurological injury in the clinical setting is limited by high cost and time requirements for the performance of the enzyme-linked immunosorbent assay (ELISA). The level of S100B at which stroke or cerebral complication can be diagnosed is unknown and its pattern of release give no information about the anatomical distribution of brain injury and functional impact. However, it can be used as a marker and early indicator of brain injury during and after cardiopulmonary bypass (Einav et al, 2008).

The results of the present study show that four different interventions were applied 95 times at 6 different time points in the intervention group (Table 15). All 20 participants in the interventional group received at least 2 interventions, with one

participant receiving 8 interventions. The median number of interventions was 5. Cerebral desaturation occurred predominantly during aortic cross clamping, distal anastomosis of coronary arteries and aortic cross clamp release.

The common interventions identified in increasing cerebral oxygen saturations from lower levels were: (Intervention-4) increasing mean arterial pressure, (Intervention 5) increasing pump flow rate, (Intervention 6) increasing partial pressure of carbon dioxide to approximately 40 mmHg and (Intervention 7) administration of red blood cells to increase haematocrit.

Increasing pump flow rates was the most common intervention used (45 times) followed by maintaining partial pressure of carbon dioxide to approximately 40 mmHg (28 times), increasing mean arterial pressure by administration of adrenalin (11 times) and administration of red blood cells to increase haematocrit (11 times). There was a highly statistically significant treatment effect within the intervention group for each intervention 4 to 7 (Tables 16 to 22) compared with no intervention. Interventions 4 to 6 significantly affected right and left cerebral oxygen saturations. However, administration of red blood cells was not found to significantly increase right (p=0.165) and left (p=0.169) cerebral oxygen saturation within the intervention group.

The findings of the study suggest that optimization of these factors during on-pump CABG would result in increased cerebral oxygen saturation levels and a reduction in neurological injury. Therefore, an algorithm incorporating these interventions can be formulated. Denault and colleagues (2007), proposed that an important requirement in

the monitoring of cerebral oxygen saturation is the elaboration of a clinical algorithm to correct decreases in cerebral saturation values. The authors suggested that factors affecting cerebral oxygen supply and demand should be optimized (Denault et al, 2007).

The present study highlighted a significant difference between the intervention and control groups in terms of cerebral desaturation time ($p<0.001$). The mean desaturation time for the control group was 63.85 minutes as compared to 24.7 minutes in the interventional group (Table 25). In a study conducted by Slater et al. (2009), patients undergoing CABG utilizing cerebral oximetry were randomized into an active monitoring and an intervention group to improve cerebral oxygen saturation. The investigators found a significant association between prolonged cerebral desaturation and cognitive decline and a three fold increase in hospital stay. However, there was no difference between cerebral desaturation rates between the intervention and control group resulting in the incidence of cognitive decline being similar. The authors ascribed this to poor compliance of the treatment protocol.

In order to establish which factors affected cerebral oxygen saturation, a backwards elimination technique was used to determine significant predictors of right and left cerebral oxygen saturation. Factors which significantly predicted right cerebral oxygen saturation whilst controlling for time and central venous oxygen saturation, were partial pressure of carbon dioxide (pCO_2) , temperature, pump flow rate (LMP), mean arterial pressure (MAP), haemoglobin (Hb), percentage isoflurane, heart rate (HR) and patient oxygen saturation (SpO_2) (Table 23). Factors which significantly predicted left cerebral oxygen saturation whilst controlling for time and central

venous oxygen saturation were, partial pressure of carbon dioxide (PCO_2), mean arterial pressure (MAP), haematocrit (Hct) and temperature (Table 24).

Central venous lines are inserted routinely during cardiac surgery. A secondary aim of the study was to determine if central venous oxygen saturation correlated with right and left cerebral oxygen saturations. Studies have shown that changes in $ScvO_2$ closely reflect circulatory disturbances during periods of hypoxia, haemorrhage and subsequent resuscitation (Rupert, Dawson, Fawcett, Rhodes, Grounds and Bennet, 2005). Recent evidence suggests that guiding therapy by using venous oxygen saturation measurement can improve outcome. One large trial in septic patients measuring central venous oxygen saturation as a therapeutic goal established a significantly decreased mortality in their patient group (Andrew, Azoulay, Antonelli, Brochard, Brun-Buisson, de Backer, Dobb, Fagon, Gerlach and Groenveld, 2006; Rivers, Nguyen, Havstad, Ressler, Muzzin, Knoblich, Peterson and Tomlanovich, 2001). Recently a study conducted by Harilall et al, (2010) found a positive correlation between central venous and cerebral tissue oxygen saturation during off-pump coronary artery bypass graft surgery.

In this study central venous oxygen saturation was not significantly related to right (p=0.244) or left (p=0.613) cerebral oxygen saturations. Therefore, central venous oxygen saturation cannot be used as a surrogate measure of cerebral tissue oxygen saturation during on-pump coronary artery bypass graft surgery. Specific monitoring of brain oxygen saturation during CABG should be advocated.

Repeated ANOVA tests were conducted to compare the intervention effect between the treatment groups over time. There was a statistically significant intervention effect for cerebral oxygen saturation (p=0.024). The results show that cerebral oxygen saturation values in the intervention group were increased when compared to the control group.

Results show that there was a statistically significant intervention effect for pump flow rates (p<0.001) profile plot (Figure 48) and mean arterial pressure (p=0.011) profile plot (Figure 49). In a study conducted by Schwartz and co workers (1995), the investigators measured cerebral blood flow during independent manipulations of arterial blood pressure and pump flow rate in order to determine whether they influence cerebral perfusion during cardiopulmonary bypass. Arterial pump flow rate and blood pressure was altered in varied sequence to four different conditions: (1) full flow (2.23 ± 0.06 L/min/m^2, mean ± standard deviation) at high pressure (61 ± 2 mm Hg), (2) full flow (2.23 ± 0.06 L/min/m^2) at low pressure (24 ± 3 mm Hg), (3) low flow (0.75 L/min/m^2) at high pressure (62 ± 2 mm Hg), and (4) low flow (0.75 L/min /m^2 at low pressure (23 ± 3 mm Hg). The investigators found that cerebral blood flow was greater at higher pressures during CPB, (Schwartz, et al 1995).

In a study conducted by Richard et al. (1997), the authors aimed to determine whether cerebral blood flow could be maintained (autoregulated) during transient falls in arterial blood pressure. Their intention was to identify patients with carotid stenosis who were at risk of stroke. Twenty-seven subjects with carotid stenosis >60% or carotid occlusion were studied. Degree of stenosis was determined using duplex ultrasound (Acuson XP) with a combination of B-mode and colour-flow Doppler

imaging. Middle cerebral artery velocity was recorded bilaterally simultaneously via the transtemporal window using 2 MHz transducers (DWL, Langerach). In conclusion they demonstrated that in a subgroup of patients with carotid artery stenosis, dynamic autoregulation was impaired, as determined by the ability of the cerebral circulation to maintain middle cerebral artery blood flow in response to a rapid reduction of arterial blood pressure.

Cerebral ischaemia can occur when cerebral oxygen is insufficient to meet the global or regional cerebral oxygen consumption. Cerebral circulation is normally regulated by several complex mechanisms, such as metabolic stimuli, chemical stimuli, perfusion pressure, and neural stimuli (Young and Ornstein, 1994). Autoregulation can become impaired by a number of causes including hypercapnia, hypoxaemia, trauma and high dose volatile anaesthetics. Abnormal autoregulation can range from minimal impairment to completely abolished. In patients with absent autoregulation, systemic hypertension may lead to cerebral haemorrhage and oedema whilst decreases in blood pressure may in turn result in ischaemia and infarction (Vavilala, Lorri, Lam and Arthur, 2002). In chronically hypertensive adults, the autoregulatory curve is shifted to the right and a MAP >160 mmHg may not cause any increase in CBF (Junger et al., 1997). Cerebral oximetry provides a simple method to identify the lower limit of autoregulation i.e., the point at which brain blood flow and tissue oxygenation become pressure dependent.

In the present study there was a highly significant intervention effect for partial pressure of carbon dioxide (p<0.001). The profile plot (Figure 56) shows that the values in the intervention group increased relative to the control group after the third

time point (Arrest). Cerebral circulation is exquisitely sensitive to changes in pCO_2 (Murkin, 2007). An increase in carbon dioxide concentration in the arterial blood perfusing the brain greatly increases cerebral blood flow. Vavilala et al. (2002) described cerebral circulation to be exquisitely sensitive to changes in partial pressure of carbon dioxide which makes it the most potent physiologic cerebral vasodilator. The rapid response of the cerebral vasculature to carbon dioxide is caused by the rapid diffusion of arterial CO_2 across the blood brain barrier (BBB) and into the perivascular fluid and cerebral vascular smooth muscle cell. Carbon dioxide causes a reduction in the perivascular pH, which leads to cerebral vasodilation and increased cerebral blood flow. The effects of hypocapnia and hypercapnia on brain circulation are well known to clinicians. Yao et al. (2000), observed that during hyperventilation the brain oximetry signals were reduced and during hypoventilation they increased. Kolb et al. (2004), measured flow velocity in the middle cerebral artery (MCA) and rSO_2. They observed that hypoxia was associated with a reduction in rSO_2, whereas during hypercapnia both rSO_2 and MCA velocity increased.

The intervention effect for fresh gas flow was also significant (p<0.001) in this study. However, both groups started and ended off at similar values. The results also showed a highly significant intervention effect for temperature (p<0.001). However, both groups started and ended off at the same values. At moderate hypothermia, autoregulation of cerebral blood flow is tightly coupled to cerebral metabolic rate of oxygen consumption. Clinical hypothermia after cardiac arrest has been shown to improve neurological outcome. However, Rees and colleagues (2001), found no differences in risk of stroke between the use of hypothermia and normothermia (OR 0.68, 95% CI, 0.43 to 1.05) (Rees, et al 2001). Nathan et al. (2001), in a study of 223

patients, found that rewarming to a nasopharyngeal temperature of 34ºC from hypothermic CPB temperature of 32ºC results in a lower frequency of neurocognitive dysfunction at 1 week and 3 months after CABG surgery. A distinct disadvantage of hypothermia is the rewarming of the patient at the end of the procedure. Placement of the arterial cannula in the ascending aorta results in the temperature of cerebral blood being close to that of the blood leaving the heat exchanger, thus it is easy to produce cerebral hyperthermia during rewarming (Houge et al, 2008).

Studies related to the effect of temperature on neurological injury during cardiopulmonary bypass have led to various observations and temperature regimens during bypass. Adequate use of hypothermia should be dictated by the patient's surgical requirement. Rewarming should be started early so as to avoid gradients of more than 2ºC between water bath and patient blood temperature especially in high risk patients (Elderly, diabetics, carotid artery disease and history of neurological injury) (Chauhan, 2009).

In this study was no intervention effect for partial pressure of oxygen (pO_2) compared with the control group (p=0.062). The profile plot (Figure 55) shows that the two group profiles were almost parallel over time except at the last time point. There was no effect of the intervention on central venous oxygen saturation when compared with the control group (p=0.845). The profile plot shows that the two group profiles were almost parallel over time.

There was no evidence of an intervention effect for Hct (p=0.897). Haematocrit was not a predictor of cerebral oxygen saturation in this study. However, studies have

linked low haematocrit levels during CPB with risk for mortality and stroke after cardiac surgery. In a study of 10,949 patients, Karkouti et al., (2005), confirmed that the risk for stroke increased 10% for each 1% decrease in haematocrit during cardiopulmonary bypass. There was a marked inflection point of higher stroke risk for haematocrit levels < 21%.

Baseline values for right and left cerebral saturation in this study fell within the normal range. Madsen et al. (2000), defined a normal rSO_2 range of 55% to 78% and observed a marked decrease in patients with chronic heart failure, reported as 20% to 58%. The observation is consistent with the findings of Konishi and Kikuchi (1995), who noted that cerebral saturation was closely correlated to cardiac index. The association between low rSO_2 and poor neurological outcome has been documented in cardiac surgery. Yao et al. (2000), examined preoperative rSO_2 in 156 cardiac surgery patients and found that patients with a baseline rSO_2 of less than 50% had an increased incidence of postoperative neurologic and cognitive deficit. The results suggest that abnormally low baseline values represent a diminished capacity for brain tissue to increase oxygen extraction in response to diminished oxygen delivery. Abnormally high rSO_2 values may also signify an underlying problem. Cerebral oxygen saturation values measured in an ischaemic region may be above normal due to the decreased oxygen consumption by injured or dead neurons. High or low rSO_2 should alert the operative team to the potential for cerebral injury during cardiac surgery.

The mean age of patients enrolled in this study was 55.3 ± 9.7 years (Table 5). The mean height and weight was 169.5 ± 7.8 and 73.67 ± 7.61 respectively. The study

consisted of 28 male and 12 female participants (Table 6). Seventy percent of the participants were male. Kishi et al. (2003), examined patient demographic influences on rSO_2. Cerebral tissue oxygen saturation appeared to be independent of weight, height, head size, or gender although it was negatively correlated with age and positively correlated with haemoglobin concentration. Misra et al. (1998), also found no association between rSO_2 and age, gender, skin colour, height and caffeine intake in 94 healthy adults. This suggests that the apparent influence of adult patient age on rSO_2 may actually reflect advancing cerebrovascular pathology in older patients.

The proportion of patients with and without diabetes did not differ significantly between the treatment groups (p=0.744) (Table 9). The number of grafts performed also did not differ significantly between the treatment groups (p=0.809) (Table 10). Body surface area, calculated pump flow rate, cardiopulmonary bypass time, cross clamp time and the quantity of adrenalin used were recorded as clinical data in the trial (Table 11). A comparison of the clinical data was performed between the interventional and control group. There was no statistically significant difference between the groups in terms of the clinical parameters except for adrenalin quantity where the control value was significantly higher than the intervention value (p=0.043). A possible explanation for lower adrenalin usage in the interventional group could be due to the maximization of pump flow rates which would increase mean arterial pressures and therefore decrease the need for adrenalin. The median number of pack cells administered per patient in the interventional group was 2 units and 1 unit in the control group. Therefore, the difference was not statistically significant (p=0.102).

The findings reveal that optimization of cerebral oxygen saturation during on-pump coronary artery bypass graft surgery positively affect markers of neurological injury (S100B). The use of any monitoring modality in the clinical setting is directly influenced by an effective treatment protocol. Formulation of a treatment protocol to prevent cerebral desaturation during coronary artery bypass graft surgery should be based on optimization of mean arterial pressure, pump flow rate and partial pressure of carbon dioxide. Monitoring cerebral oxygen saturation for the early detection of hypoxic conditions during cardiac surgery is a fundamental requirement.

CHAPTER SIX: CONCLUSION

The results of the study show that there was a highly significant difference in the change in S100B concentrations pre and post surgery between the interventional and control groups. The control group showed a significantly higher increase in S100B concentration over time than the intervention group. The findings highlight the positive effect of optimizing cerebral oxygen saturation using an interventional protocol during on-pump coronary artery bypass graft surgery. Recent studies have proposed that an important requirement in the monitoring of cerebral oxygen saturation is the elaboration of a clinical algorithm to correct decreases in cerebral saturation values (Denault et al, 2007).

The common interventions used in the study to increase cerebral oxygen saturation included, increasing mean arterial pressure, increasing and maximizing pump flow rates and increasing partial pressure of carbon dioxide to approximately 40 mmHg. The finding suggests that optimization of these factors during on-pump CABG would result in increased cerebral oxygen saturation levels and a reduction in neurological injury. Therefore, an algorithm incorporating these interventions can be formulated. Cerebral desaturation time was significantly reduced in the interventional group, further supporting the effect of the interventional protocol. A recent study conducted on patients randomized into an active monitoring or intervention group to improve cerebral oxygen saturation found no differences in cerebral desaturation rates between the groups. Therefore, the incidence of cognitive decline was similar. Investigators ascribed this to poor compliance of the treatment protocol (Slater et al, 2009).

Predictors of cerebral oxygen desaturation included, partial pressure of carbon dioxide (pCO_2), temperature, pump flow rate (LMP), mean arterial pressure (MAP), haematocrit, heart rate (HR) and patient oxygen saturation (SpO_2). Results of the study show that there was a significant intervention effect for pump flow rates, mean arterial pressure and partial pressure of carbon dioxide. Therefore, optimization of these factors increased cerebral oxygen saturation and positively affected S100B which is a known marker of neurological injury.

Coronary artery bypass graft surgery has unequivocally increased life expectancy in a broad spectrum of patients with ischaemic heart disease. Remarkable progress has also been made in the understanding of the control of cerebral circulation. This is in part due to multidisciplinary basic science research and clinical research (Selnes and McKhann, 2005). However, neurologic injury after CABG remains a significant problem that is increasing as coronary surgery is being performed on older patients with associated comorbidity. Central nervous system complications related to cardiac surgery remains a fertile area of research. The aetiology of neurologic injury is multifactorial, with hypoperfusion and cerebral embolism playing the largest roles. Neurological complications following cardiac surgery substantially increases patient mortality as well as the financial burden on health care resources, thus reducing the clinical effectiveness of the procedure (Ganushchak, Fransen, Visser, de jong and Maessen, 2004). Understanding the mechanisms of cerebral injury may result in the development of effective management strategies to further reduce the risk (Murkin, 2006). The role of biochemical markers for the evaluation of surgical techniques is much simpler when compared to the ‘gold standard’ of prospective neuropsychological or morphological investigation such as magnetic resonance

imaging or computed tomography. S100B protein can be used as a marker, as an early warning system and prognostic tool for the detection of neurological injury during coronary artery bypass graft surgery.

In this study central venous oxygen saturation did not correlate with cerebral oxygen saturations. Therefore, central venous oxygen saturation cannot be used as a surrogate measure of cerebral tissue oxygen saturation during on-pump coronary artery bypass graft surgery. Specific monitoring for brain oxygen saturation and an effective treatment protocol to deal with cerebral desaturation during CABG must be advocated.

LIMITATIONS

The use of any monitoring modality can result in false positives. It is therefore, important to verify that the electrodes are well positioned and that there is no leakage of light as a consequence of peeling of the adhesive patch. The frontal lobe is mainly supplied by the anterior cerebral artery, but some portions of the region exist in the watershed area between the anterior and middle cerebral artery. Therefore, hypoperfusion of the posterior cerebral territory could be missed. The NIRS device analysis algorithm assumes a fixed ratio of venous to arterial blood which may vary in certain pathologic states, e.g., cerebral oedema (Denault et al., 2007). The issue of extracranial contamination in cerebral monitoring still remains an issue of considerable debate. In particular, when cerebral monitoring is used for recognition of cerebral ischaemia during internal and external carotid artery clamping (Samra et al., 2000).

The use of S100B as marker of neurological injury in the clinical arena is limited by high financial costs and the time required for the performance of the enzyme-linked immunosorbent assay (ELISA). The level of S100B at which stroke or cerebral complication can be diagnosed is unknown and its pattern of release give no information about the anatomical distribution of brain injury and functional impact (Einav et al, 2008). In this study the level of S100B does not tell us about patient clinical outcomes i.e. neurological injury.

Finally, patients undergoing coronary artery bypass graft surgery with the use of cardiopulmonary bypass at Inkosi Albert Luthuli Central Hospital, Department Cardiothoracic Surgery, should undergo periodic neurodevelopmental surveillance for early detection of neurocognitive impairment so that rehabilitation could be instituted early. Little is known about the status of the cerebral vasculature and underlying cerebrovascular disease. Neurologists should therefore play an active role in identifying those at risk and postoperative change in neurological condition.

CHAPTER SEVEN: REFERENCES

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APPENDICES

APPENDIX: A

Timeframe

SEPT 2009 – DEC 2009 (4 MONTHS)

Introduction to proposal
Literature review and identification of methodology
Background
Submission of proposal

DEC 2009 – FEB 2010 (3 MONTHS)

Consent to notify patients of study
Consent of cardiac staff and collection
Selection of patients (study population)

FEB 2010 – MAY 2010 (4 MONTHS)

Collection of blood samples from arterial lines to measure serum S100B
Data recording
Measuring cerebral oximetry

JUNE 2010 – AUG 2010 (3 MONTHS)

Analysing
Presentation of results

AUG2010 – OCT 2010 (3 MONTHS)

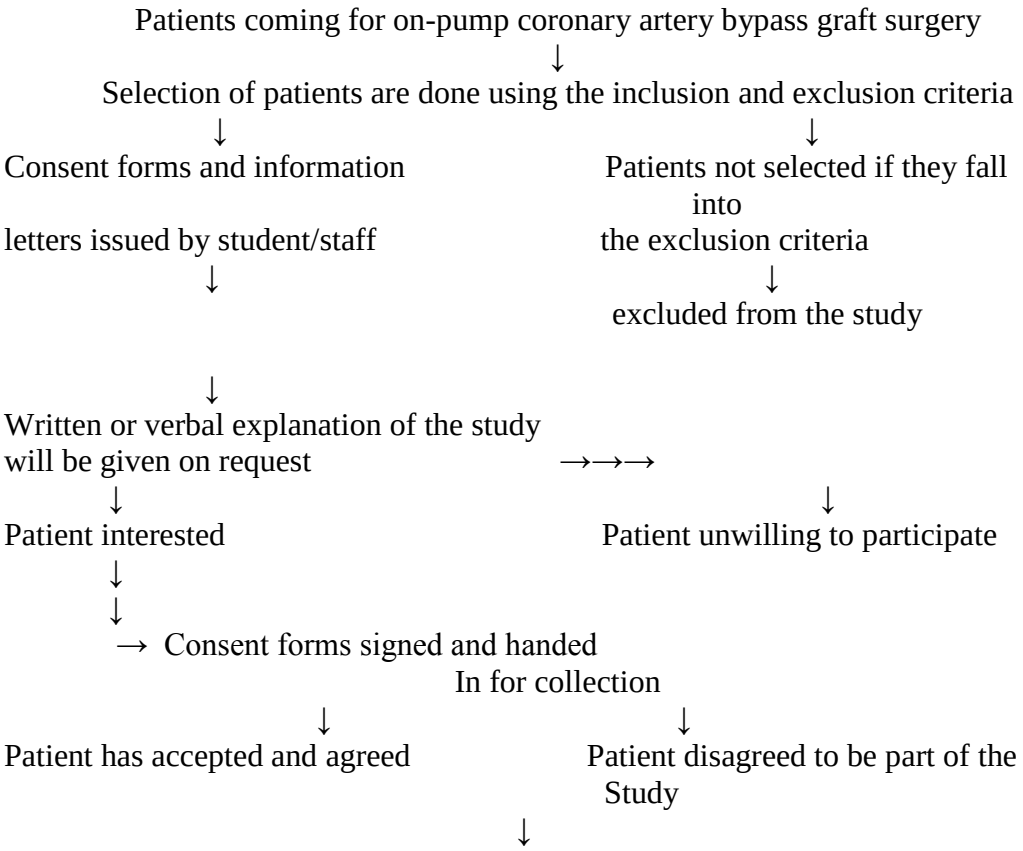
Bringing all information together

OCT 2010 – JAN 2011 (4 MONTHS)

Final write up
Correction of all information

APPENDIX: B

FLOW CHART- SUMMARISING ACTIVITIES OF THE RESEARCH PROCESS



APPENDIX: C

DURBAN UNIVERSITY of TECHNOLOGY

20 January 2010

Reference: Proposal Ratification: Y HARILALL, Student number 20150784

Dear Mr Harilall

DOCTORS DEGREE IN TECHNOLOGY: CLINICAL TECHNOLOGY

This serves to confirm the ratification of your research proposal by the Higher Degrees Committee, at its meeting on 17 December 2009, as follows:

1. Research proposal and provisional thesis title:

   THE EFFECT OF OPTIMIZING CEREBRAL TISSUE OXYGEN SATURATION ON MARKERS OF NEUROLOGICAL INJURY DURING CORONARY ARTERY BYPASS GRAFT SURGERY

   Promoter: Prof JK Adam

   Co-promoter/s: Prof A Reddi

   Please note that any proposed changes in the thesis title require the approval of your promoter/s, the Faculty Research Committee, as well as ratification thereof by the Higher Degrees Committee.

2. Research budget to the amount of R24 999.88

   Please note that this funding is not paid directly to you but is controlled by your promoter. Any proposed changes to this funding allocation require the approval of your promoter and the Faculty Research Committee.

The Institutional Research Committee has stipulated that:

(a) Ownership of any patent registered in respect of the results of your Masters/Doctors Degree in Technology studies be retained by you as the initiator of the project;
(b) Should you make any profit from the results of your Masters/Doctors Degree in Technology, you will be required to repay, *pro rata* , the funding investment which the University has made in approving your request for funding;
(c) If the University provided the equipment/materials for the creation of artefacts, this cost must be refunded to the University if such artefacts are sold;
(d) The University must be given first refusal in respect of any possible future sale by you of any patent that may be registered in respect of your said project.

May we remind you that in terms of Rule G25(2)(b), if you fail to obtain the Masters/Doctors degree within the maximum time period allowed after first registering for the qualification, the Senate may refuse to renew your registration or may impose any conditions it deems fit. You may apply to the Faculty Research Committee for an extension.

Please note that you are required to re-register each year.

You are invited to apply for a Postgraduate Award from the Postgraduate Development and Support Directorate. The forms are available on the DUT website at www.dut.ac.za; please note that conditions apply. You are further invited to contact the PGDS office to enquire about further support for your research studies.

Should you experience any problems relating to your research, your promoter must be informed of the matter as soon as possible. If the difficulties persist, you should then approach your Head of Department and thereafter the Executive Dean of the Faculty.

Please refer to the 2009 General Rule Book concerning the rules relating to postgraduate studies, which include *inter alia* acceptable minimum and maximum timeframes, submission of thesis/dissertations, etc. You are also advised to read the Postgraduate Students' Guide which is available on the DUT website.

Please do not hesitate to contact this office for any assistance. We wish you success in your studies.

Kind regards,

Ms N Muller

Manager: Postgraduate Development and Support Directorate (Acting)

Cc Faculty officer: Mr V Singh

TIP Research Finance: Ms R Govender

Head of Department: Mrs P Pillay

Supervisor: Prof JK Adam

APPENDIX:D

DEPARTMENT OF HEALTH

PROVINCE OF KWAZULU-NATAL

INKOSI ALBERT LUTHULI CENTRAL HOSPITAL

DEPARTMENT:
800 Bellair Road, Mayville, 4091
Private Bag X03, Mayville, 4058
Tel.: 031 240 1000, Fax.: 031 240 1050
Email.: @ialch.co.za

21st September 2009

Faculty Research Committee
Durban University of Technology
DURBAN

Re: STUDY PROPOSAL BY YAKEEN HARILALL

Topic : The Effect of Optimizing Cerebral Tissue Oxygen Saturation on Neurological Injury during Coronary Artery Bypass Graft Surgery

The Department of Cardiothoracic Surgery at Inkosi Albert Luthuli Central Hospital gives permission for the above-mentioned study to go ahead.

Yours sincerely

[redacted]

A. REDDI
HEAD
CARDIOTHORACIC SURGERY

APPENDIX: E

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

Letter of Information and Consent

Title of the Research Study:
The effect of optimizing cerebral tissue oxygen saturation on markers of neurological injury during coronary artery bypass graft surgery.

Principal Investigator:
Mr Yakeen Harilall, student enrolled for the Doctorate Degree: Clinical technology (Cardiovascular Perfusion) at Durban University of Technology.

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

The purpose of this study is to determine if changes made during open heart surgery using the heart lung machine will increase the amount of oxygen in the brain. If the oxygen levels in the brain can be maintained then these methods can be used in for all patients undergoing open heart surgery.

Outline of the Procedures:
During surgery blood samples of approximately 1-2.5ml will be taken over and above routine tests by the investigator before and after the operation to measure the levels of

S100B protein in blood. Blood samples will be taken from a tube which is routinely inserted during surgery therefore you will not endure any added pain. Sensors will also be placed on the forehead to measure brain oxygen levels. This is not a routine procedure.

Risks or Discomforts to the Subject:

There are no risks or side effects involved. Blood samples will be taken from the tube which is routinely inserted during surgery. Therefore, you will not feel any discomfort or pain. The sensors that will be placed on your forehead will not cause any discomfort.

Benefits:

The new information gained from the study may help to improve patients undergoing open heart surgery and shorten their hospital stay.

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

The subject may be withdrawn from the study if they require any other surgical procedures to be performed at the same time.

Remuneration:

There will be no remuneration for the participant.

Costs of the Study:

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

Confidentiality:

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

Research-related Injury:

There will not be any research related injuries. Your withdrawal at any time will not affect your medical treatment.

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

Mr Yakeen Harilall	Prof Jamila Adam	Prof A.Reddi
Principal Investigator	Promoter	Co/Promoter
0832778586	031 373 5291	031 2402114

Statement of Agreement to Participate in the Research Study:

(I,……subject's full name,

ID number…….., have read this document in its entirety and understand its contents. Where I have had any questions or queries, these have been explained to me by …….to my satisfaction. Furthermore, I fully understand that I may withdraw from this study at any stage without any adverse consequences and my future health care will not be compromised. I, therefore, voluntarily agree to participate in this study.

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

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

Witness name ……..……. **Witness signature**……..…….
Date:……..……

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

APPENDIX: F

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

Isivumelwano Socwaningo Olwenziwayo

Isihloko socwaningo Olwenziwayo:

Lolucwaningo lumayelana nokuthi singawukhuphukisa kanjani umoya (O2) owanele ozoya engqondweni ezigulini ezihlinzwa imithambo yenhliziyo.

Umcwaningi Omkhulu:

UMnu. Yarkeen Harilall ongumfundi eNyuvesi yase-Durban University of Technology, owenza iziqu zobudokotela emkhakheni we-Clinical Technology kwi-Cardiovascular Perfusion.

Isingeniso kanye Nenhloso:

Uyamenywa ukuba udlale indima kulolucwaningo. Lemininingwane ebhalwe kulencwadi izokusiza ukuthi uqonde kahle ukuthi lolucwaningo lumayelana nani kanti futhi ungasizakala kanjani kwi-bypass. Uma kunemibuzo engachazekanga kahle kulencwadi, ungangabazi ukubuza umhloli Inhloso yalolucwaningo ukuthola umangabe lukhona ushintsho ekusetshenzisweni kwe-bypass ukukhuphula izinga lomoya (O2) engqondweni. Uma lelizinga lomoya (O2) lingagcinwa, kungaba yicebo

elihle kakhulu elinga setshenziswa ezigulini ekudingeka zihlinzwe inhliziyo. Singakwazi ukuthola iziguli ezisencupheni futhi ngokuzayo sishintshe izimpilo zazo ukuze kube nemiphumela engcono uma kuhlinzwa.

Indlela yokwenza lolucwaningo:

Umcwaningi uzothatha amasampula egazi amancane ngaphambi kokuhlinzwa. Lamasampula egazi azocwaningwa ukuthola amazinga e-Serum S100B protein ngokusebenzisa umshini wase-Lab.

Lamasampula azothathwa ngalesisikhathiuhlinzwa ngalokho angeke ubuzwe ubuhlungu kanti futhi lamasampula azolahlwa kuqedwa ngawo. Kuphindwe kupbekwe amaphepha amancadi esiphongeni azobheka izinga lomoya (O2) engqondweni.

Ubungozi noma Ubuhlungu:

Abukho ubungozi noma ukungaphatheki kahle uma kuzokwenziwa lolucwaningo. Amasampula egazi azothathwa ngalesisikhathi ulele uhlinzwa ngalokho-ke angeke ubuzwe ubuhlungu noma ukungaphatheki kahle.

Umvuzo:

Lemininingwano emisha ezotholakala kulolucwaningo luzosiza ukwenza kancono imiphumela yokuhlinza ezigulini ezisencupheni.

Isizathu/Izizathu ezingenza ukube ungabe usaba inxenye yalolucwaningo:

Njengob auyinxenye yalolucwaningo, kuzothathwa nje umthambo enyaweni uxhunye emithambeni yenhliziyo. Uma kutholakala ukuthi kufanele wenziwe okunye ngaphandle kwalokhu okushiwo ngaphezulu, lokho kuzokwenza ukuthi ungabe usaba yinxenye yalolucwaningo.

Ukubhadalwa:

Ayikho imali ozoyithola ngokudlala indima kulolucwaningo.

Imali ozoyikhokha kulolucwaningo:

Ayikho imali ezonenezelwa ngokudlala noma ngokuba yinxenye yalolucwaningo kuphela nje uzokhokhela imali-le ebekumele uyikhokhele.

Imfihlakalo:

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

Izingozi ezingenzeka:

Ubungozi angeke kubekhona kulolucwaningo. Kanti futhi ukuphuma kwakho nangoma yisiphi isikhathi angeke kukunikeze inkinga.

Abantu ongaxhumana nabo uma uhlangabezana nenkinga noma unemibuzo:

UMn. Yakeen Harilall	Prof. Jamila Adam	Prof. A. Reddi
Umcwaningi Omkhulu	Umgqugquzeli	Umgqugquzeli
0832778586	031 373 5291	031 240 2114

Isivumelwano sokuba yinxenye yalolucwaningo:

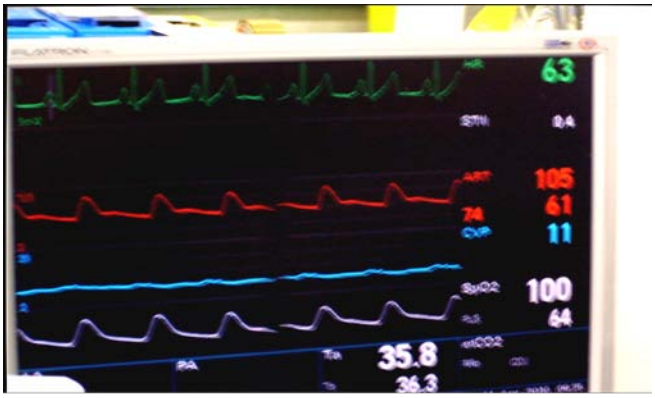
(Mina…….(igama eliphelele),
(Inamba ye-ID)……..ngifundile futhi ngaqonda ngalolucwaningo. Lapho enginemibuzo khona, ngizengayithola incazelo ecacile ku……..Ngaphezu kwalokhu ngiyaqonda ukuthi ngingayeka ukuba yinxenye yalolucwaningo ngaphandle kokuphazamiseka kwempilo yami. Ngiyavuma ukuba yinxenye noma ngidlale indima kulolucwaningo.

Igama lesiguli…… Sayina…….
Usuku…….

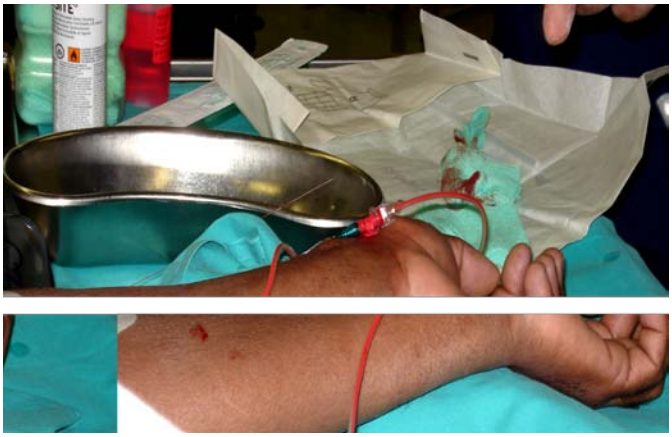
Umcwaningi…….. Sayina……...
Usuku……..

Umholi…….. Sayina……
Usuku……

APPENDIX: G



Display of routine patient monitoring parameters

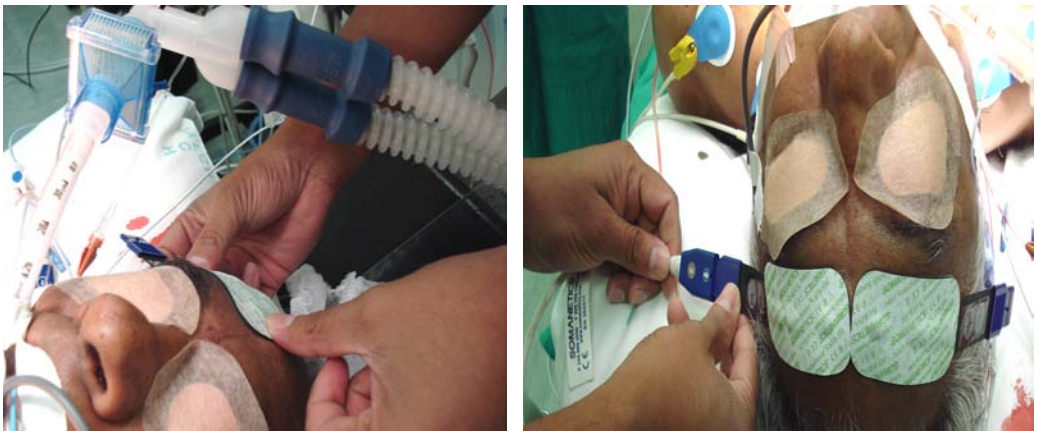


Insertion of a radial arterial line

Edwards Lifesciences (Vigileo) cardiac output and central venous oxygen saturation monitor used in the trial

APPENDIX: H

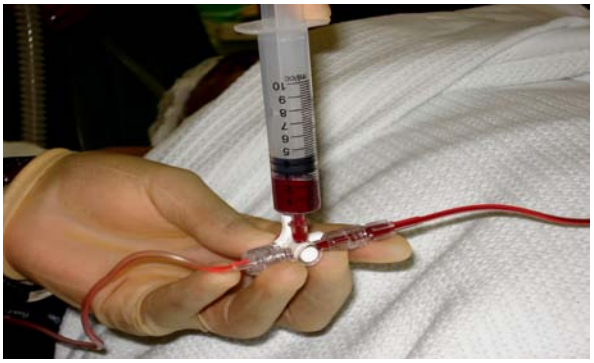
Calibration of the Vigileo monitor using baseline central venous blood gases, height, weight and baseline haematocrit



Placement of Cerebral somasensors

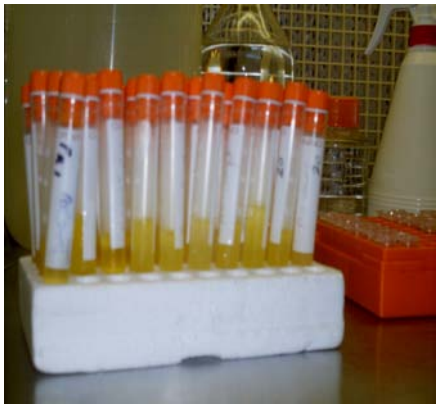
Baseline values of cerebral oxygen saturation (Green)

APPENDIX: I



Arterial blood (1-2.5 ml) taken for S100B measurement

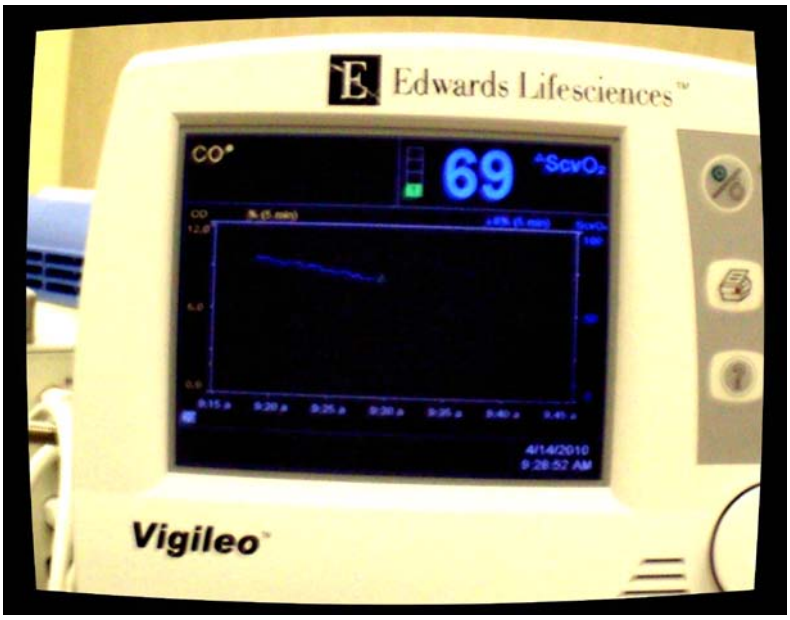
Investigator uses a pipette to collect serum



Storage of serum in cryovials

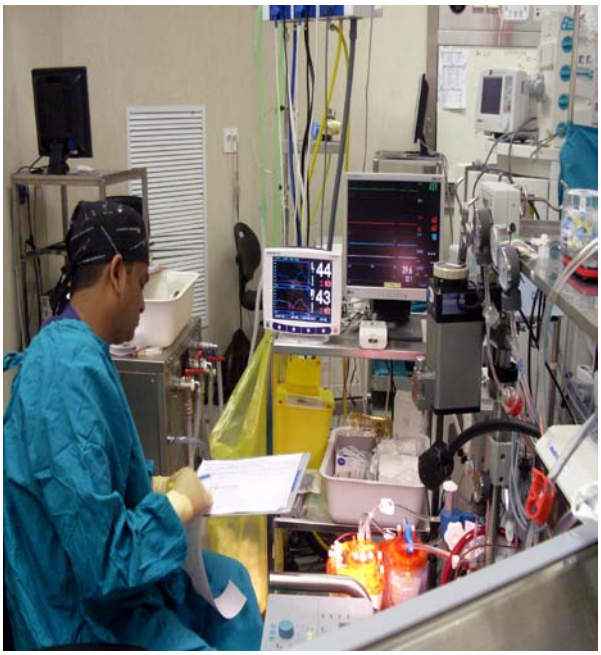
Storage at - 20°C in a biofreezer

APPENDIX: J

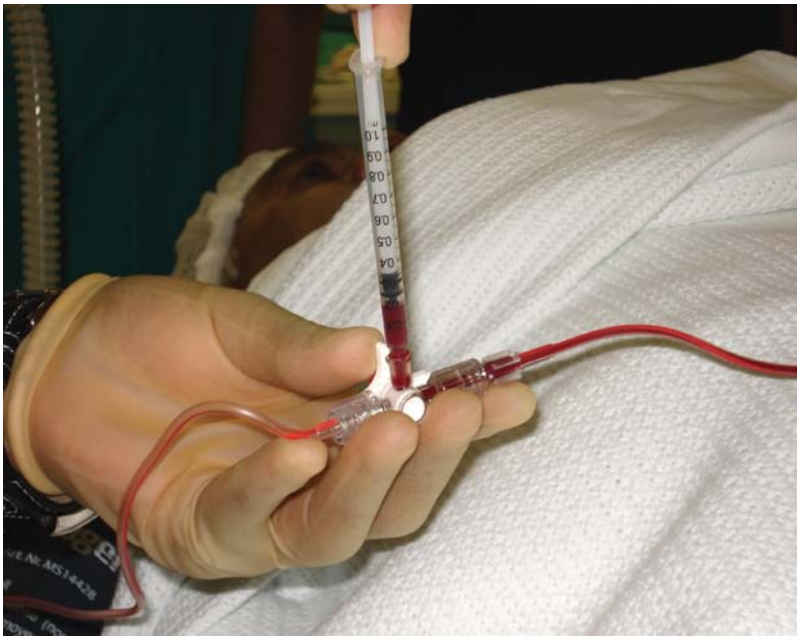


Edwards monitor used for central venous oxygen saturation

Invos (5100C) cerebral oxygen saturation



Heart lung machine (oxygenator sampling port) Inkosi Albert luthuli Central Hospital



Arterial line (A.line)

APPENDIX: K

Components and reagents (ELISA)

The various reagents and components supplied in the ELISA kit are listed below

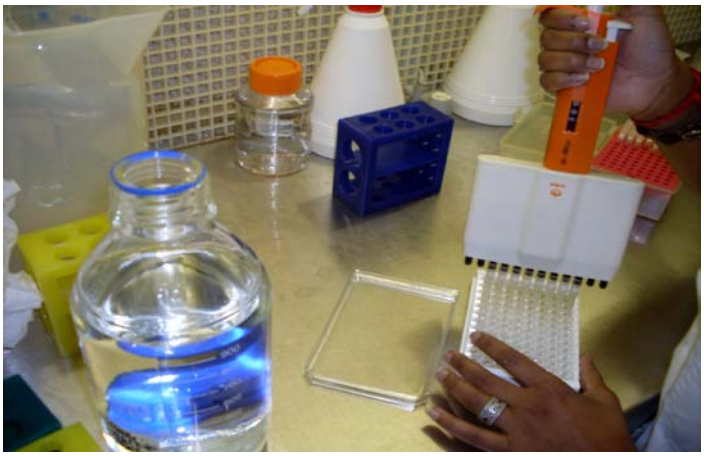
Item	**Volume (Quantity)**
Antibody-Coated Microtiter strips	1 pc/ 96 wells
Biotin Labelled Antibody Concentrate	0.15ml
Streptavidin-HRP conjugate	13ml
Human S100B Master Standard (lyoph)	1 vial
Quality control high (lyophilized)	1 vial
Quality control low (lyophilized)	1 vial
Biotin Ab diluent	13ml
Dilution Buffer	20ml
Wash solution concentrate	100ml
Substrate solution	13ml
Stop solution	13ml

APPENDIX: L

Master Standard Prep

Prepared standards

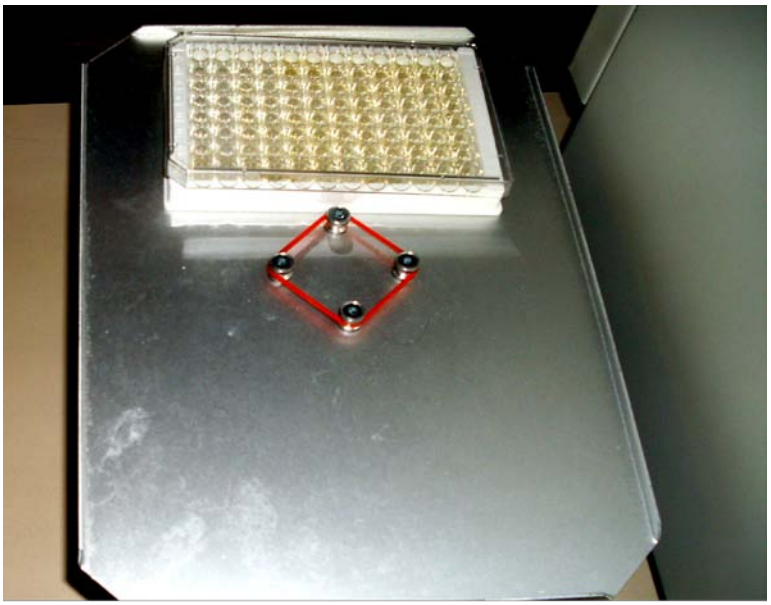
Preparation of Biotin labelled Antibody by the principle investigator



Wash solution used for wells

APPENDIX: M

Duplicate allocation of standards, controls and samples



Orbital microtiter plate shaker

APPENDIX: N

Washing the wells with wash solution

Inverting the plate over a paper towel

Microplate reader used to establish the absorbance at 450 nm

PERFUSION CHART: INKOSI ALBERT LUTHULI CENTRAL HOSPITAL: Control group

NAME	DATE	IP NUMBER	M	F	AGE	Type 1 Diabetes	Type 11 Diabetes	Serum S100B	
								Pre	Post

OPERATION	HEIGHT	WEIGHT	BSA	LPM	OXYGENATOR	MAX Flow rate	NUMBER OF GRAFTS
						L/min	

	Time Periods	TIME	LMP	ART P	FIO2	GAS LPM	T1	T2	C/Ve SATS	ACT	Hb	Ph	PO2	PCO2	STD BIC	BASE	K+	Na+	GLU
	BASELINE GAS																		
1	5min into CPB																		
2	Aortic cross clamp																		
3	After arrest																		
4	Distal anast																		
5	Proximal anast																		
6	During rewarm																		
7	Clamp release																		
8	CPB termination																		

	Time Periods	Hct	rSO2 Right	rSO2 Left	lact	Ca2+	%Iso	HR	SpO2
1	5min into CPB								
2	Aortic cross clamp								
3	After arrest								
4	Distal anast								
5	Proximal anast								
6	During rewarm								
7	Clamp release								
8	CPB termination								

					TIME (1)			TIME (2)			TIME (3)			TIME (4)			TIME (5)		
Time period rSO2 value <75% baseline																			
Time period rSO2 value <70% baseline																			
Time period rSO2 value <40% baseline																			

					TIME Period		TIME Period		TIME Period		TIME Period		TIME Period		
Time period rSO2 value <75% baseline															
Time period rSO2 value <70% baseline															
Time period rSO2 value <40% baseline															

CPB ON	**1.**	**2.**	**3.**	**CLAMP ON**	**1.**	**2.**	**URINE PRE**	
CPB OFF				**CLAMP OFF**			**URINE POST**	
TOTAL CPB				**TOTAL**			**TOTAL**	

FLUIDS ADDED	AMOUNT	TIME	DRUGS ADDED	AMOUNT	TIME	Red blood cells (Pack cells)

PERFUSION CHART: INKOSI ALBERT LUTHULI CENTRAL HOSPITAL : Interventional group

NAME	DATE	IP NUMBER	M	F	AGE	Type 1 Diabetes	Type 11 Diabetes	Serum S100B
								Pre Post

OPERATION	HEIGHT	WEIGHT	BSA	LPM	OXYGENATOR	MAX Flow rate	NUMBER OF GRAFTS
						L/min	

	Time Periods	TIME	LMP	ART P	FIO2	GAS LPM	T1	T2	C/Ve SATS	ACT	Hb	Ph	PO2	PCO2	STD BIC	BASE	K+	Na+	GLU
	BASELINE GAS																		
1	5min into CPB																		
2	Aortic cross clamp																		
3	After arrest																		
4	Distal anast																		
5	Proximal anast																		
6	During rewarm																		
7	Clamp release																		
8	CPB termination																		

	Time Periods	Hct	rSO2 Right	rSO2 Left	lact	Ca2+	%Iso	HR	SpO2
1	5min into CPB								
2	Aortic cross clamp								
3	After arrest								
4	Distal anast								
5	Proximal anast								
6	During rewarm								
7	Clamp release								
8	CPB termination								

					TIME (1)			TIME (2)			TIME (3)			TIME (4)			TIME (5)		
Time period rSO2 value <75% baseline																			
Time period rSO2 value <70% baseline																			
Time period rSO2 value <40% baseline																			

					TIME Period		TIME Period		TIME Period		TIME Period		TIME Period		
Time period rSO2 value <75% baseline															
Time period rSO2 value <70% baseline															
Time period rSO2 value <40% baseline															

	Interventions 15sec <70%	TIME	LMP	ART P	FIO2	GAS LPM	T1	T2	VEN SATS	ACT	Hb	Ph	PO2	PCO2	STD BIC	BASE	K+	Na+	GLU
	BASELINE GAS																		
	1																		
	2																		
	3																		
	4																		
	5																		
	6																		
	7																		
	8																		
	9																		
	10																		

rSO2 Right	rSO2 Left	lact	Ca2+	%Iso	Time period

CPB ON	**1.**	**2.**	**3.**	**CLAMP ON**	**1.**	**2.**	**URINE PRE**	
CPB OFF				**CLAMP OFF**			**URINE POST**	
TOTAL CPB				**TOTAL**			**TOTAL**	

FLUIDS ADDED	AMOUNT	TIME	DRUGS ADDED	AMOUNT	TIME	Red blood cells (Pack cells)