CORRELATION BETWEEN CEREBRAL TISSUE OXYGEN SATURATION AND CENTRAL VENOUS OXYGEN SATURATION DURING OFF-PUMP CORONARY ARTERY BYPASS GRAFT SURGERY

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Submitted in partial fulfilment of the requirements for the degree of

MASTERS IN TECHNOLOGY (CLINICAL TECHNOLOGY)

In the

Department of Clinical Technology

Faculty of Health Sciences

Durban University of Technology

February 2009

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 Dr 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

Currently, off-pump coronary artery bypass surgery (OPCAB) is a selectively employed technique for myocardial revascularization used in the majority of heart units worldwide. This strategy obviates the documented deleterious effects of cardiopulmonary bypass. However the occurrence of neurological sequelae associated with OPCAB ranges from minor cognitive dysfunction to major stroke. Haemodynamic instability throughout the positioning, stabilization and interruption of coronary blood flow are regarded as important factors that affect the performance of off-pump surgery. Fluctuations during the perioperative period, in particular manipulation of the heart could result in temporary brain hypoperfusion and neurological sequelae. To predict those patients that are predisposed to cerebral complications, investigators have used neurological monitoring, in particular Near-infra red spectroscopy (NIRS) during cardiac surgery.

Aims and Objectives of the study

This prospective, observational study was carried out to assess the correlation between cerebral oxygen saturation and central venous saturation during OPCAB surgery. Central venous saturation is an important variable used to assess global tissue perfusion and could therefore be advocated as a surrogate measure of cerebral oxygen saturation. In addition variables such as mean arterial (MAP) pressure, heart rate (HR), patient oxygen saturation (SpO_2), partial pressure of carbon dioxide ($PcvCO_2$), haematocrit (Hct) and lactate were also measured to determine if they were independent predictors of cerebral desaturation. This study is one of the first done in the South African population group.

Methodology

Twenty patients undergoing OPCAB surgery from the Cardiothoracic unit at Inkosi Albert Luthuli Central Hospital, Durban, South Africa were recruited in the trial. Cerebral somasensors were placed on the patients forehead to measure left and right cerebral saturations. These sensors were linked by cables to the cerebral monitor (NIRS), INVOS model 5100C. Eight time periods throughout the surgical procedure whereby patients would be haemodynamically unstable were identified. These time periods included, post induction and pre sternotomy, pre and post placement of swabs beneath the heart, pre and post placement of the stabilizer device (Octopus), pre and post snaring of the LAD (left anterior branch of the coronary arteries), pre anastomosis and during anastomosis of the coronary arteries, second sample during anastomosis and post anastomosis, pre and post removal of swabs from beneath the heart, pre and post transfer of the patient to the ICU bed. These time periods constituted the sampling period pre and post manoeuvres.

Eight paired measurements, i.e., MAP, $PaCO_2$, HR, Hct, lactate, SpO_2, central venous saturation ($ScvO_2$) and cerebral oxygen saturation (rSo_2) per patient were taken during these time periods. Recording of cerebral saturations and blood samples from the central venous line were taken during these eight time periods in order to determine the correlation between central venous and cerebral oxygen saturations.

Results

Strong positive correlations between central venous saturation and cerebral saturation presented in majority of the sampling time periods throughout the study (post induction and pre sternotomy, post placement of swabs beneath the heart, post snaring of the LAD (left anterior branch of the coronary arteries, pre anastomosis and during anastomosis of the coronary arteries, second sample during

anastomosis, pre and post transfer of the patient to the ICU bed). The positive correlation indicates that central venous saturation can be used as a surrogate measure of cerebral oxygen saturation during OPCAB surgery.

Conclusion

The absence or poor correlation of MAP, HR, $PcvCO_2$, heamatocrit, lactate, and patient saturation to cerebral saturation in this study suggests that insertion of a central venous line (CVP) during OPCAB should be a fundamental clinical requirement.

ACKNOWLEDGEMENTS

I wish to extend my sincere appreciation to:

Professor A Reddi, my external supervisor for his expert advice, constant encouragement and guidance. I sincerely thank him for being my mentor and for the opportunity of working under his expert guidance.

Dr. Bruce Biccard, for his constant support, dedication, constructive criticism, encouragement, guidance, assistance, intellectual insight, motivation and patience during the preparation involved in this dissertation.

Dr JK Adam, my internal supervisor. I sincerely thank her for added supervision, encouragement, guidance and dedication to this project.

Dr. M. Munasur, for his support and encouragement.

Dr. M. Joshua, Medical manager of Inkosi Albert Luthuli Central Hospital for granting me permission to access cardiac patients as well as theatre nursing staff for their support.

The Department of Cardiothoracic Surgery, Cardiovascular Perfusion and Anaesthetics, for their support, encouragement and assistance in the collection of patient samples and data.

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LIST OF ABBREVIATIONS

OPCAB - Off pump coronary artery bypass

NIRS - Near infrared spectroscopy

MAP - Mean arterial pressure

HR - Heart rate

SpO_2 - Patient saturation

$PcvCO_2$ - Partial pressure of carbon dioxide (central venous)

$PaCO_2$ - Partial pressure of carbon dioxide

Hct - Haematocrit

rSO_2 - Cerebral oxygen saturation

CVP - Central venous line

CBP - Cardiopulmonary bypass

CABG - Coronary artery bypass graft

NP - Neuropsychologic impairment

EEG - Electroencephalogram

ATP - Adenosine triphosphate

CMR - Cerebral metabolic rate

$CMRO_2$ - Cerebral metabolic rate of oxygen consumption

CBF - Cerebral blood flow

ICA - Internal carotid artery

MCA - Middle cerebral artery

BBB - Blood brain barrier

CSF - Cerebrospinal fluid

SAH - Subarachnoid haemorrhage

CPP - Cerebral venous pressure

CVP - Central venous pressure line

CPP - Cerebral perfusion pressure

SCADs - Small capillary arteriolar dilatations

CNS - Central nervous system

CI - Cardiac index

SvO_2 - Mixed venous saturation

$ScvO_2$ - Central venous oxygen saturation

TEE - Transoesophageal echocardiography

RVEDP - Right ventricular end diastolic pressures

LAP - Left atrial pressure

RAP - Right atrial pressure

Cx - Circumflex artery

TCD - Transcranial Doppler ultrasonography

HITS - High intensity transient signals

BHS - Beating heart surgery

LED - Light emitting diode

GLM - Generalized linear model

CHAPTER ONE - INTRODUCTION

Cardiopulmonary bypass (CPB) as a surgical technique 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, about 650 000 people in the USA and 800 000 worldwide undergo coronary artery bypass grafting (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 was the product of a series of technical and scientific advances thus involving surgical, anaesthetic, and perfusion strategies (Selnes et al., 1999). Despite these advances, adverse neurobehavioral outcomes continue to occur. 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.

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 mandating urgent attention (Wolman, Nussmeier, Aggarwal, Kanchuger, Roach and Newman, 1999). 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 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, extra corporeal circulation is associated with a complex inflammatory cascade, which may contribute to the development of postoperative neurologic morbidity.

Currently, off-pump coronary artery bypass surgery (OPCAB) is a selectively employed technique for myocardial revascularization in the majority of heart units worldwide. 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 strategy obviates the documented deleterious effects of cardiopulmonary bypass. Bowles and colleagues suggest 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 were 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).

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. 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. Some of the 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).

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. 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). Neurological monitoring during the operative period can reveal processes associated with central nervous system injury, and therefore provide a model for exploration of strategies to improve perioperative care.

Central venous oxygen saturation ($ScvO_2$) during cardiac surgery, an important variable employed to assess global tissue perfusion may be used as a surrogate of cerebral oxygen saturation (rSO_2) and by implication the adequacy of cerebral oxygen delivery and consumption. Central venous saturation is therefore, of critical clinical significance (Pearse, Deborah, Fawcett, Rhodes, Grounds and Bennett, 2005).

Closer attention must be drawn to the possible detrimental effects of sustained haemodynamic change on major organ function. Especially if the total time required for anastomosis is prolonged and haemodynamic instability gets worse. 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.

The aim of the study is to investigate the correlation between cerebral tissue oxygen saturation and central venous saturation during off-pump coronary artery bypass graft surgery. The primary objectives are to determine if a correlation exists between central venous saturation and cerebral tissue oxygen saturation using the cerebral oximeter and central venous blood gases with the hypothesis that trends in these variables are related. Our second objective is to determine whether mean arterial pressure (MAP), partial pressure of carbon dioxide ($PaCo_2$), heart rate, haematocrit, lactate and patient oxygen saturation (SpO_2) could be identified as independent predictors which influence central venous and cerebral oxygen saturations during off-pump coronary bypass graft surgery.

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.

CHAPTER TWO: STUDY BACKGROUND AND LITERATURE REVIEW

2.1 STUDY BACKGROUND

2.1.1 INTRODUCTION

Surgical revascularization of the coronary arteries remains the foundation of cardiothoracic surgery. The enduring nature of coronary artery bypass grafting bespeaks of its proven history and efficacy. It is a technique that can be reproducibly performed by different surgeons with varying degrees of technical skill and acumen with generally positive results. 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.

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 etiology 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 (OPCAB) 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.

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 (du Plessis, 1997).

2.1.2 NEUROPHYSIOLOGY

2.1.2.1 CEREBRAL PHYSIOLOGY

The adult human brain weighs approximately 1350g and represents about 2% of the total body weight. It receives between 12-15 % of the cardiac output. The high flow rate is a reflection of the brain's high metabolic rate. At rest, the brain consumes oxygen at an average rate of about 3.5ml/100g/min. Entire brain oxygen consumption is about 47ml/min. Normal cerebral physiologic values for the various regions of the brain are shown in Table 2.1

Table 2.1 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

Approximately 60% of the brain energy consumption is used in generating adenosine triphosphate (ATP) to support electrophysiological function (Malcom, 1991). The depolarization – repolarization activity that occurs and that is reflected in the EEG requires energy expenditure for the maintenance and restoration of ionic gradients. The 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 is expended in neuronal functioning including generation of electrical activity by the pyramidal cells. Approximately 40% of the energy is used for basal needs, whereas functional activity consumes 60% (Figure 2.1) (Guyton and Hall, 2000).

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 are important in the reuptake of neurotransmitters and in the delivery and removal of metabolic substrates and wastes (Rod, Trent and Stephens, 2006).

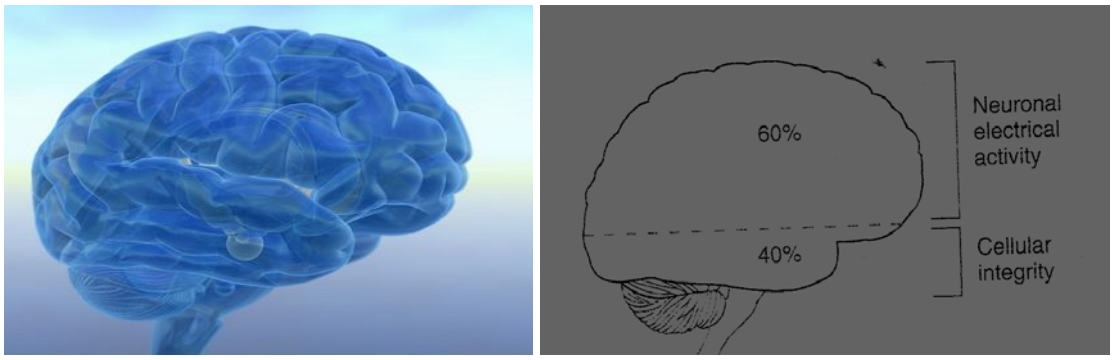


Figure 2.1 Normal brain oxygen requirements (Morgan & Mikhail, 2002: p553)

2.1.3 CEREBRAL METABOLISM

The cerebral metabolic rate (CMR) is usually expressed in terms of oxygen consumption ($CMRO_2$), which averages 3-3.8ml/100g/min. Cerebral metabolic rate of oxygen extraction is greatest in the grey matter of the cerebral cortex and 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, ATP stores become depleted with resultant irreversible cellular injury. Neuronal cells normally utilize glucose as their primary energy source. Brain glucose consumption is approximately 5mg/100g/min, of which over 99% is metabolized aerobically. Cerebral metabolic rate of oxygen consumption ($CMRO_2$), therefore, normally parallels glucose consumption. Acute hypoglycaemia which is sustained is equally devastating as hypoxia. Paradoxically, hyperglycemia can exacerbate global brain tissue injury. This occurs by accelerating cerebral acidosis and cellular injury (Guyton, 1991).

2.1.4 CEREBRAL BLOOD FLOW

One of the prime purposes of cerebral perfusion is to ensure oxygen delivery to the brain. Cerebral blood flow (CBF) is coupled to cerebral oxygen metabolism to ensure appropriate oxygen delivery (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 supply will lead to loss of consciousness within ten seconds and irreversible ischaemia occurring within minutes. Thus the primary function of cerebral circulation is to ensure uninterrupted supply of oxygen to the brain (Groves, 2003).

Under normal circumstances cerebral blood flow (CBF) is maintained at a relatively constant rate of 50ml/100g/min, flow in gray matter is about 80ml/100g/min while that in white matter is estimated to be 20ml/100g/min. Total Cerebral blood flow (CBF) in adults averages 750ml/min (15 -20 % of cardiac output). Flow rates below 20 – 25 ml/100g/min are usually associated with cerebral impairment, as evidenced by slowing on the electroencephalogram (EEG). Cerebral blood flow (CBF) rates between 15 -20 ml/100g/min typically produce a flat (isoelectric) EEG (Figure 2.2a and Figure 2.2b), while values below 10ml/100g/min are usually associated with irreversible brain damage (Morgan & Mikhail, 2002).

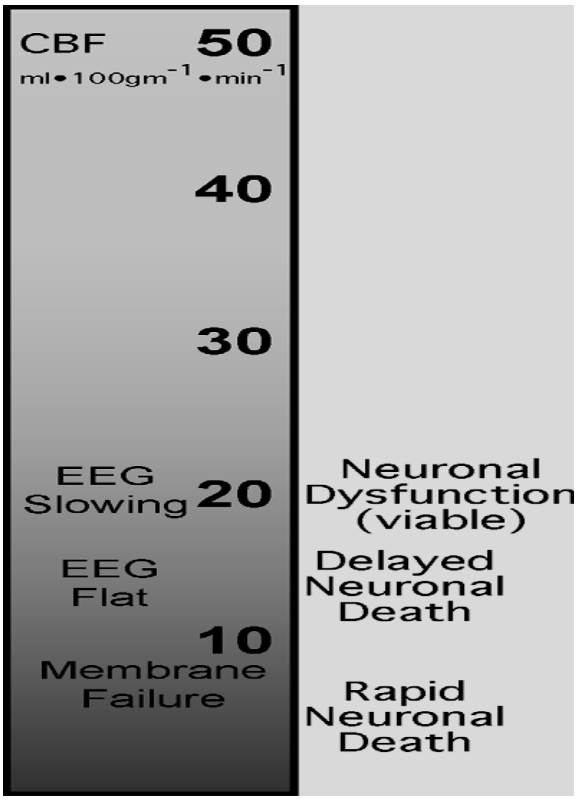


Figure 2.2a Illustration of neuronal dysfunction at flow rates of 20ml/100g/min which progresses to membrane failure and neuronal death at lower cerebral blood flow rates

(Patel, 2007)

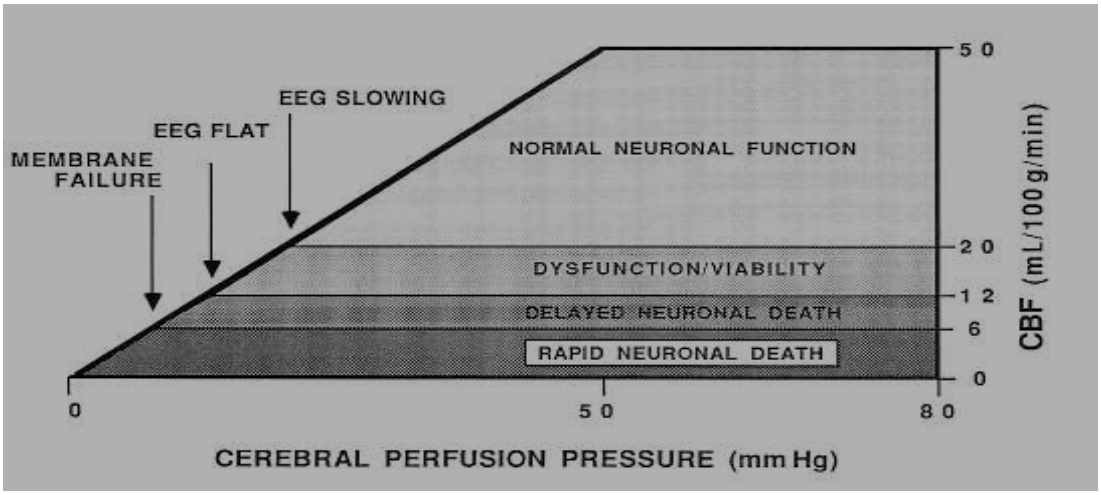


Figure 2.2b The relationship between cerebral blood flow (CBF), electroencephalogram (EEG) and neuronal viability (Patel, 2007)

2.1.5 CEREBROVASCULAR ANATOMY

2.1.5.1 ARTERIAL SUPPLY

The two internal carotid arteries (anterior circulation) and the two vertebral arteries (posterior circulation) supply blood 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 side. The internal carotid artery (ICA) supplies the brain and the ipsilateral eye. There are four segments of the ICA: cervical, petrous, cavernous, and supralinoid, describing its course as it enters the cranium. The ophthalmic, posterior, communicating, anterior choroidal, and anterior perforating arteries are all branches of the ICA. They provide most of the blood supply to the cerebrum. All areas of the brain supplied by the main branches of the ICA have good collateral circulation except the area supplied by the middle cerebral artery (MCA). As a result, the MCA territory is prone to ischaemia (Gary, Thibodeau and Patton, 2003).

Posterior circulation is comprised of the two vertebral arteries and the basilar artery. The vertebral arteries are 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 (Fig 2.3a). Each anterior spinal ramus originating 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 supplies the cerebellum and lower brainstem. The basilar artery ascends ventral to the pons and terminates in the pontomesencephalic junction.

It 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 2.3a, 2.3b) represents an anastomosis of the basal cerebral arteries and the potential collateral circulation. The main function of the circle of Willis is to provide collateral flow to the part of the brain with insufficient blood flow. In the Circle of Willis the two internal carotids are joined together by the anterior communicating artery while the posterior communicating artery links the internal carotid system with the basilar artery. Figure 2.3a illustrates potential collaterals via the communicating arteries. These connections make the collateral circulation. This is a safety mechanism allowing brain areas to continue receiving adequate blood supply even when there is a blockage somewhere in an arterial system. When all arteries are functioning normally, their blood supplies will not mix where they meet in the Circle because the pressure of their streams will be equal. As long as the Circle of Willis can maintain blood pressure at fifty percent of its normal level, no infarction or death of tissue will occur in an area where a blockage exists. Collateral circulation is not always sufficient to prevent stroke. Some people lack one or more of the communicating arteries in the Circle of Willis. This means that, if a blockage develops, blood cannot be redistributed from another arterial system and stroke will occur (McCaffrey, 1999).

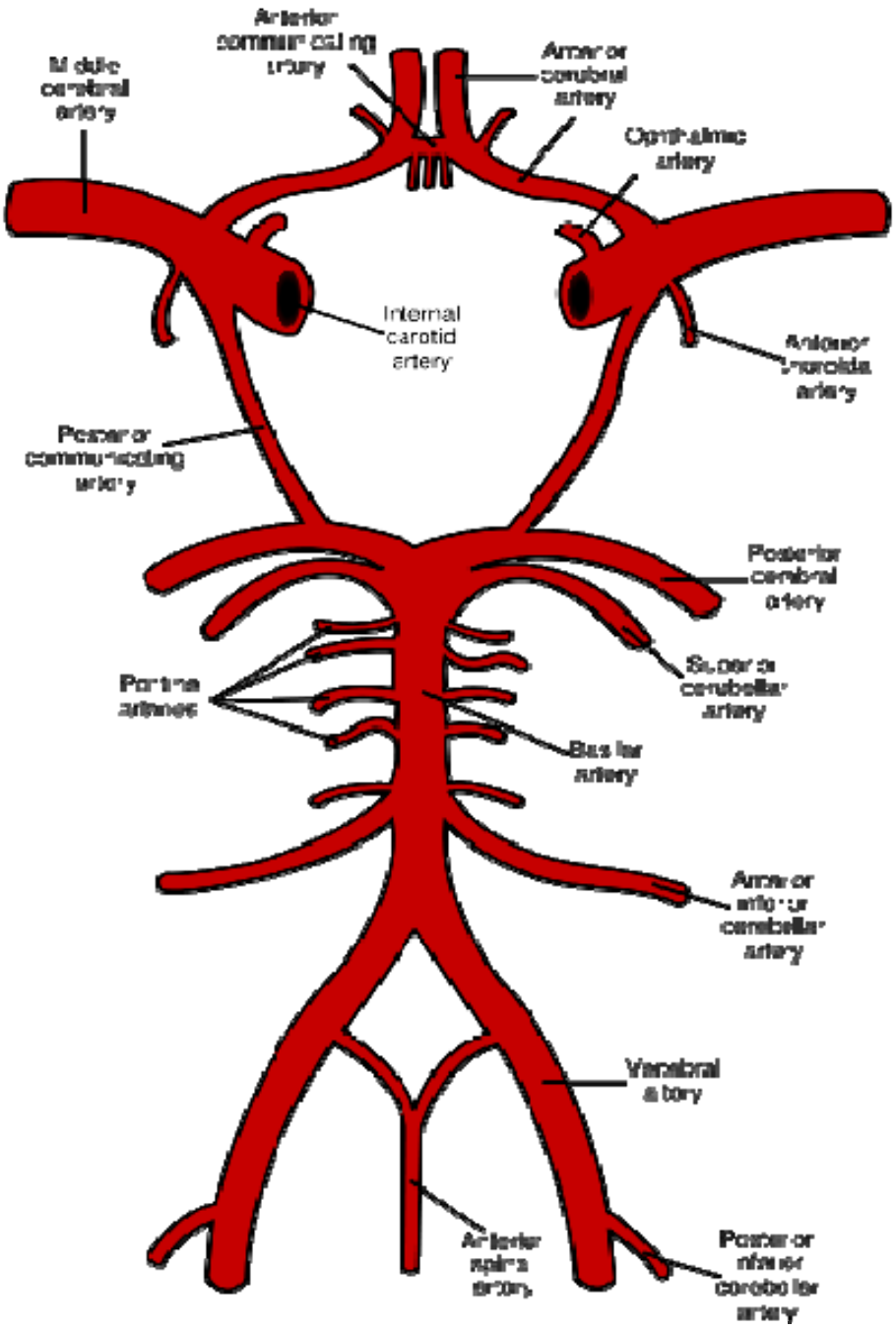


Figure 2.3(a) The Circle of Willis showing the potential collaterals via the communicating arteries (Ganong, 2003).

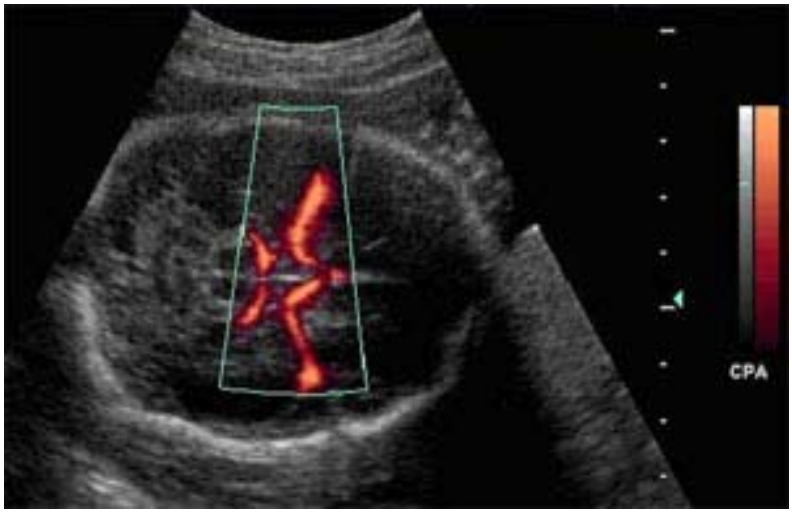


Figure 2.3(b) Angiogram showing The Circle of Willis (Hans, Kretschmann and Wolfgang, 1992).

2.1.5.2 VENOUS DRAINAGE

The venous system of the brain consists of superficial and deep cerebral veins. The superficial veins drain 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 to form the great vein of Galen, which is part of the deep venous system. Both superficial and deep veins including the vein of Galen drain into the major dural venous sinuses, which, in addition to receiving blood from the brain, also reabsorb cerebrospinal fluid from the subarachnoid space (Guyton and Hall, 2000). The walls of the cerebral veins are very thin while the walls of the dural sinuses are fibrous. Both the veins and the sinuses lack valves. The dural sinuses eventually drain

into one of the two internal jugular veins, as shown in Figures 2.4 and 2.5 (Rod, Trent and Stephens, 2006).

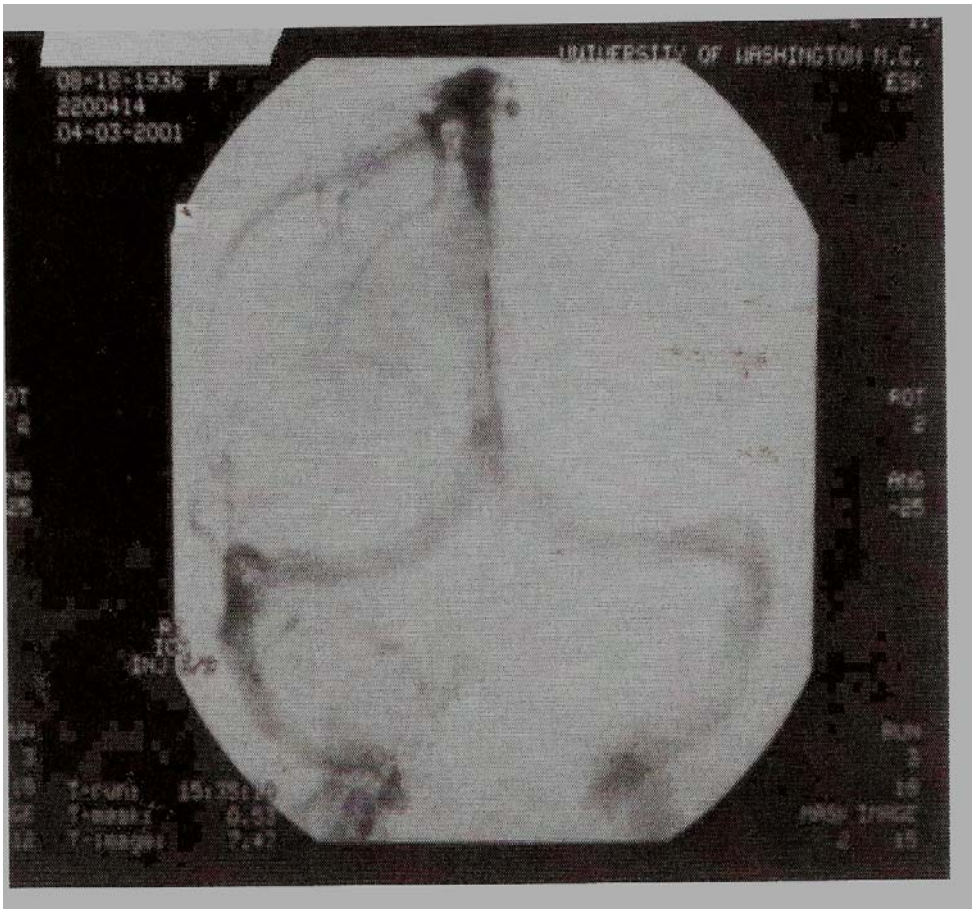


Figure 2.4 Venous angiogram demonstrating the drainage from sagittal sinus into the two transverse sinuses, which became the sigmoid sinuses. The final drainage is into the two internal jugular veins (Vavilala et al., 2002:p249).

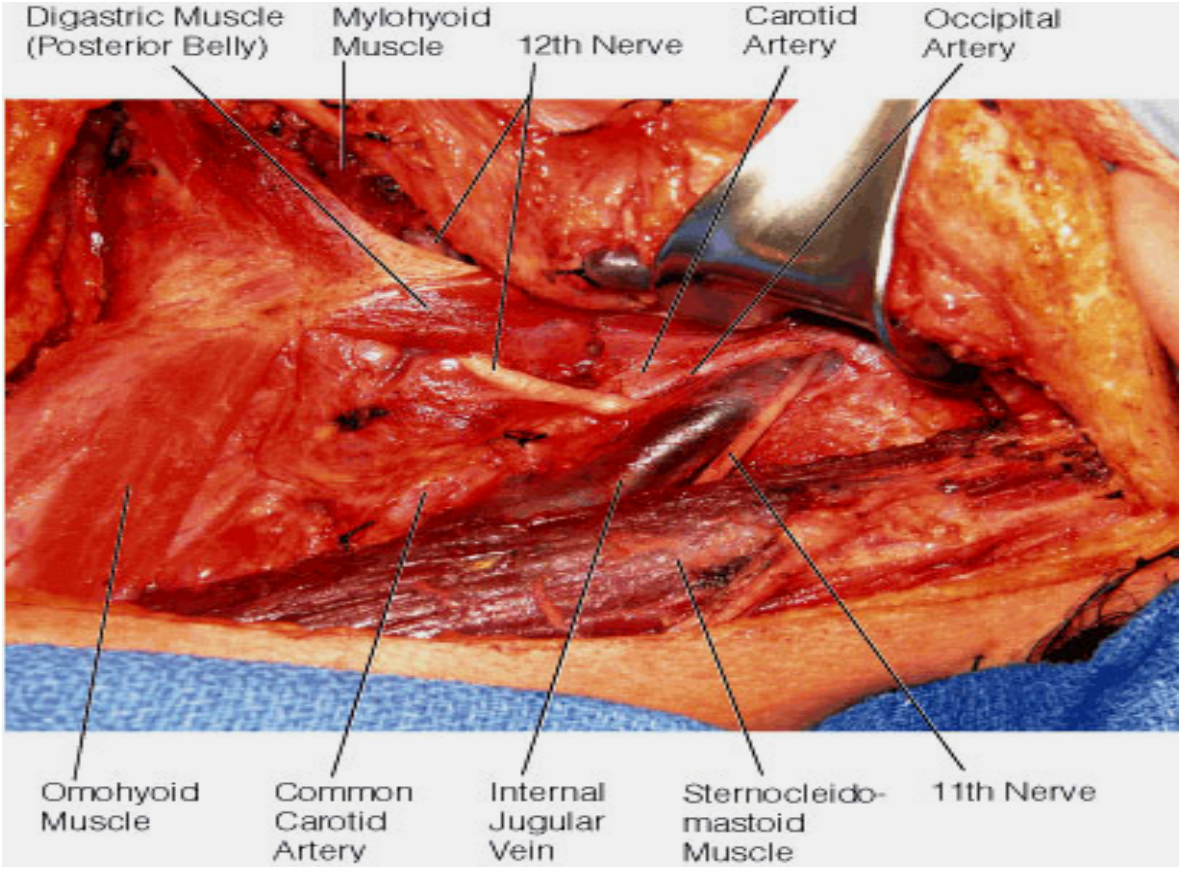


Figure 2.5 Diagram showing the location of the internal jugular vein (Web MD. Medscape.com article 482768, 2004)

2.1.6 REGULATION OF CEREBRAL CIRCULATION

Cerebral circulation is tightly regulated with a number of homeostatic mechanisms. The major factors that influence cerebral circulation are (1) metabolism, (2) partial pressure of carbon dioxide ($PaCO_2$), (3) partial pressure of oxygen (PaO_2), (4) viscosity, and (5) blood/cerebral perfusion pressure (Guyton and Hall, 1997).

2.1.6.1 Flow - Metabolism coupling

In the absence of pathology, cerebral blood flow is closely coupled to cerebral metabolism. This occurs at both, global and regional level. During periods of central

nervous system activation, CBF increases to accommodate the rapid increase in cerebral metabolic rate for oxygen ($CMRO_2$) necessitated by the increased energy requirements for synaptic transmission. Flow- metabolism coupling is an important control of cerebral circulation. It is a 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). Flow- metabolism coupling can be observed at different stages of sleep where light or deep sleep is associated with declines in CBF, and rapid eye movement (REM) sleep shows cerebral blood flow similar to the awake state (Madsen et al., 1991).

2.1.6.2 Increase of cerebral blood flow in response to excess carbon dioxide concentration.

An increase in carbon dioxide concentration in the arterial blood perfusing the brain greatly increases cerebral blood flow. The cerebral circulation is exquisitely sensitive to changes in $PaCO_2$. In normal individuals cerebral blood flow increases linearly by 2% to 4% per mmHg $PaCO_2$ within the range of 25 to 75mmHg. Thus $PaCO_2$ is the most potent physiologic cerebral vasodilator.

Changes in CBF occur within seconds after $PaCO_2$ 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, this 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 CSF pH gradually decreased toward baseline and CSF bicarbonate concentration also decreased and CBF increased. The relationship of change between arterial PCO_2 and CBF is demonstrated in Figure 2.6. A 70% increase in arterial PCO_2 approximately doubles the cerebral blood flow.

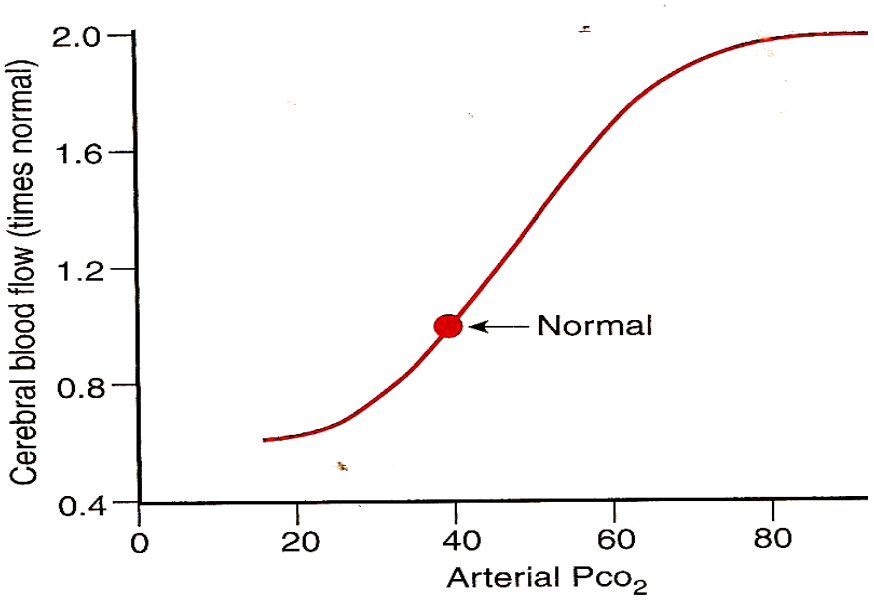


Figure 2.6 Relationship between arterial PCO_2 and cerebral blood flow (Guyton and Hall, 2000; p 710).

Although cerebral blood flow is altered in response to changes in $PaCO_2$, 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 $PaCO_2$ 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 2.7.

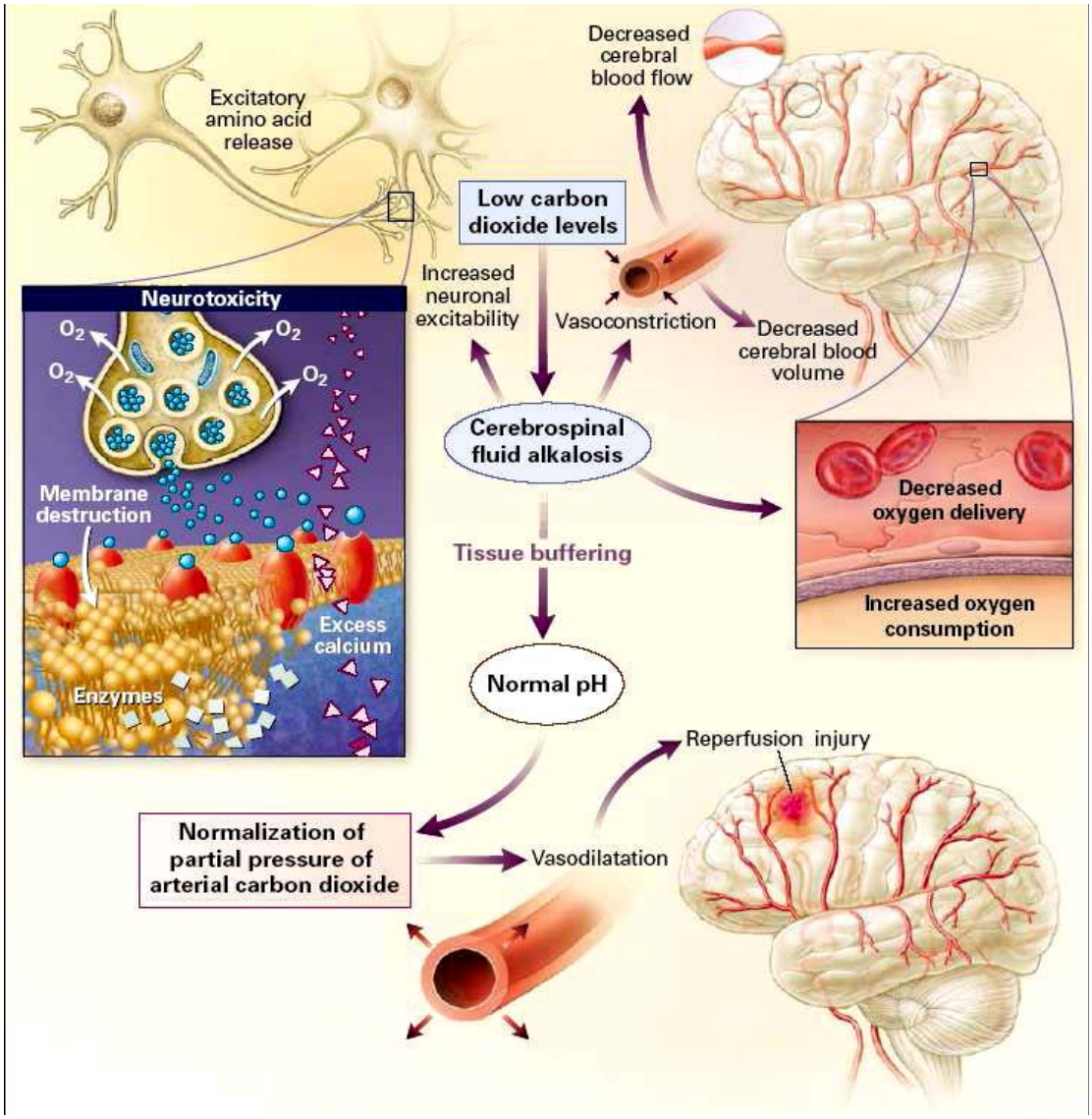


Figure 2.7 Negative effects of hypocapnia (Naik, 2007)

2.1.6.3 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 the healthy. Patients in Cardiac failure demonstrate reduced CO_2 vasoreactivity that is associated with a reduction in left ventricular ejection fraction (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).

2.1.6.4 Oxygen deficiency as a regulator of cerebral blood flow

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 hypoxemia is not as quick as the response to changes in $PaCO_2$, because equilibration of CBF takes approximately 6 minutes after the establishment of hypoxemia (Gary et al, 2003). On the other hand, the effect of hyperoxemia 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 20mmHg. 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). PaO_2 levels of less than 60 mmHg result in a sharp upswing of the PaO2 curve (Figure 2.8). This results in increased cerebral blood flow.

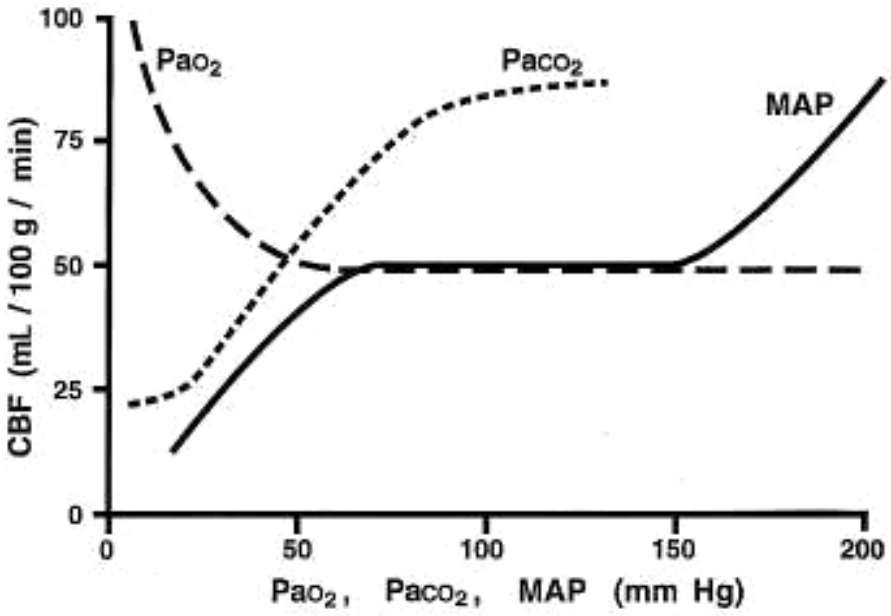


Figure 2.8 Change in PaO_2 / when PaO_2 is less than 60mmHg, CBF increases rapidly (Guyton 8th Edition, 1991)

2.1.6.5 Temperature

Cerebral metabolic rate decreases by 6 to 7 percent for every one degree drop in temperature. Hypothermia decreases the rate of energy utilization associated with both electrophysiological and basal components as seen in Figure 2.9. 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. Cerebral blood flow and cerebral metabolic rate 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).

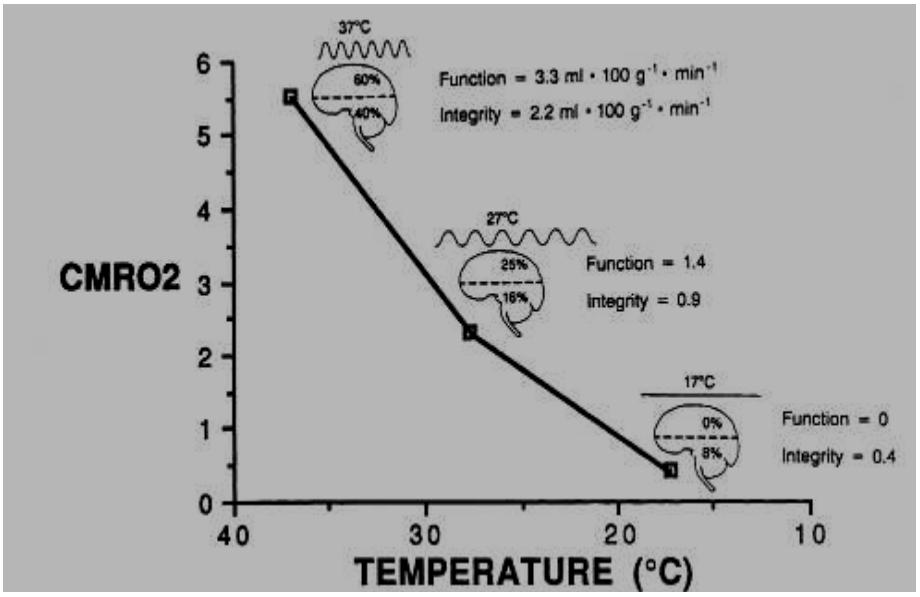


Figure2.9 Effect of temperature on cerebral metabolic rate. (Naik, 2007)

2.1.6.6 Effect of viscosity on cerebral blood flow

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).

2.1.6.7 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 50mmHg demonstrate a slowing on the EEG, those with a CPP of 25-40 mmHg typically have a flat EEG.

Sustained perfusion pressures less than 25mmHg result in irreversible brain damage (Morgan & Mikhail, 2000).

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 and 160 mmHg as demonstrated in Figure 2.10. 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.

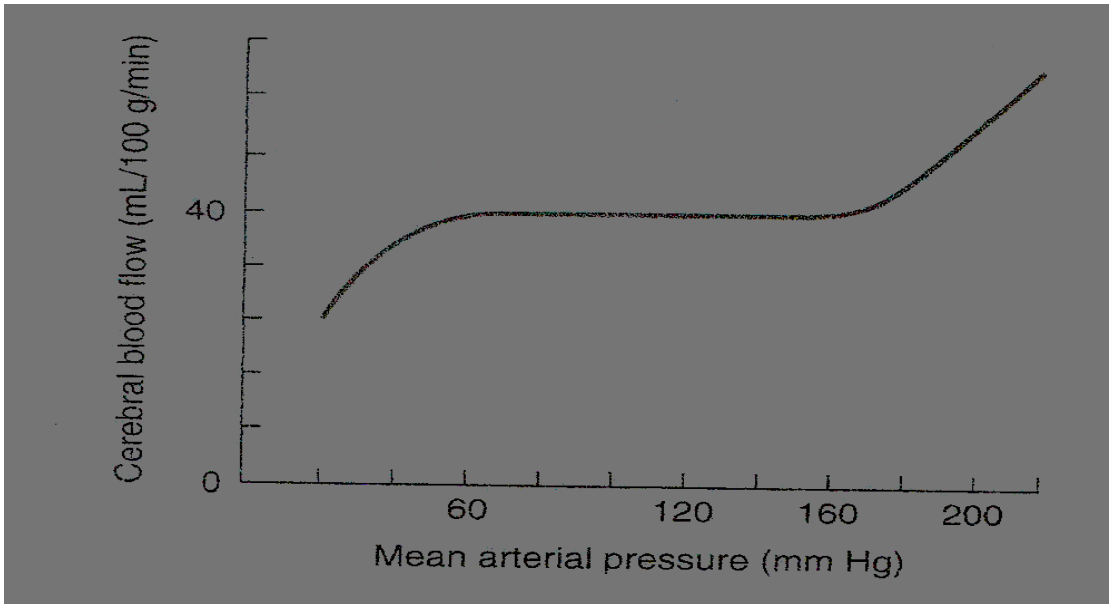


Figure 2. 10 Cerebral autoregulation curve (Morgan & Mikhail, 2002 p554)

2.1.7 MECHANISMS OF CEREBRAL INJURY DURING CARDIAC SURGERY

2.1.7.1 Cerebral hypoperfusion

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 (Caplan, 1998).

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).

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 (Croughwell, Newman, Blumenthal, White, Lewis, Frasco and Smith, 1994; Edmonds, 2002). 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 (Figure 2.11a). The authors deduced that a reduction in MAP during CPB of ≥10mmHg 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). Figure 2.11 (a) 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 2.11(b) shows disruption in blood flow in the brain. The colorized (NMR) nuclear magnetic resonance imaging shows that an individual can suffer a stroke if blood flow is disrupted.

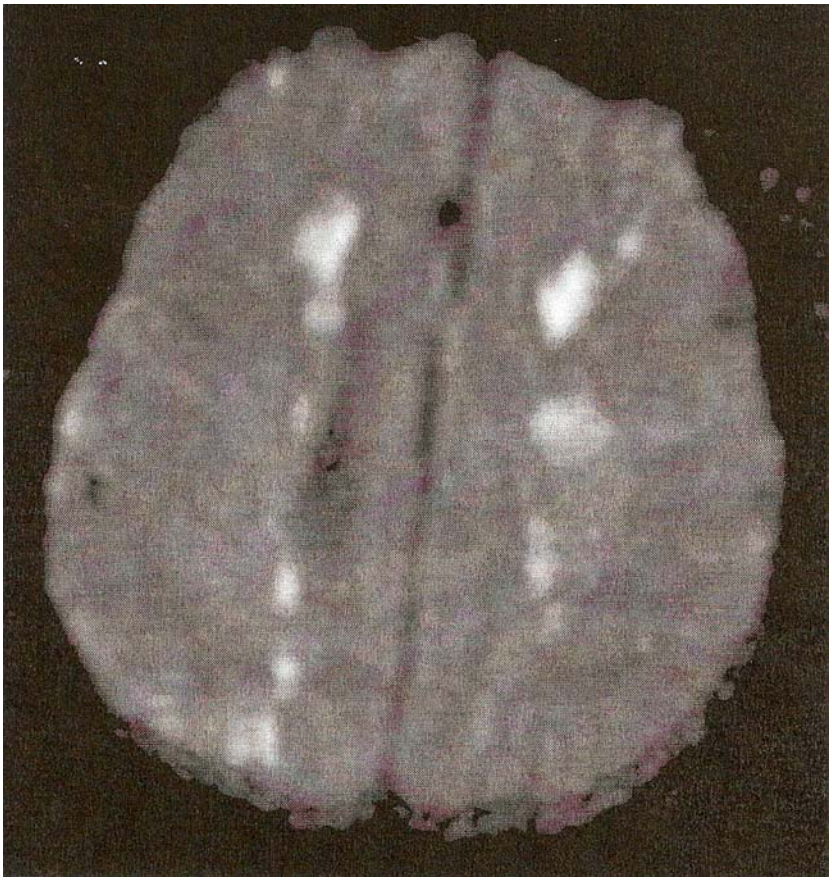
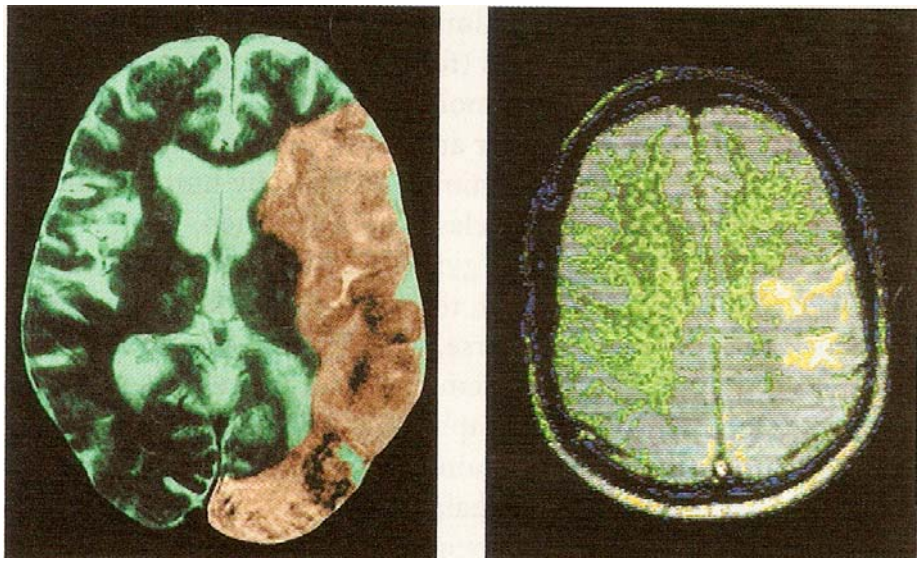


Figure 2.11 (a) Magnetic resonance image with stroke after cardiac surgery

Anterior



(A) (B)

Posterior

Figure 2.11 (b) (A) MRI (magnetic resonance imaging) of a massive stroke in the left side (viewer's right) of the brain. (B) Colorized NMR (nuclear magnetic resonance) showing disruption of blood flow to the left side (viewer's right) of the brain (yellow). This disruption could cause stroke. (Rod et al, 2006)

2.1.7.2 Cerebral embolism

It has been established that cerebral injury from cardiac surgery is primarily ischaemic, secondary to embolism and cerebral hypoperfusion. Between 30 to 50 percent of preoperative strokes that are detected with brain imaging occur as a result of cerebral macroembolism arising from the ascending aorta (Blauth, Cosgrove and Webb, 1992; Djaiani, Fedorko, Borger, Mikulis, Carroll, Cheng, Karkouti, Beattie and Karski, 2004; Hogue, Murphy and Schechtman, 1999; Lilosky, Marrin, Caplan, Baribeau and Weintraub, 2003; Wareing, Davila, Barzilia, Murphy and Kouchoukos,

1992). Microemboli are either gaseous or particulate in composition. Gaseous emboli is said to arise from an open left sided cardiac chamber or from air entrained into the CPB circuit (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).

2.1.7.3 Atherosclerosis of the Aorta

Published clinical investigations and autopsy reports have linked atherosclerosis of the aorta to neurological injury after cardiac surgery (Blauth et al., 1992; Wareing et al., 1992). Studies have shown that atherosclerosis of the ascending aorta detected during the time of surgery was an independent predictor of stroke (Wareing et al., 1992; Hogue et al., 1999; Djaiani et al., 2004). Mackensen et al., (2003) found that patients with severe atherosclerosis were linked to higher numbers of cerebral microembolic signals during CABG surgery and were prone to higher rates of postoperative neurocognitive dysfunction as compared to patients without severe atherosclerosis. Epiaortic ultrasound scanning has been identified as the most sensitive means for detecting atherosclerosis of the ascending aorta (Hogue et al., 2006; Wareing et al., 1992). Regardless of whether transoesophageal or epiaortic echocardiography is used clinically as a method of detection, the frequency of

neurological episodes and the severity of aortic atherosclerotic disease have been well documented (Hogue et al., 2006; Wareing et al., 1992).

Surgical manipulation such as aortic cannulation, aortic cross clamping, or proximal coronary artery anastamosis have been postulated to be the primary cause of atheroembolism due to disruption of atheroma. Disruptions of atherosclerotic lesions have been verified in a study consisting of 472 patients. During the study epiaortic ultrasound scanning was performed before and after cardiopulmonary bypass. Mobile lesions of the ascending aorta were identified in 10 patients after surgery at the sites of aortic cross clamping or cannulation (Ura, Sakata, Nakayama and Tomoko, 2000). Three of the ten patients identified, endured stroke. 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.

2.1.7.4 Atrial fibrillation

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.

2.1.7.5 Perioperative Anaemia

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 conducted on dogs found that the compensatory responses were sufficient to meet cerebral metabolic demand to a haematocrit 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 his randomized trial.

2.1.7.6 Hyperglycemia

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. Hyperglycemia (>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).

2.1.7.7 Lipid embolism from Pericardial Suction Aspirate

Small capillary arteriolar dilations ("SCADs") histologically staining positive for lipid material were found at autopsy in brain microvessels of patients dying after cardiac

surgery (Moody et al., 1995). Studies have suggested that the source of SCADs was fat arising from the cardiotomy suction aspirate that is returned to the CPB reservoir (Brooker, Brown, Moody, Hammon, Reboussin, Deal, Ghazi and Stump, 1998). A study conducted during dog CPB illustrated that arterial line filtration was inefficient at decreasing SCADs as compared with processing of cardiotomy suction aspirate with a cell saver (Kincaid, Jones, Stump, Brown, Moody, Deal and Hammon, 2000). These findings have led investigators to either discard or process pericardial aspirate with a cell saver.

2.1.8 CEREBRAL INJURY AFTER CARDIAC SURGERY

2.1.8.1 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, 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). Strokes are often caused by atheriosclerotic plaques present in the feeder arteries that supply blood to the brain.

Atheriosclerotic 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.

2.1.8.2 Pathophysiology

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). Atheriosclerosis 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)

When oxygen or glucose becomes depleted in ischaemic brain tissue, the production of high energy phosphates such as adenosine triphosphate (ATP) fails, thus the energy dependant processes necessary for tissue cell survival also fails. This sets off a series of interrelated events that result in cellular injury and death. One of the major causes of neuronal injury is the release of the excitatory neurotransmitter glutamate. The concentration of glutamate outside the cells of the nervous system in normal cases are kept low by uptake carriers, which are powered by the concentration gradients of ions

mainly sodium across the cell membrane. However, stroke cuts off the supply of oxygen and glucose which powers the ion pump that maintains these gradients. As a result the transmembrane ion gradients run down, and glutamate transporters reverse their direction, causing the release of glutamate into the extracellular space. Glutamate in turn acts on receptors in nerve cells producing an influx of calcium which activates enzymes that digest the cells proteins, lipids and nuclear material. The influx of calcium also leads to mitochondrial failure, which further leads toward energy depletion and may trigger cell death due to apoptosis (Guyton and Hall, 2000).

2.1.8.3 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 lost 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, lost 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).

2.1.9 NEUROCOGITIVE CHANGES FOLLOWING CARDIAC SURGERY

2.1.9.1 (a) Delirium

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).

2.1.9.2 (b) Inability to focus attention, confusion and disorientation

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).

2.1.9.3 (c) Memory formation disturbance

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).

2.1.9.4 (d) Abnormality of awareness and effect

Patients may present with hallucinations or distortions of reality. Commonly these are visual distortions, and can take the form of masses of small crawling creatures or distortions in size or intensity of the surrounding environment. Their emotional states may also fluctuate. Delirious patients experience different phases, for example, terror, sadness and jocularity (Delirium- Cleveland Clinic).

2.1.9.5 (e) Delirium and Dementia

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).

2.2 LITERATURE REVIEW

2.2.1 HISTORY OF CORNARY ARTERY BYPASS GRAFT SURGERY

Prior to the development and advances in extracorporeal circulation or cardiopulmonary bypass (CPB) which is currently used worldwide for open heart surgery, anastomosis on coronary circulation was performed on the beating heart with minimal success, due largely to poorly evolved surgical techniques. Revived interest and enthusiasm for the procedure began 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 prohibitive neurological complications ranging from minor cognitive disorders to major stroke (Reddi, Munasur and Kleinloog, 2006).

Each year, about 800 000 people worldwide undergo coronary artery bypass grafting (CABG). 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. Cerebral dysfunction after cardiac operations in which cardiopulmonary bypass (CPB) is used is regarded as one of the most serious and costly complications. In the formative years of CPB, this problem was largely attributed to the use of the pump oxygenator. During the past three decades, however, advanced knowledge and improvements in operative and perfusion techniques have greatly reduced the levels of cerebral complications (The warm heart investigators, 1994).

2.2.2 INCIDENCE OF NEUROLIGICAL DYSFUNCTION ASSOCIATED CARDIOPULMONARY BYPASS.

Recognition of the brain as a potential target of injury during cardiopulmonary bypass (CPB) has been greatly magnified as the mortality risk for CPB related complications has declined (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; Newman et al., 2001). 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 the many patients in functional terms, a proportion of patients with cognitive decline become sufficiently disabled thus affecting their routine daily functions and work (Roach et al., 1996). The reasons cited for these neurological deficits are multifactorial and include cerebral hypoperfusion, age, emboli of air or atheromatus material, haemorrhage, presence of extracranial carotid artery disease, and metabolic abnormalities (Blauth, 1995; Lazar, Menzion, 1998; Bull, Meumayer, Hunter, Keksz, Sethi, Mclntyre and Bernhard, 1993). 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 (Blauth, Arnold, Kohner and Taylor, 1986).

Edmunds (1997), reported that major neurological injury occurs in 3.1% of cardiac patients. It was also responsible for a 21% postcoronary bypass mortality rate, prolongation of time spent in the intensive care unit and in hospital stay. Furthermore, hospital boarding charges, rehabilitative and outpatient support costs increased by 5 to 10 times.

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).

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 Mangano1990; Newman, Kirchner, Phillips, Graver, Grocott, Jones, Malk, Reves and Blumenthal, 1996).

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 (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 confounded by neurologic or neuropsychologic dysfunction after surgery.

2.2.3 STROKE AFTER CORONARY ARTERY BYPASS

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 (Hashimoto, Martin, 1982; Coffey, Massey, Roberts, Curtis, Jones and Pryor, 1983) and from 1.5% to 5.2 % in prospective studies (Roach et al., 1996).

Stroke following CABG is reported to occur more commonly than stroke after other surgical procedures (Limburg, Wijdicks, Li, 1998). 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).

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). Other contributing mechanisms of stroke include arteriosclerotic 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).

Despite the technical advances and improvement in surgical techniques, along with the introduction of membrane oxygenators and in line filtration systems, a persistent stroke rate associated with CABG is still prevalent. 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).

2.2.4 EFFECT OF AGE ON NEUROLOGICAL OUTCOME

Cerebral injury in the aged is an important cause of adverse outcomes after cardiac surgery. In particular, elderly patients with other comorbidities. 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 (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 a 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).

Figure 2.12, 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.

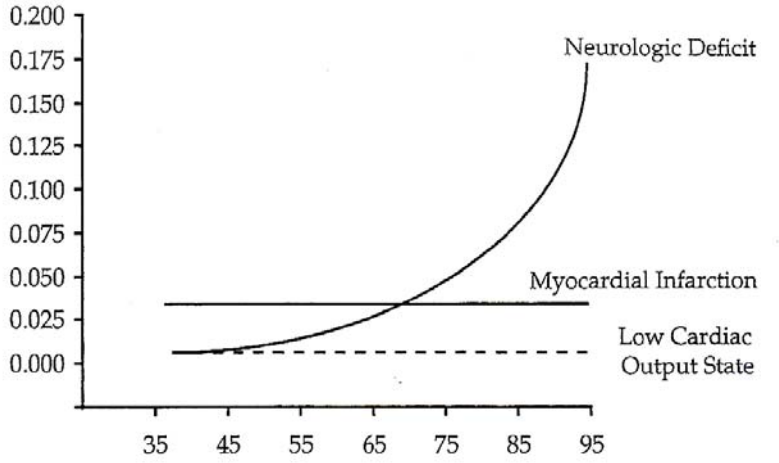


Figure 2.12 Effect of advanced age on the predicted probability of neurologic and cardiac morbidity (Tuman et al., 1992)

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. They made use of Epiaortic Doppler scanning to show the relationship between age and atherosclerosis of the ascending aorta as demonstrated in Figure 2.13.

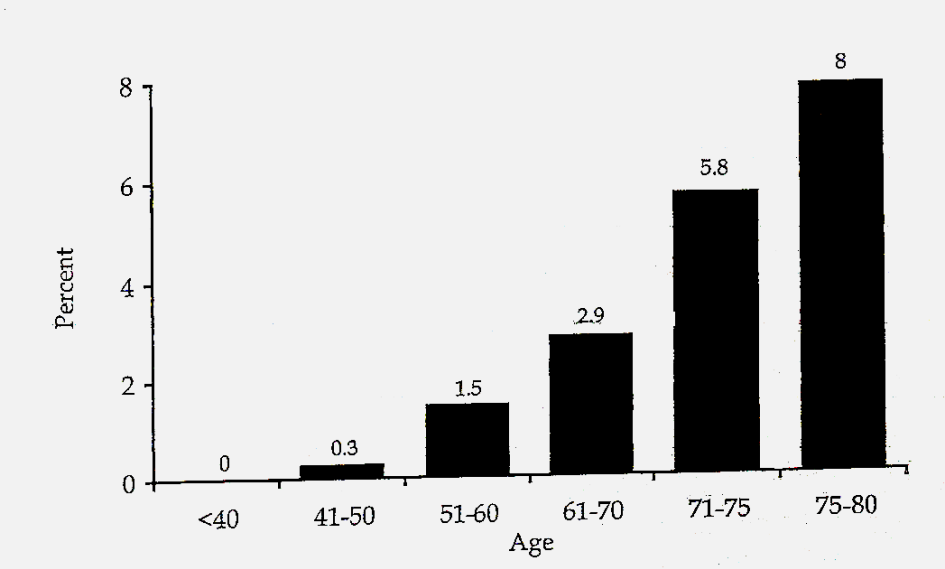


Figure 2.13 Relationship between age and atherosclerosis of the ascending aorta detected using ultrasonic imaging (David- Roman et al,1991)

2.2.5 OFF- PUMP CORONARY ARTERY BYPASS GRAFT SURGERY(OPCAB)

Direct myocardial revascularization without cardiopulmonary bypass, in order to reduce the surgical invasiveness, is a selectively employed technique used in heart units world wide. Off pump coronary artery bypass graft surgery (CABG) has become an accepted method of coronary revascularization since it obviates most of the perioperative and postoperative morbidity related to on pump CABG. Zamvar et al. (2002), reported that there is a significant reduction in the incidence of neuropsychologic impairment with avoidance of cardiopulmonary bypass. 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).

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. It has been expanded because of the advantage of avoiding cardiopulmonary bypass (CPB) related complications, which may have an impact on the neuropsychiatric outcome after cardiovascular procedures. .

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. Off-pump coronary artery bypass (OPCAB) has been shown to reduce the number of cerebral microemboli generated during coronary surgery. In a prospective trial Diegler and colleagues 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).

Neurological complications attributed to extensive atherosclerosis of the 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. There 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, 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 can 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). In a retrospective review of 1389 standard CABG patients and 483 OPCAB patients, Ricci et al. (2001), found that CPB was a significant predictor of stroke in univariate regression analysis (Ricci et al, 2001). Similar findings were reported by Hernandez et al. (2001), who 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. Thus, although large retrospective studies have shown little reduction in postoperative stroke rate after OPCAB when compared to on pump CABG, eliminating CPB does appear to significantly reduce the incidence of Type 1 neurologic injuries especially for patients who are at increased risk for such complications.

2.2.5.1 Heamodynamic changes during Off-pump CABG

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 bad effects on organ function.

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, this was also associated with both regional systolic dysfunction and restrictive diastolic filling, which indicates 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 heamodynamic 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.

2.2.5.2 Partial Aortic Clamp during Off- Pump surgery

Currently beating heart surgery operations are done as multi-vessel OPCAB procedures, which employ the use of a partial aortic clamp to perform proximal anastomosis. Although literature has repeatedly reported and identified clamp application and removal as the greatest source of emboli which is closely linked to neurologic outcomes. In a study of heparin bonded circuits using transcranial Doppler to detect cerebral emboli, Aldea, Lilly, Gaudiani, Gara, Stein, Bao, Treanor, Osman, Shapira, Lazar and Shemin, (1997), reported that the release of the partial aortic clamp was associated with the greatest number of emboli.

Omar et al. (2004), used transcranial Doppler ultrasonography (TCD) to compare the number and nature of intraoperative microemboli in patients undergoing off pump and on pump cardiac surgery procedure (Figures 2.13 and 2.14). High intensity transient signals (HITS) were detected using TCD ultrasonography which result from an increase in the ultrasound signal reflected from the microemboli compared with surrounding blood which provided an index of microemboli entering the cerebral circulation. The median number of microemboli in the off pump and on pump coronary artery bypass grafting groups were 40 (28-80) and 275 (199-472) respectively. In the on pump group, 24% of microemboli occurred during cardiopulmonary bypass and 56% occurred during aortic manipulation (cannulation, decannulation, application and removal of the cross or side clamp).

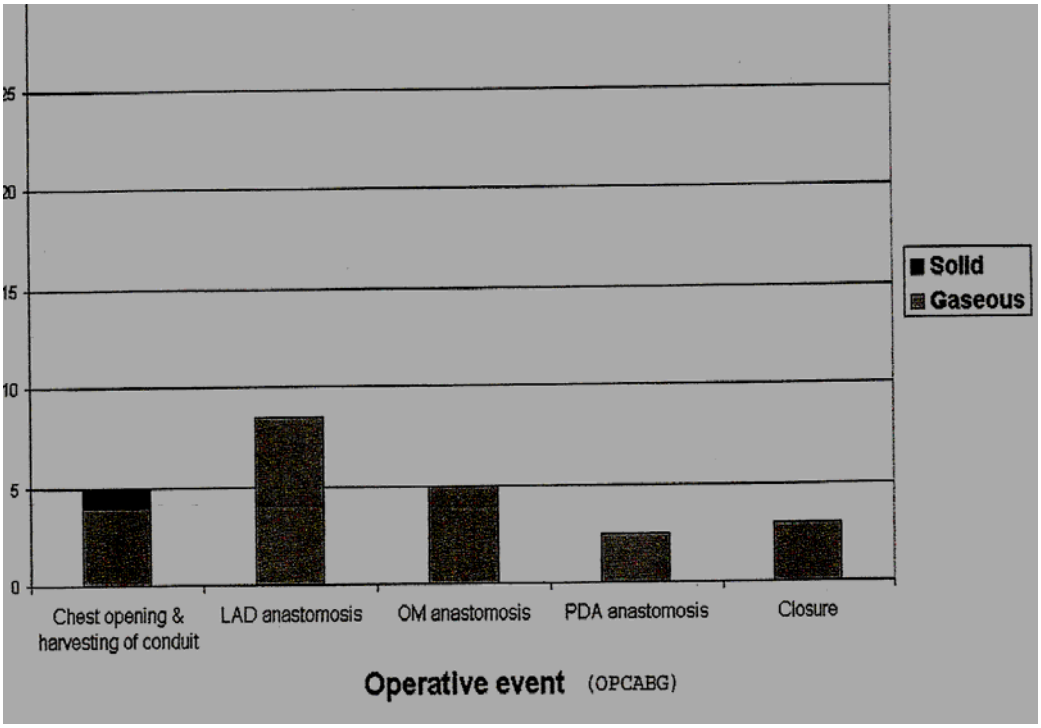


Figure 2.14 Gaseous and solid microembolization during the course of off-pump coronary artery bypass grafting. LAD, left anterior descending ; OM, obtuse marginal; PDA, posterior descending artery (Omar et al, 2004).

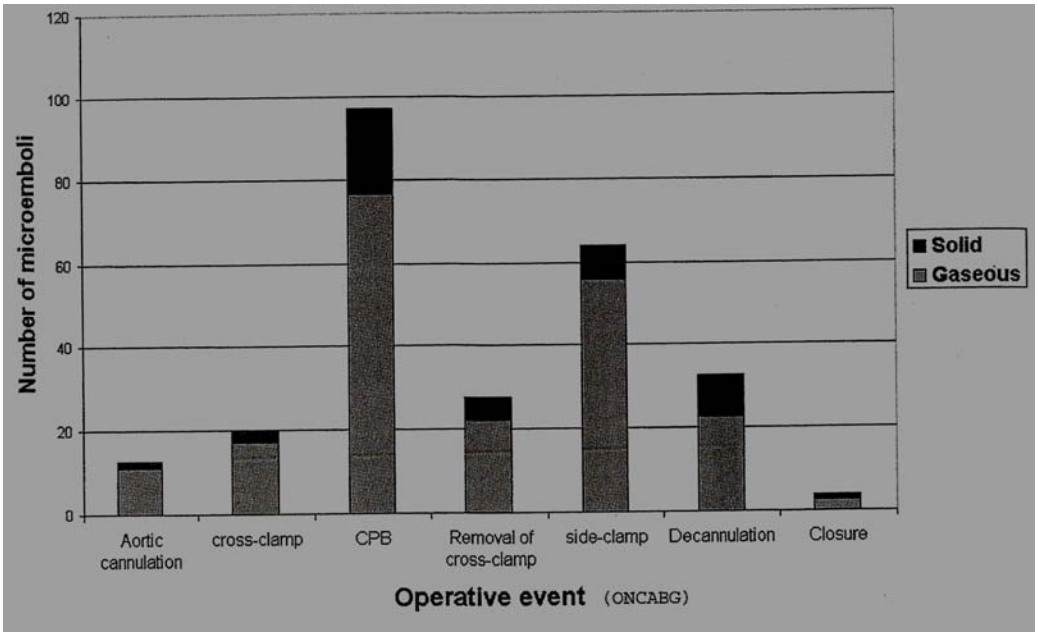


Figure 2.15 Gaseous and solid microembolization during on-pump CABG (Omar et al, 2004).

2.2.5.3 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. Gold et al. (1995), prospectively examined perfusion pressure in two groups of patients undergoing CABG and demonstrated an improved neurological outcome in patients perfused between 80 and 100 mmHg.

Cerebral venous hypertension, arising as a consequence of surgical dislocation of the heart during either beating heart surgery (BHS) or conventional CPB, can be important in decreasing cerebral ischaemia, especially in patients with cerebrovascular disease. 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 BHS 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).

The relative importance of cerebral hypoperfusion is still controversial. Therefore, the direct relationship between cerebral perfusion and neurological injury needs to be well supported. Newman et al. (1995), examined the relationship between intraoperative mean arterial pressure and the incidence of postoperative neuropsychological dysfunction. Multivariable linear regression analysis failed to show any association between the time and degree of intraoperative hypotension and the development of postoperative cognitive decline.

2.2.6 Monitoring brain oxygen saturation during Coronary bypass surgery

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 (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).

Neurologic monitoring in the perioperative period has been extensively reviewed and is widely recommended for high risk patients (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 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).

2.2.6.1 NIRS TECHNOLOGY

Near infrared spectroscopy technology (Figure 2.16) 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 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 730nm and 810nm. 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).

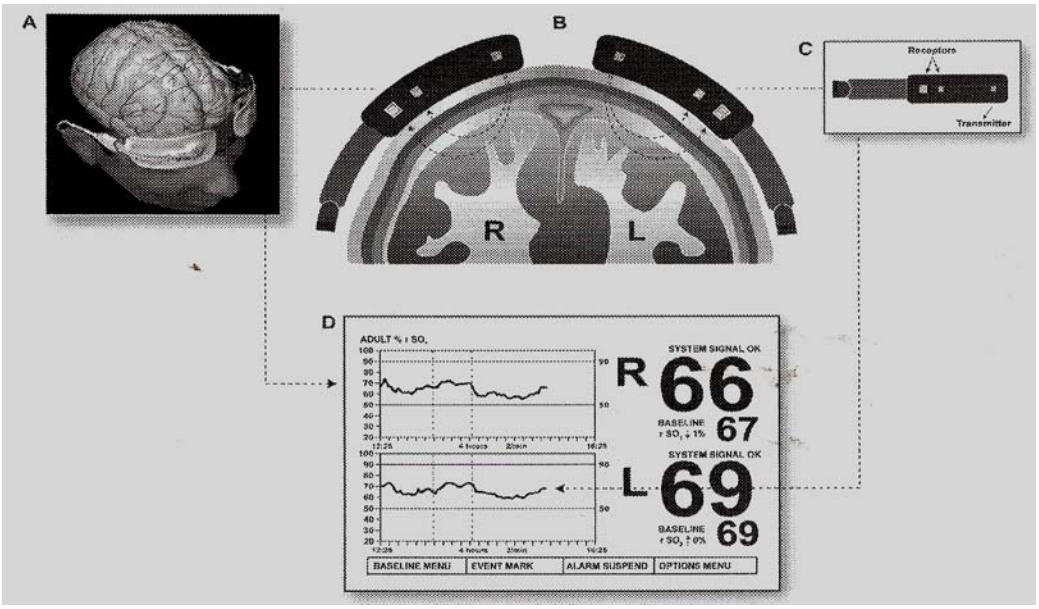


Figure 2.16 Operating principles of the use of near- Infrared spectroscopy (Denault et al., 2007) Invos Cerebral Oximeter

(A)The electrodes are positioned in the forehead. (B) Signals from both hemispheres are transmitted to a display. (C) The signals are coming from an optode that has 1 transmitter and 2 receptors.The signal originating from the proximal receptors are subtracted from the distal ones .Therefore, only information from the deeper part of the brain is displayed. (D) on the screen, the large number indicates the ongoing brain oximetry values and the small number the baseline value obtained at the beginning of the recording from both the right (R) and the left (L) hemisphere.

2.2.6.2 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, 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).

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 algorithm is 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.

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).

2.2.7 Central venous oxygen saturation monitoring

Continuous monitoring of central venous oxygen saturation has been proposed as a prognostic indicator in several pathological conditions, including cardiac diseases, sepsis and trauma (Alessandro, Chiara, Lucia, Giovanni, Rosario, Marco, Franco and Adriano, 2009). Scalea, Hartnett, Duncan, Atweh, Philips, Sclafani, Fuortes, and Shaftan (1990), found that ScvO2 measurement is a trustworthy parameter to estimate blood loss, especially in patients who showed ScvO2 values below 65% despite having stable clinical signs. Recently low central venous oxygen saturation has been associated with increased risk of postoperative complications in high risk patients (Pearse, Dawson, Fawcett, Rhodes, Grounds, and Bennett, 2005). The prognostic significance of ScvO2 less than 65% has been well demonstrated in myocardial infarction, cardiac

failure, trauma and severe sepsis (Rady, Rivers, Martin, Smithline, Appleton, Nowak, 1992; Ander, Jaggi, Rivers, Rady, Levine, Levine, Masura, Gryzbowski, 1998). In a study conducted by Hendrik, Matthias, Barbara, Ninja, Francesca, David, Jukka, Takala and Stephan (2007), the authors used ScvO2 to guide optimization of haemodynamics in ninety eight unplanned admissions to a multidisciplinary ICU and concluded that low ScvO2 values in unplanned admissions are associated with increased mortality. Bloos and Reinhart (2005), showed that length of hospital stay decreased in cardiac patients using ScvO2 as a parameter for increasing systemic oxygen supply.

Although central venous oxygen saturation (ScvO2) and mixed venous oxygen saturation (SvO2) have been proposed to be markers of adequate oxygen supply and demand, the relationship between them is controversial (Reinhart, Kuhn, Hartog and Bredle 2004). In septic ICU patients, investigators observed a clinical link between the presence of global tissue hypoxia, the generation of inflammatory mediators, and mitochondrial impairment of oxygen utilization (Boulos, Astiz, Barua, 2003). Sudden decreases in mixed venous oxygen saturation in these septic patients is said to have both diagnostic and prognostic significance (Krafft, Steltzer, Hiesmayr, 1993). Against this background, the rationale for using central venous oxygen saturation as a surrogate measure of mixed venous oxygen saturation to detect and treat global tissue hypoxia was the basis for its use in the Early Goal Directed Therapy in Severe Sepsis and Septic Shock Study conducted by Rivers et al, 2001. The question of whether ScvO2 is the numeric equivalent to SvO2 has been examined in a number of studies, which continues to fuel this debate (Ladakis, Myrianthefs and Karabinis, 2001; Edwards and Mayall, 1998). A recent study conducted by Chawla et al, 2004 showed that ScvO2 values were approximately 5% higher than SvO2 values which was likely secondary to

the contributions of deoxygenated blood from the coronary sinus (Chawla, Zia and Gutierrez, 2004). Irrespective of whether the ScvO2 value equals the SvO2 value, the presence of a low ScvO2 levels in patients with early sepsis portends increased morbidity and mortality, and correcting this value according to a consensus derived algorithm improves morbidity and mortality (Rivers, 2006). According to various authors, haemodynamic assessment using physical examination, vital signs, central venous pressure and urinary output fails to detect supply dependency or global tissue hypoxia (Wo, Shoemaker, Appel, 1993; Cortez, Zito, Lucas, 1977; Rady, Rivers, and Nowak, 1996).

Using central venous oxygen saturation as a potential target variable for haemodynamic optimisation is appropriate because central venous catheterization is routinely performed in cardiac surgery patients. Central venous oxygen saturation can be easily screened and pre-emptive measures are possible without any major changes to the infrastructure of the operative area.

CHAPTER THREE: MATERIALS AND METHODOLOGY

The aim of the study was to investigate the correlation between cerebral tissue oxygen saturation and central venous oxygen saturation during off – pump coronary artery bypass graft surgery. The principle objective of the study was to determine if a correlation existed between central venous oxygen saturation and cerebral oxygen saturation. The secondary objective was to determine whether mean arterial pressure (MAP), partial pressure of carbon dioxide ($PaCO_2$), heart rate, haematocrit, lactate and patient oxygen saturation (SpO_2) could be identified as independent predictors which influenced central venous saturation and cerebral oxygen desaturation during off-pump coronary bypass graft surgery.

The study design was a prospective, observational study to assess the correlation between cerebral oxygen saturation and central venous saturation. The study included twenty (20) patients recruited from Inkosi Albert Luthuli Central Hospital. The data collection resulted in a sample size of 160 paired measurements of cerebral and central venous saturations. Eight paired samples per patient pre and post interventions were taken. Previous studies have shown this sample size to be adequate to determine a correlation between central and cerebral venous saturations. (Mishra et al., 2003; Chernov, Efimova, Akhamedov and Lishmanov, 2006; Cua, Hoffman, Taeed, Weinstein, Gomey, Olshove and Craeven, 2004; Diegeler et al., 2000; Sakamoto, Duebenel, Laussen and Jonas, 2004). In addition, the sample size was adequate to determine whether MAP, HR, Hct, SpO_2 $PaCO_2$, and lactate were independent predictors of cerebral or central venous saturation. The patient number recruited for the study was verified by the head statistician from the Medical Research Council and

was sufficient to show statistical significance. The plan of the entire research process was set as in Appendix A and Appendix B.

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

3.1 SELECTION CRITERIA

Inclusion criteria

a) Age over 18yrs.

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

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

Exclusion criteria

a) Patients who are pregnant.

b) Stroke in patient's history or with persistent neurological residue.

c) Unilateral occlusion of carotid artery greater than 70%, bilateral occlusion of carotid artery greater than 50%.

d) Combined Cardiac procedure, ie CABG plus heart valve replacement.

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

f) Symptomatic chronic pulmonary disease requiring long term medication.

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

h) Conversion to on-pump surgery.

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 (Appendix C and D). In order to facilitate the study the research plan was presented to the Department of Cardiothoracic surgery, Anaesthetics, Perfusion and Cardiac nursing staff at Inkosi Albert Luthuli Central Hospital.

Patients who met the inclusion criteria were recruited in the cardiac ward and a 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 F and G 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 off pump coronary artery bypass surgery).

When patients where brought to theatre, the investigator cleaned the patients forehead with alcohol prep swabs thus preventing any grit, dust or sweat from affecting the readings of the electrodes . Two cerebral somasensors were placed on the patients forehead to measure left and right cerebral saturations. These sensors were linked by

cables to the cerebral monitor which displayed a graphic reading of the left and right cerebral saturations. A baseline reading of left and right cerebral saturations were recorded before the patients were anesthetized. Patients were not exposed to the discomfort of needles or the endurance of pain during the placement of electrodes. Monitoring devices included ECG electrodes, transduction of the arterial line inserted routinely by the anaesthetist for the measurement of invasive blood pressure or mean arterial pressure and pulse oximetry using a pulse oximeter to measure patient saturation was performed, baseline blood gases were also taken.

Patients were given a general anaesthetic and a central venous line (CVP) which is routinely placed into the internal jugular vein was inserted by the anaesthetist. Central venous saturation gives a global estimate of tissue perfusion and is used for the administration of fluids and drugs during surgery. The proximal port was used for the transduction and blood sampling for the measurement of central venous saturations. As patients were anesthetised during insertion of the central venous catheter no pain or discomfort was felt.

3.2 Sites from which samples were taken

Table 3.1: Sampling sites

1.Central venous saturation	($ScvO_2$) Blood gas from CVP
2.Cerebral oxygen saturation	(rSO_2) NIRS monitoring\ patches placed on the patients forehead
3. Patient saturation	(SpO_2) Oxygen saturation monitoring using a pulse oximeter placed on the patients finger
4. Heart rate	(HR) ECG monitor
5. Mean arterial pressure	(MAP) A.line (Arterial line)
6. Partial pressure of carbon dioxide ($PaCO_2$)	Blood gas
7. Haematocrit	(HCT) Blood gas
8. Lactate	Blood gas

In order to determine the second objective of the study which was to determine whether MAP, HR, Hct, SpO_2 $PaCO_2$, and lactate could be identified as independent predictors which influence central venous saturation and cerebral oxygen desaturation during off-pump coronary bypass graft surgery, they had to be measured. A baseline reading of MAP, SpO_2, HR, and cerebral saturations were recorded on a data recording spread sheet (refer to appendix H) and on computer.

Crucial time periods throughout the surgical procedure were identified. These periods represented the times when patients would be haemodynamically unstable. The time periods are listed below and constitute the sampling time periods. Recording of cerebral saturations and blood samples from the central venous line were taken during these eight time periods in order to determine the correlation between central venous and cerebral oxygen saturations.

3.3 Data collection per paired sample. (Pre and post manoeuvres)

Eight paired measurements ie Mean arterial pressure (MAP), partial pressure of carbon dioxide ($PaCO_2$), heart rate, Haematocrit (Hct), lactate, patient oxygen saturation (SpO_2), central venous saturation ($ScvO_2$) and cerebral oxygen saturation (rSO_2) per patient were taken during the following time periods:

1. Post induction and pre sternotomy.
2. Pre and post placement of swabs beneath the heart.
3. Pre and post placement of the stabilizer device (Octopus).
4. Pre and post snaring of the LAD (left anterior branch of the coronary arteries).
5. Pre anastomosis and during anastomosis of the coronary arteries.
6. Second sample during anastomosis and post anastomosis.
7. Pre and post removal of swabs from beneath the heart.
8. Pre and post transfer of the patient to the ICU bed

3.4 Blood sample collection and analysis

Blood samples where collected using heprinized blood gas syringes. The syringes were marked according to the different time periods. Blood samples were analysed using the Roche Omni S blood gas analyser located in the cardiac theatre for instant blood gas results. The results of the samples were recorded on the data recording sheet after each blood gas was analysed. Blood samples were discarded once data was recorded.

3.5 Cerebral monitoring

Cerebral monitoring constituted the use of an Invos Near- infrared spectroscopy monitor (NIRS), model 5100-C to measure cerebral oxygen delivery and consumption. Monitoring of cerebral tissue oxygenation constituted the placement of patches (electrodes) on the patient's forehead just below the hairline. 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 730 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.

3.6 Statistical methodology

The statistical significance of the data was assessed and evaluated by a statistician. SPSS version 15.0 (SPSS Inc, Chicago, Illinois, USA) and Stata version 10.0 (Statacorp, Texas, USA) were used to analyse the data. Descriptive statistics were presented as mean, standard deviation and range for quantitative normally distributed variables, while frequency and percentage were reported for categorical variables. Pearson's correlation analysis was used to determine the direction, strength and significance of the correlation between X and Y variables at each time point for the cross sectional analysis. Longitudinal analysis involved using generalized linear models to determine the effect of several independent variables on one dependant variable, taking into account the effect of time and the repeated measurements (within-subjects effects) of the dependant and independent variables over time, as well as interaction effects between time and the independent variables.

CHAPTER FOUR: RESULTS

4.1 Demographics and baseline characteristics:

Twenty participants were enrolled into the study and all 20 completed follow up. Their mean age was 57.9 years with a standard deviation of 10.7 years and a range from 35 to 76 years. The descriptive statistics for age are shown in Table 4.1.

Table 4.1: Summary statistics for age

N	Valid	20
	Missing	0
Mean		57.90
Std. Deviation		10.667
Minimum		35
Maximum		76

The study consisted of 70% males, 14 of the 20 participants were male and 6 were female as shown in Table 4.2.

Table 4.2: Gender distribution

		Frequency	Percent
Valid	Male	14	70.0
	female	6	30.0
	Total	20	100.0

The summary statistics for height and weight for patients enrolled in the study are shown in Table 4.3 The mean height was 165.15 ± 7.48 and weight 73.67 ± 7.61.

Table 4.3: Summary statistics for height and weight

		ht (cms)	Wt (kg)
N	Valid	20	20
	Missing	0	0
Mean		165.15	73.670
Std. Deviation		7.485	7.6104
Minimum		148	57.0
Maximum		176	87.6

Baseline patient monitoring parameters were taken for all patients. Mean arterial pressure (MAP), Heart rate (HR), Patient saturation (SpO_2) and cerebral oxygen saturation right (rSO_{2R}) and left (rSO_{2L}) are shown in Table 4.4. The mean values for MAP was 86.90 ± 18.71, HR was 78.30 ± 17.58, SpO_2 99.60 ± .821, rSO_{2R} was 56.65 ± 6.32 and rSO_{2L} was 56.0 ± 6.98.

Table 4.4 Baseline readings of monitoring parameters.

		MAP baseline	HR baseline	Patient saturation baseline	Cerebral oxygen saturation right at baseline	Cerebral oxygen saturation left at baseline
N	Valid	20	20	20	20	20
	Missing	0	0	0	0	0
Mean		86.90	78.30	99.60	56.65	56.00
Std. Deviation		18.719	17.586	.821	6.327	6.981
Minimum		59	56	97	47	46
Maximum		124	114	100	66	68

4.2 Correlation between Central Venous Oxygen Saturation and Cerebral Oxygen Saturation using the Cerebral Oximeter and Central Venous Blood Gases.

A cross sectional and longitudinal statistical analysis to determine the correlations between central venous oxygen saturation and cerebral oxygen saturation.

4.2.1 Cross sectional analysis

The cross sectional analysis was performed separately at each time point listed in Table 4.5 below. There were several significant moderate to strong positive correlations between central venous oxygen saturation and both right and left cerebral oxygen saturation at most time points. A p value of <0.05 was regarded as statistically significant. The time periods that showed strong positive correlations included post induction, pre-sternotomy, pre-placement of swabs, post-snaring of the LAD (Left anterior descending branch of the coronary arteries), pre-anastomosis, during anastomosis (1), during anastomosis second sample (2), post-anastomosis, pre and post swab

removal as well as post transfer to the ICU bed. The time periods listed constituted majority of the sampling periods.

In general the right cerebral side seemed to correlate better with central venous oxygen saturation than the left. The corresponding scatterplots are shown in Figures 4.1 and 4.2. These plots show that all correlations were in a positive direction but slopes varied slightly. The cluster of points is closer in Figure 4.2 (right side) than in Figure 4.1, indicating that the correlation was, in general better on the right.

Table 4.5: Cross-sectional Pearson's correlation analysis between central venous oxygen saturation and right and left cerebral oxygen saturation.

- Correlation is significant at the 0.05 level (2-tailed).

** Correlation is significant at the 0.01 level (2-tailed).

Time			Cerebral oxygen saturation left	Cerebral oxygen saturation right
1. Post induction	Central venous oxygen saturation	Pearson Correlation	.512(*)	.570(**)
		Sig. (2-tailed)	.021	.009
		N	20	20
2. Pre sternotomy	Central venous oxygen saturation	Pearson Correlation	.605(**)	.666(**)
		Sig. (2-tailed)	.005	.001
		N	20	20
3. Pre placement of swabs	Central venous oxygen saturation	Pearson Correlation	.542(*)	.533(*)
		Sig. (2-tailed)	.014	.015
		N	20	20
4. Post placement of swabs	Central venous oxygen saturation	Pearson Correlation	.416	.632(**)
		Sig. (2-tailed)	.068	.003
		N	20	20
5. Pre octopus	Central venous oxygen saturation	Pearson Correlation	.372	.470(*)
		Sig. (2-tailed)	.107	.036
		N	20	20

6. Post octopus	Central venous oxygen saturation	Pearson Correlation	.343	.388
		Sig. (2-tailed)	.139	.091
		N	20	20
7. Pre snaring of LAD	Central venous oxygen saturation	Pearson Correlation	.407	.549(*)
		Sig. (2-tailed)	.075	.012
		N	20	20
8. Post snaring	Central venous oxygen saturation	Pearson Correlation	.544(*)	.605(**)
		Sig. (2-tailed)	.013	.005
		N	20	20
9. Pre anastomosis	Central venous oxygen saturation	Pearson Correlation	.562(**)	.602(**)
		Sig. (2-tailed)	.010	.005
		N	20	20
10 During anastomosis (1)	Central venous oxygen saturation	Pearson Correlation	.557(*)	.562(**)
		Sig. (2-tailed)	.011	.010
		N	20	20
11. During anastomosis (2)	Central venous oxygen saturation	Pearson Correlation	.477(*)	.667(**)
		Sig. (2-tailed)	.034	.001
		N	20	20
12. Post anastomosis	Central venous oxygen saturation	Pearson Correlation	.468(*)	.499(*)
		Sig. (2-tailed)	.037	.025
		N	20	20
13. Pre swab removal	Central venous oxygen saturation	Pearson Correlation	.459(*)	.408
		Sig. (2-tailed)	.042	.074
		N	20	20
14. Post swab removal	Central venous oxygen saturation	Pearson Correlation	.326	.415
		Sig. (2-tailed)	.161	.069
		N	20	20
15. Pre transfer to ICU bed	Central venous oxygen saturation	Pearson Correlation	.408	.763(**)
		Sig. (2-tailed)	.074	.000
		N	20	20
16. Post transfer to ICU bed	Central venous oxygen saturation	Pearson Correlation	.485(*)	.715(**)
		Sig. (2-tailed)	.030	.000
		N	20	20

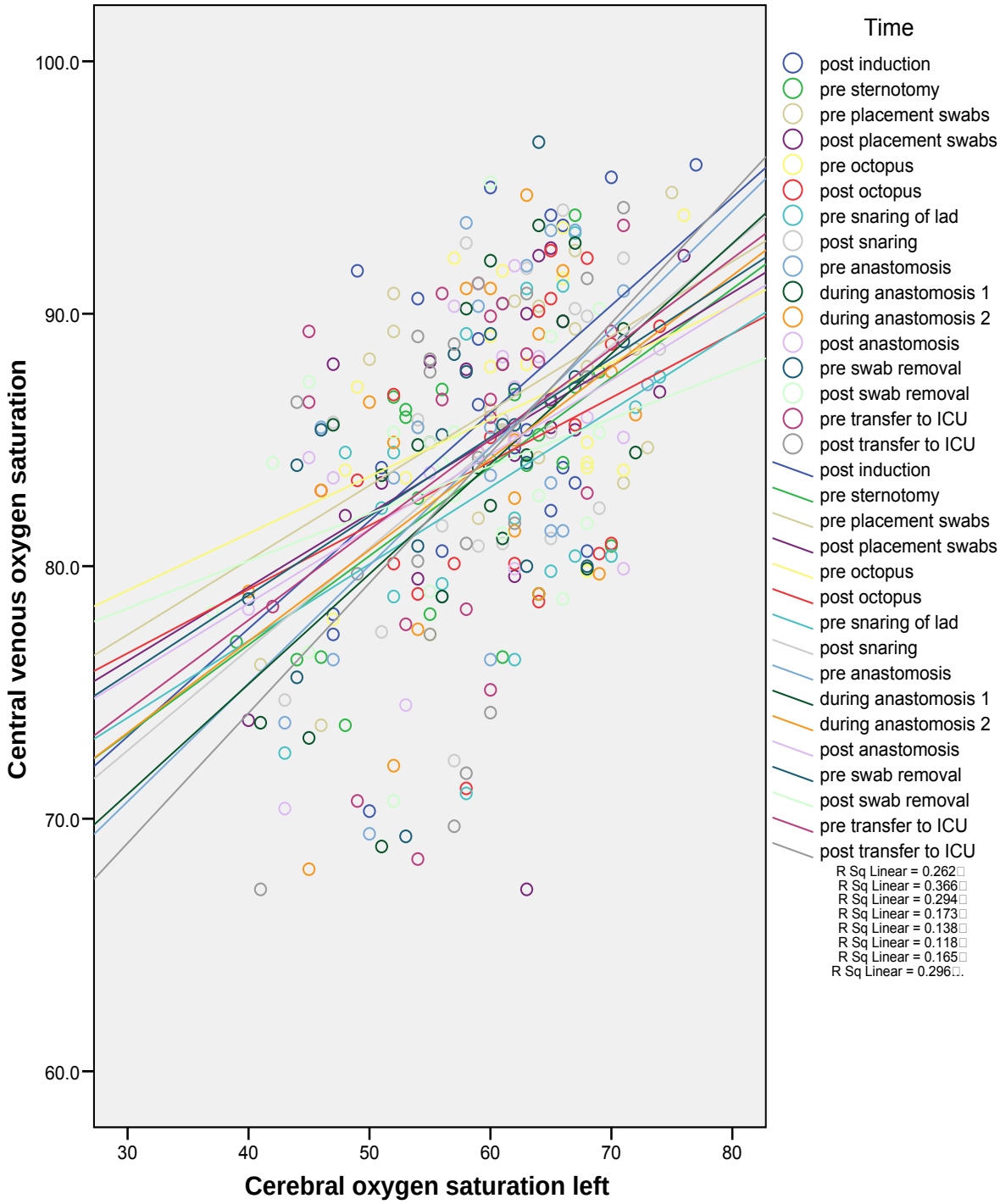


Figure 4.1: Scatterplot of Central Venous Oxygen Saturation by Cerebral Oxygen Saturation on the left side

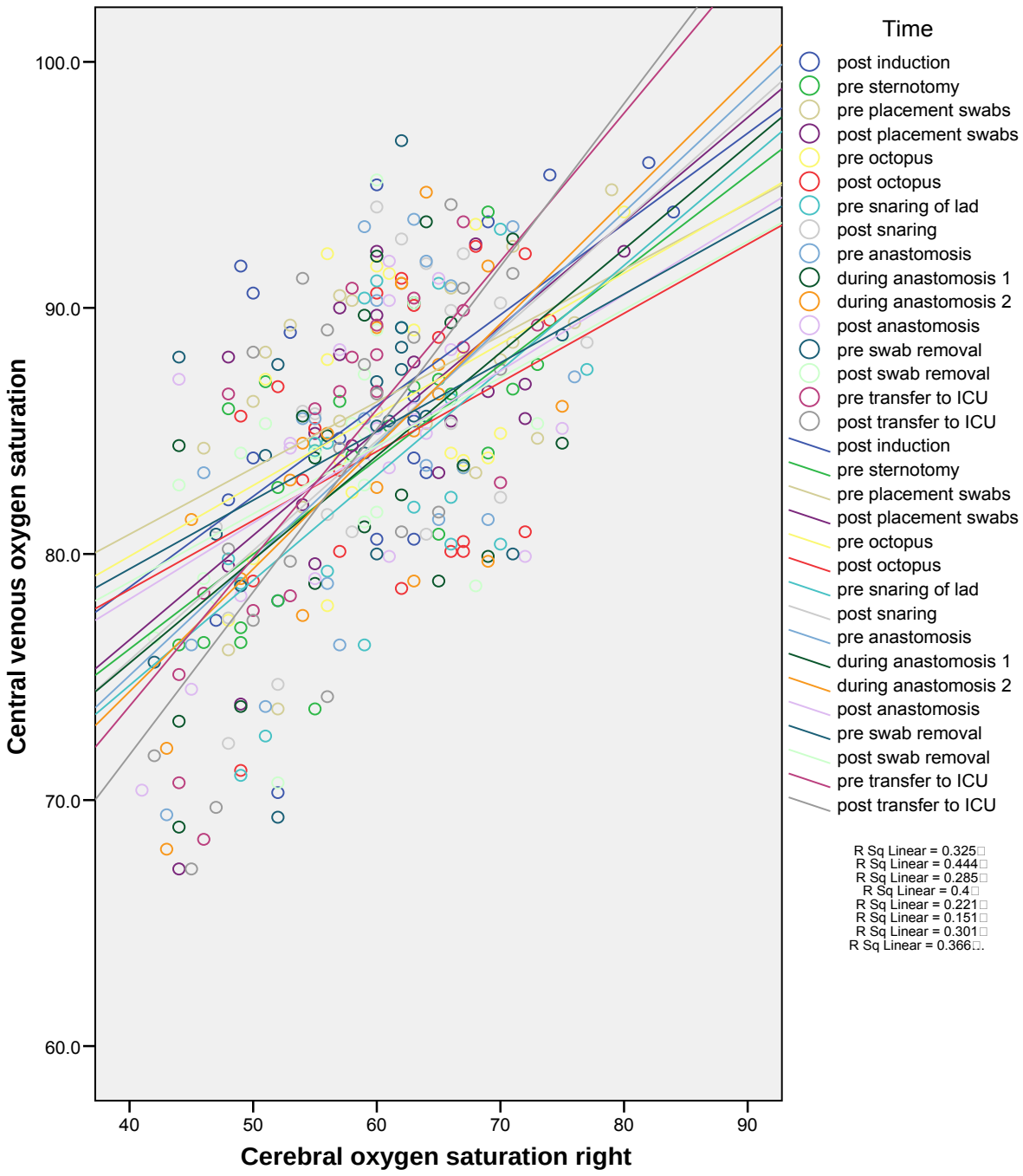


Figure 4.2: Scatterplot of Central Venous Oxygen Saturation by Cerebral Oxygen Saturation on the right side

4.2.2 Longitudinal analysis

Generalized linear models with robust standard error estimates to account for the repeated measurements over time (within subjects effects) were used to assess relationships between the dependant variable (cerebral oxygen saturation) and the independent variable (central venous oxygen saturation). The effect of time was taken into account as well as the change in central venous oxygen saturation over time (interaction effect).

Left: Cerebral oxygen saturation

Table 4.6 shows that there was no effect of time, nor interaction between time and central venous oxygen saturation on left cerebral oxygen saturation. The only significant effect was that of central venous oxygen saturation ($p<0.001$). The coefficient was 0.760, indicating that with every one unit increase in left cerebral oxygen saturation, there was a corresponding 0.760 unit increase in central venous oxygen saturation.

Table 4.6: Parameter estimates for effect of time, Central venous oxygen saturation and the interaction between time and Central venous saturation on left cerebral oxygen saturation

```
Generalized linear models                         No. of obs      =       320
Optimization     : ML                             Residual df     =       316
                                                  Scale parameter =  55.05233
Deviance         =  17396.53612                   (1/df) Deviance =  55.05233
Pearson          =  17396.53612                   (1/df) Pearson  =  55.05233

Variance function: V(u) = 1                       [Gaussian]
Link function    : g(u) = u                       [Identity]

                                                  AIC             =  6.858582
Log pseudolikelihood = -1093.373194               BIC             =  15573.75

                              (Std. Err. adjusted for 20 clusters in studyno)
------------------------------------------------------------------------------
             |               Robust
       rS02L |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
        Time |   1.063273   1.208685     0.88   0.379    -1.305707    3.432252
       Scv02 |   .7603957   .2047789     3.71   0.000     .3590365    1.161755
   timescv02 |  -.0141787   .0143129    -0.99   0.322    -.0422314     .013874
       _cons |  -3.964815   17.95858    -0.22   0.825    -39.16297    31.23335
------------------------------------------------------------------------------
```

Right: Cerebral oxygen saturation

Table 4.7 shows that there was no effect of time, nor interaction between time and central venous oxygen saturation on right cerebral oxygen saturation. The only significant effect was that of central venous oxygen saturation ($p<0.001$). The coefficient was 0.879, indicating that with every one unit increase in right cerebral oxygen saturation, there was a corresponding 0.879 unit increase in central venous oxygen saturation.

Table 4.7: Parameter estimates for effect of time, Central venous oxygen saturation and the interaction between time and Central venous saturation on right cerebral oxygen saturation

```
Generalized linear models                         No. of obs      =       320
Optimization     : ML                             Residual df     =       316
                                                  Scale parameter =  51.44828
Deviance         =  16257.65725                   (1/df) Deviance =  51.44828
Pearson          =  16257.65725                   (1/df) Pearson  =  51.44828

Variance function: V(u) = 1                       [Gaussian]
Link function    : g(u) = u                       [Identity]

                                                  AIC             =  6.790875
Log pseudolikelihood = -1082.540058               BIC             =  14434.87

                              (Std. Err. adjusted for 20 clusters in studyno)
------------------------------------------------------------------------------
             |               Robust
       rS02r |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
        Time |   .5218844   .9156741     0.57   0.569    -1.272804    2.316573
       Scv02 |   .8786812   .1711777     5.13   0.000      .543179    1.214183
   timescv02 |   -.007819   .0110006    -0.71   0.477    -.0293798    .0137418
       _cons |  -13.83622    13.9715    -0.99   0.322    -41.21985    13.54741
------------------------------------------------------------------------------
```

4.3 Independent predictors which influence cerebral desaturation during Off-pump coronary artery bypass graft surgery.

The second objective of the study was to determine whether Central venous saturation, MAP, $PcvCO_2$, HR, Hct, lactate and SpO2 could be identified as independent predictors which influence cerebral oxygen desaturation during off-pump coronary bypass graft surgery.

Left: Cerebral oxygen saturation

Table 4.8 (for left cerebral oxygen saturation) shows that after adjustment for other predictors, the estimate for $Scv0_2$ remained statistically significant but changed to a correlation coefficient of 0.457. Heart rate and $PcvCO_2$ were also significant predictors. The other variables were not significant predictors of left cerebral oxygen saturation.

Table 4.8: GLM parameter estimates for left cerebral oxygen saturation – full model

```
Iteration 0:   log pseudolikelihood =  -1021.702

Generalized linear models                         No. of obs      =       319
Optimization     : ML                             Residual df     =       309
                                                  Scale parameter =  36.58463
Deviance         =  11304.65041                   (1/df) Deviance =  36.58463
Pearson          =  11304.65041                   (1/df) Pearson  =  36.58463

Variance function: V(u) = 1                       [Gaussian]
Link function    : g(u) = u                       [Identity]

                                                  AIC             =  6.468351
Log pseudolikelihood =  -1021.70204               BIC             =  9523.206

                              (Std. Err. adjusted for 20 clusters in studyno)
------------------------------------------------------------------------------
             |               Robust
       rS02L |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
        Time |  -.1546179   .1072311    -1.44   0.149    -.3647871    .0555512
       Scv02 |   .4754806   .1313621     3.62   0.000     .2180156    .7329455
          HR |   .1335291   .0498328     2.68   0.007     .0358586    .2311996
         MAP |  -.0500465   .0463906    -1.08   0.281    -.1409705    .0408775
      PcvCO2 |   .3780011   .1662311     2.27   0.023     .0521941    .7038081
         HCT |   .2715761   .3087265     0.88   0.379    -.3335167    .8766689
        lact |    .294011   1.582724     0.19   0.853    -2.808072    3.396093
        fio2 |   9.880291   7.967749     1.24   0.215     -5.73621    25.49679
  Sp02baseline |  -1.508473   1.137218    -1.33   0.185     -3.73738    .7204345
       _cons |   129.9531   123.4517     1.05   0.292    -112.0078    371.9141
------------------------------------------------------------------------------
```

After backward stepwise elimination of non significant variables in the model, Table 4.9 shows the reduced model. Time, $Scv0_2$, HR, $PcvCO_2$ and baseline Sp02 were significant predictors of left cerebral oxygen saturation. The final predictive mode was:

rS02L = (-0.221*time) + (0.530*$Scv0_2$) + (0.110*HR) + (0.405*$PcvCO_2$) + (-2.458* Sp02 baseline) + 234.04

Table 4.9: GLM parameter estimates for left cerebral oxygen saturation – reduced model

```
Iteration 0:   log pseudolikelihood = -1032.5205

Generalized linear models                         No. of obs      =       319
Optimization     : ML                             Residual df     =       313
                                                  Scale parameter =  38.65181
Deviance         =  12098.01699                   (1/df) Deviance =  38.65181
Pearson          =  12098.01699                   (1/df) Pearson  =  38.65181

Variance function: V(u) = 1                       [Gaussian]
Link function    : g(u) = u                       [Identity]

                                                  AIC             =    6.5111
Log pseudolikelihood = -1032.520506               BIC             =  10293.51

                              (Std. Err. adjusted for 20 clusters in studyno)
------------------------------------------------------------------------------
             |               Robust
       rS02L |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
        Time |  -.2208781    .083232    -2.65   0.008    -.3840098   -.0577463
       Scv02 |   .5303714    .145087     3.66   0.000     .2460062    .8147366
          HR |   .1100165   .0491533     2.24   0.025     .0136779    .2063552
       PcvC02 |   .4047435   .1442157     2.81   0.005      .122086     .687401
 Sp02 baseline |   -2.45811   1.099555    -2.24   0.025    -4.613197   -.3030218
       _cons |   234.0432   117.7173     1.99   0.047     3.321529    464.7649
------------------------------------------------------------------------------
```

Right: Cerebral oxygen saturation

Table 4.10 shows that $Scv0_2$ remained a significant predictor of right cerebral oxygen saturation but the adjusted estimate changed to a correlation coefficient of 0.683. $PcvCO_2$ was the other significant predictor. All others were not significantly independently associated with right cerebral oxygen saturation.

Table 4.10: GLM parameter estimates for right cerebral oxygen saturation – full model

```
Iteration 0:   log pseudolikelihood =  -992.5079

Generalized linear models                         No. of obs      =       319
Optimization     : ML                             Residual df     =       309
                                                  Scale parameter =  30.46544
Deviance         =  9413.819949                   (1/df) Deviance =  30.46544
Pearson          =  9413.819949                   (1/df) Pearson  =  30.46544

Variance function: V(u) = 1                       [Gaussian]
Link function    : g(u) = u                       [Identity]

                                                  AIC             =  6.285316
Log pseudolikelihood = -992.5078995               BIC             =  7632.376

                              (Std. Err. adjusted for 20 clusters in studyno)
------------------------------------------------------------------------------
             |               Robust
       rS02r |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
        Time |  -.1807464    .107024    -1.69   0.091    -.3905096    .0290168
       Scv02 |   .6827138   .1327006     5.14   0.000     .4226254    .9428022
          HR |   .0392158   .0363779     1.08   0.281    -.0320837    .1105152
         MAP |  -.0176225   .0256246    -0.69   0.492    -.0678459    .0326008
      PcvC02 |   .5310485   .1225615     4.33   0.000     .2908325    .7712646
         HCT |    .101353    .154064     0.66   0.511    -.2006068    .4033128
        lact |  -.5264567   1.382485    -0.38   0.703    -3.236078    2.183165
        fio2 |  -5.231776   7.409516    -0.71   0.480    -19.75416    9.290609
Sp02baseline |  -2.697376   1.016959    -2.65   0.008    -4.690578   -.7041733
       _cons |   247.3634   109.6034     2.26   0.024     32.54466    462.1822
------------------------------------------------------------------------------
```

After backward stepwise elimination of non significant variables in the model, Table 4.11 shows the reduced model. Scv02, $PcvCO_2$ and baseline $Sp0_2$ were significant predictors of right cerebral oxygen saturation. The final predictive mode was:

rS02r = (-0.171*time) + (0.674*$Scv0_2$) + (0.591*$PcvCO_2$) + (-2.6* $Sp0_2$ baseline) + 236.6

Table 4.11: GLM parameter estimates for right cerebral oxygen saturation – reduced model

```
Iteration 0:   log pseudolikelihood = -999.53189

Generalized linear models                         No. of obs      =       319
Optimization     : ML                             Residual df     =       314
                                                  Scale parameter =  31.33008
Deviance         =   9837.64542                   (1/df) Deviance =  31.33008
Pearson          =   9837.64542                   (1/df) Pearson  =  31.33008

Variance function: V(u) = 1                       [Gaussian]
Link function    : g(u) = u                       [Identity]

                                                  AIC             =  6.298006
Log pseudolikelihood = -999.5318933               BIC             =  8027.375

                              (Std. Err. adjusted for 20 clusters in studyno)
------------------------------------------------------------------------------
             |               Robust
       rS02r |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
        Time |  -.1713635   .0951042    -1.80   0.072    -.3577643    .0150373
       Scv02 |   .6738433   .1148854     5.87   0.000     .4486721    .8990145
      PcvCO2 |   .5914112   .0872512     6.78   0.000     .4204019    .7624205
Sp02baseline |   -2.59987   .8191947    -3.17   0.002    -4.205462   -.9942779
       _cons |   236.5554   86.62489     2.73   0.006     66.77378    406.3371
------------------------------------------------------------------------------
```

4.4 Other predictors of cerebral desaturation

The third objective of the study was to determine whether other factors in the absence of central venous oxygen saturation could be identified as independent predictors which influence cerebral oxygen desaturation during off-pump coronary bypass graft surgery.

Excluding central venous oxygen saturation from the models resulted in worse fitting overall models. However, there were still several parameters which remained significant predictors of left and right cerebral oxygen saturation.

Table 4.12 shows the predictors of left cerebral oxygen saturation in the absence of central venous oxygen saturation. However, the R^2 (coefficient of determination) value for this model was low (27.8%) compared with the R^2 (coefficient of determination) value for the model in Table 4. 9 which was 46.4%.

Left: Cerebral oxygen saturation

Table 4.12: GLM parameter estimates for left cerebral oxygen saturation (excluding central venous oxygen saturation)– reduced model

```
Iteration 0:   log pseudolikelihood = -1079.9947

Generalized linear models                         No. of obs      =       319
Optimization     : ML                             Residual df     =       315
                                                  Scale parameter =  51.72121
Deviance         =  16292.18256                   (1/df) Deviance =  51.72121
Pearson          =  16292.18256                   (1/df) Pearson  =  51.72121

Variance function: V(u) = 1                       [Gaussian]
Link function    : g(u) = u                       [Identity]

                                                  AIC             =  6.796205
Log pseudolikelihood = -1079.994699               BIC             =  14476.15

                              (Std. Err. adjusted for 20 clusters in studyno)
------------------------------------------------------------------------------
             |               Robust
       rS02L |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
        Time |  -.3134622   .0871061    -3.60   0.000     -.484187   -.1427373
          HR |   .1433838   .0570008     2.52   0.012     .0316642    .2551033
      PcvCO2 |   .5391077   .1576439     3.42   0.001     .2301313    .8480841
       _cons |   26.04692   9.705394     2.68   0.007     7.024693    45.06914
------------------------------------------------------------------------------
```

Table 4.13 shows the predictors of right cerebral oxygen saturation in the absence of central venous oxygen saturation. However, the R^2 (coefficient of determination) value for this model was low (38.8%) compared with the R^2 (coefficient of determination) value for the model in Table 4.11 which was 59.8%.

Right: Cerebral oxygen saturation

Table 4.13: GLM parameter estimates for right cerebral oxygen saturation (excluding central venous oxygen saturation)– reduced model

```
Iteration 0:   log pseudolikelihood = -1066.5446

Generalized linear models                         No. of obs      =       319
Optimization     : ML                             Residual df     =       315
                                                  Scale parameter =  47.53856
Deviance         =    14974.646                   (1/df) Deviance =  47.53856
Pearson          =    14974.646                   (1/df) Pearson  =  47.53856

Variance function: V(u) = 1                       [Gaussian]
Link function    : g(u) = u                       [Identity]

                                                  AIC             =  6.711878
Log pseudolikelihood =  -1066.54456               BIC             =  13158.61

                              (Std. Err. adjusted for 20 clusters in studyno)
------------------------------------------------------------------------------
             |               Robust
       rS02r |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
        Time |   -.263607    .103445    -2.55   0.011    -.4663554   -.0608586
      PcvC02 |   .7292329   .1314894     5.55   0.000     .4715184    .9869473
Sp02baseline |  -2.458486   .9682023    -2.54   0.011    -4.356128   -.5608443
       _cons |    274.017   95.83457     2.86   0.004     86.18472    461.8493
------------------------------------------------------------------------------
```

Table 4.14 and 4.15 below shows the model for the basic monitoring parameters used during cardiac surgery, these included Time, Patient saturation, Heart rate, Mean arterial pressure and fio2.Central venous was excluded from this model. Patient saturation and heart rate were the only significant predictors of left and right cerebral oxygen saturation.

Left: Cerebral oxygen saturation

TABLE 4:14: GLM parameter estimates for left cerebral saturation (excluding central venous saturation)

Model of basic parameters monitored during surgery

```
. glm rS02L (Time Sp02 HR MAP fio2)

Iteration 0:   log pseudolikelihood = -1105.1038

Generalized linear models                         No. of obs      =       320
Optimization     : ML                             Residual df     =       314
                                                  Scale parameter =  59.61752
Deviance         =  18719.90147                   (1/df) Deviance =  59.61752
Pearson          =  18719.90147                   (1/df) Pearson  =  59.61752

Variance function: V(u) = 1                       [Gaussian]
Link function    : g(u) = u                       [Identity]

                                                  AIC             =  6.944399
Log pseudolikelihood = -1105.103769               BIC             =  16908.65

                              (Std. Err. adjusted for 20 clusters in studyno)
------------------------------------------------------------------------------
             |               Robust
       rS02L |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
        Time |  -.3564793   .0982828    -3.63   0.000    -.5491101   -.1638485
        Sp02 |   2.664788   .7003542     3.80   0.000     1.292119    4.037457
          HR |   .1648324   .0800553     2.06   0.039     .0079268    .3217379
         MAP |   -.045692   .0693346    -0.66   0.510    -.1815853    .0902012
        fio2 |   11.69602   9.359985     1.25   0.211    -6.649218    30.04125
       _cons |  -222.3696   71.40647    -3.11   0.002    -362.3237   -82.41552
------------------------------------------------------------------------------
```

Right: Cerebral oxygen saturation

TABLE 4:15: GLM parameter estimates for right cerebral saturation (excluding central venous saturation)

Model of basic parameters monitored during surgery

```
. glm rS02r Time Sp02 HR MAP fio2

Iteration 0:   log pseudolikelihood = -1138.1559

Generalized linear models                         No. of obs      =       320
Optimization     : ML                             Residual df     =       314
                                                  Scale parameter =  73.29741
Deviance         =   23015.3868                   (1/df) Deviance =  73.29741
Pearson          =   23015.3868                   (1/df) Pearson  =  73.29741

Variance function: V(u) = 1                       [Gaussian]
Link function    : g(u) = u                       [Identity]

                                                  AIC             =  7.150974
Log pseudolikelihood = -1138.155893               BIC             =  21204.13

                              (Std. Err. adjusted for 20 clusters in studyno)
------------------------------------------------------------------------------
             |               Robust
       rS02r |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
        Time |  -.3413998   .1130394    -3.02   0.003    -.5629529   -.1198467
        Sp02 |   2.558732   .6171581     4.15   0.000     1.349125     3.76834
          HR |   .0770977   .0830689     0.93   0.353    -.0857143    .2399097
         MAP |  -.0081556   .0518702    -0.16   0.875    -.1098194    .0935082
        fio2 |   1.271085    9.09535     0.14   0.889    -16.55547    19.09764
       _cons |  -200.3009   61.04104    -3.28   0.001    -319.9391   -80.66267
------------------------------------------------------------------------------
```

CHAPTER FIVE: DISCUSSION

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 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). However, not all studies of cerebral oximetry have indicated clinical benefit. In a review of cerebral oximetry by Taillefer and Denault, the authors tabulated the results of NIRS studies based on literature search as of February 2004. No discrimination was made based on the device being investigated and they concluded that evidence of clinical effectiveness was lacking (Taillefer and Denault, 2005).

In this cohort of patients undergoing off pump coronary artery bypass (OPCAB) graft surgery, the prospective investigation was to determine the correlation between central venous saturation ($ScvO_2$) and cerebral oxygen saturation (rSO_2). If a correlation could be shown then central venous saturation could be used as a surrogate measure of cerebral saturation to guide therapy during off-pump coronary artery bypass graft surgery. This is the first study analysing the correlation between $ScvO_2$ and rSO_2 perioperatively in a well defined group of patients undergoing OPCAB surgery at different points in time and correlating $ScvO_2$ to rSO_2.

The cross sectional analysis that was performed at each time point showed several significant moderate to strong positive correlations between central venous saturation and both right and left cerebral saturation (Table 4.5). A p value of < 0.05 was considered statistically significant. Our results showed strong correlations in majority of the 16 time periods used for sampling. The high value of the correlation coefficient suggest that $ScvO_2$ parallels rSO_2 sufficiently and therefore $ScvO_2$ could be used as a surrogate marker of rSO_2.

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 venous saturation measurement can improve outcome. One large trial in septic patients measuring central venous 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). In a study conducted by Daubeney and colleagues (1996), venous oxygen saturation sampled at the jugular bulb ($SjvO_2$) and rSO_2 generally correlated well. Jugular bulb oxygen saturation represents the average saturation obtained from cranial venous drainage (Huang, Okudera, Ohta and Robbins, 1984). Although Daubeney demonstrated a good correlation, discrepancies appeared at the extremes of saturation. The authors noted that the magnitude and the direction of the difference between rSO_2 and SjO_2 varied with the absolute values of SjO_2. In this case for high values of SjO_2, rSO_2 is low, whereas at low values of SjO_2, rSO_2 is disproportionately high. Thus, severe desaturation of jugular venous blood would not always be recognised. In the study rSO_2 rarely rose to more than 90%. Therefore it

would be difficult to determine when cerebral metabolism ceases during profound hypothermia. In our study hypothermia would have no bearing since OPCAB is done at normothermia. Jugular bulb oxygen saturation monitoring during ischaemia is however unreliable, since its accurate determination requires the sampling of continuously flowing blood (de Vries, Visser, Bakker and Diephuis, 1997).

Baseline values for right cerebral saturation (56.65 ± 6.32) and left cerebral saturation (56.00 ± 6.98) taken in our 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 who noted that cerebral saturation was closely correlated to cardiac index (Konishi and Kikuchi, 1995). 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 OPCAB surgery.

The duration of surgery does not appear to conversely affect the correlation between rSO_2 and $ScvO_2$ in this study. Left and right cerebral saturation was not affected by

time, or interactions between time and central venous oxygen saturation on left and right cerebral saturation. Indeed the only independent predictor of rSO_2 was the venous oxygen saturation ($p<0.001$) as described in table 4.6. and 4.7. A coefficient of 0.760, indicated that with every one unit increase in left cerebral oxygen saturation, there was a corresponding 0.760 unit increase in central venous oxygen saturation. A coefficient of 0.879, also indicated that with every one unit increase in right cerebral oxygen saturation, there was a corresponding 0.879 unit increase in central venous oxygen saturation.

In the present study, right cerebral measurements showed a higher correlation to central venous saturation at most sampling points than the left cerebral saturation. Shinoura, Yauada, (2003), found that there was a slight increase in right sided cerebral saturations in patients placed in the head down position. A study conducted by Andropoulos et al. (2004), found decreased rSO_2 on the left side during regional low flow perfusion. The authors attributed this to inadequate flow across the circle of Willis secondary to anatomic variations or abnormalities.

In this study the cluster of points are closer on the right side (Figure 4.2) as compared the left (Figure 4.1), indicating that the correlation was higher on the right. These findings merit increased and closer monitoring of left cerebral saturation by clinicians. The aetiology of a "lower" left rSO_2 values in these patients is unknown.

Indications for cerebral monitoring should include patients presenting with bilateral carotid artery disease. Misra, Stark, Dujovny, Wideman and Ausman, (1997), demonstrated marked position related declines in rSO2 in patients with carotid stenosis. Cerebral oximetry has been widely used in the detection of regional cerebral

ischaemia from carotid occlusion during carotid endarterectomy (William, Mead, Picton, Farrell, Mortimer and McCollum, 1995; Carlin, McGraw, Calimlim and Mascia, 1998; Lee, Melnyk and Kuskowski, 2000). Williams studied the effect of contralateral carotid stenosis on oxygen saturation (rSO_2) of both cerebral hemispheres monitored by reflective near-infrared spectroscopy (NIRS) during carotid surgery. Near infrared spectroscopy was compared to ipsilateral transcranial Doppler ultrasonography (TCD) of the middle cerebral artery and jugular bulb venous oxygen saturation ($JvSO_2$) in 54 patients undergoing carotid endarterectomy. He noted that the greatest change in rSO_2 occurred on the operative side, as opposed to the side of the carotid artery occlusion. However, a contralateral carotid artery occlusion did not reliably predict the need for a shunt. He, therefore, concluded that cerebral monitoring remained essential, although only required on the operative side. In the study conducted by Carlin et al. (1998), regional cerebral oxygen saturation (rSO2) was monitored continuously during CEA. He found that cerebral rSO2 decreased significantly on carotid cross-clamp in patients undergoing awake CEA. Haemodynamically stable patients demonstrated no evidence of clinically important brain ischaemia when rSO_2 decreased to 63% (mean decrease of 7.2%). Two haemodynamically unstable patients had evidence of global brain ischaemia when rSO_2 was less than 48% (mean decrease of 36%). The findings suggest that cerebral oximetry reflects CBF, and it may be an effective, noninvasive method of monitoring regional cerebral oxygenation during CEA. Significant reductions in regional rSO_2 may be tolerated without evidence of brain ischaemia. The authors suggested that further studies are needed to define a rSO_2 threshold that reflect clinically important ischaemia.

Lee, Melnyk and Kuskowski, (2000), measured cerebral oximetry and internal carotid artery stump pressures during carotid endarterectomy to assess whether cerebral oximetry could be used as a noninvasive and reliable alternative to monitor cerebral blood flow and the need for selective carotid artery shunting. Carotid endarterectomy procedures were performed in 27 patients wherein a cerebral oximeter was placed on the ipsilateral forehead preoperatively. Stump pressure data as well as cerebral oximetry readings at baseline, and before and after carotid artery clamping were gathered. The differences between baseline and clamped carotid artery oximetry readings were calculated for each subject and divided by the baseline reading to provide an adjusted measure of percent oximetry change. This normalized percent change in cerebral oximetry readings was then correlated with stump pressure. Carotid artery stump pressures correlated closely with the normalized change in cerebral oximetry readings (r = -0.57, p = 0.002). There was no morbidity or mortality from the 27 carotid endarterectomy procedures performed. The authors deduced that carotid endarterectomy can be performed safely with cerebral oximetry as a simple, noninvasive, and reliable alternative to internal carotid artery stump pressure measurements in determining the need for selective carotid artery shunting.

Samra et al. (2002), observed that selective occlusion of the external carotid artery produced an average rSO_2 decrease of 3%. Declines of more than 10% were associated with neurologic evidence of focal ischaemia. In a study conducted by Richard, Hugh, Markus, (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. In a number of their cases this technique identified impaired autoregulation in patients in whom CO_2 reactivity was in the normal range. Patients for CABG are usually associated with a 3-12% incidence of carotid artery stenosis. The presence of carotid artery stenosis increases the risk of stroke after CABG (Salisdis, Latter, Steinmetzok, Balir and Graham, 1995). Due to low pressure circulation and heparin dosing during on pump CABG, some surgeons prefer carotid endarterectomy (CEA) and OPCAB in one sitting (Meharwal, Mishra and Trehan, 2002). A second limitation to our study was that patients were not screened, using Doppler ultrasound for carotid bruit.

The correlation between central venous saturation and cerebral saturation in this study indicate that central venous saturation can be used as a surrogate measure of cerebral oxygen saturation, for neurologically asymptomatic patients undergoing OPCAB.

Baseline values for mean arterial pressure (MAP) 86.90 ± 18.7, heart rate (HR) 86.90 ± 18.7 and patient saturation (SpO_2) 99.6 ± 0.82 were also taken. The variables, such as, MAP, HR, partial pressure of carbon dioxide central venous ($PcvCO_2$), haematocrit, lactate, and patient saturation (SpO_2) were assessed to determine whether they were independent predictors that influenced cerebral oxygen desaturation during the OPCAB procedure. Haemodynamic deterioration during coronary anastomosis is the main problem

of the OPCAB procedure and numerous studies have reported the changes of haemodynamic variables before and after anastomosis. The exact mechanism that results in deterioration in cardiac function on manipulation of the heart is not fully understood. Factors such as right ventricular outflow tract obstruction and altered left ventricular geometry leading to mechanical interference of the pumping action lead to reductions in stroke volume, cardiac index and MAP (Shinn et al., 2004). Murkin et al. (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 MAP is maintained. When associated with significant decrease in cardiac output, whether due to arrhythmia, dislocation of the heart, subclinical ischaemia, or a combination of these factors, blood flow to the brain may be significantly compromised.

This study aimed to determine the effects of haemodynamic change during OPCAB on MAP, HR, $PcvCO_2$, haematocrit, lactate, and SpO_2. Although haemodynamic variables have been associated with decreased cerebral blood flow, the study would show HR as an independent predictor of rSO_2 on the left. The results in table 4.8 for left cerebral saturation showed that after adjustment for other predictors, the estimate for $ScvO_2$ remained statistically significant but changed to a correlation coefficient of 0.457. Heart rate and $PcvCO_2$ were also significant predictors. Other variables were not significant predictors of left cerebral saturation. Table 4.10 showed that $ScvO_2$ also remained a significant predictor of right cerebral oxygen saturation but the adjusted estimate changed to a correlation coefficient of 0.683. $PcvCO_2$ and baseline SpO_2 were the other significant predictors. Others were not significant.

The management of patients undergoing OPCAB has generally been focused on the maintenance of HR, MAP and cardiac rhythm between stable limits during coronary anastomosis (Doolan, Jones, Kalman, Buxton and Tonkin, 1997; Ascione, Caputo, Calori, Lloyd, Underwood and Angelini, 2000; Balser, 2001). In this study MAP was not a predictor of cerebral saturation probably due to the principle of cerebral autoregulation which states that over a wide mean arterial pressure range (50 to 150 mmHg), cerebral blood flow remains independent of perfusion pressure. (Liu, Sun and Hang, 1998; Jalowiecki, Ploro and Dzlurdzlk, 1998). Pressure autoregulation can be described as the ability of the brain to maintain total and regional CBF despite large changes in systemic arterial blood pressure, independently of flow-metabolism coupling (Hindman, Dexter, Ryu, Smith and Cutkomp, 1994).

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 >160mmHg 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.

Haematocrit was not a predictor of cerebral saturation in this study. However, emerging data 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% . The brain compensates for reduced arterial oxygen content by increasing oxygen extraction and cerebral blood flow (Cook et al, 1998). Off-pump coronary artery bypass patients are not subjected to cardiopulmonary bypass and the effects of haemodilution, which may explain why haematocrit was not identified as an independent predictor of rSO_2.

Lactate was also not a predictor of cerebral saturation in this study. Blood lactate concentration has proven to be one of several reliable parameters for evaluating haemodynamic states. In general the increase of lactate indicates diminishing tissue perfusion and oxygen delivery (Charpie, Dekson and Goldberg, 2000). In the absence of oxygen, anaerobic metabolism remains the only manner in which ATP synthesis can continue. The end result of anaerobic metabolism is the generation of lactate.

Partial pressure of carbon dioxide was identified as a major predictor of cerebral saturation in this study. 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 (MCAV) and rSO_2. They observed that hypoxia was associated with a reduction in rSO_2, whereas during hypercapnia both rSO_2 and MCAV increased. Clinically, partial pressure of carbon dioxide is not important due to the maintenance of this parameter within the normal range by mechanical ventilation during OPCAB surgery.

The mean age of patients enrolled in this study was 57.9 ± 10.66 years (Table 4.2). The mean height and weight was 165.15 ± 7.48 and 73.67 ± 7.61 respectively. The study consisted of 14 male and 6 female participants who were enrolled into the study (Table 4.1). Seventy percent of the participants were male. In a recent study Kishi et al. (2003), examined surgical patient demographic influences on rSO_2. The measure appeared to be independent of weight, height, head size, or gender although it was negatively correlated with age and positively correlated with haemoglobin concentration. In contrast Misra et al. (1998), 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.

Removing central venous oxygen saturation resulted in worse fitting overall models (Table 4.14 and 4.15). However, there were still parameters which remained

significant predictors of left and right cerebral oxygen saturation, namely, heart rate (HR) and patient saturation (SpO_2). However, the correlation is too poor to be considered clinically useful. Therefore, central venous saturation should be considered a minimum requirement for surrogate monitoring of cerebral oxygenation.

CHAPTER SIX: CONCLUSION

The results of the study show that strong positive correlations between central venous saturation and cerebral saturation exist in majority of the sampling time periods throughout the study. Right and left cerebral saturations are not affected by time or interactions between time and central venous saturation. The positive correlation indicates that central venous saturation can be used as a surrogate measure of cerebral oxygen saturation during OPCAB surgery. The absence or poor correlation of MAP, HR, $PcvCO_2$, heamatocrit, lactate, and patient saturation suggests that insertion of a central venous line (CVP) during OPCAB should be a fundamental clinical requirement. During cardiac surgery central venous monitoring should be included as one of the basic requirements, together with other monitoring parameters. Although the management of patients undergoing OPCAB has generally focused on the maintenance of HR, MAP and cardiac rhythm between stable limits (Doolan et al., 1997; Ascione et al., 2000; Balser et al., 2001), these parameters do not indicate global oxygen consumption. The exclusion of central venous saturation from the model to determine other predictors of cerebral desaturation resulted in poor correlations between cerebral saturation and other variables. It is with this clinical evidence that we highlight the importance of using this variable as a tool to guide therapy.

Remarkable progress has 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 greater comorbidity. The aetiology of neurologic injury is multifactorial, with hypoperfusion and cerebral embolism playing the largest roles. Off-pump coronary artery bypass has been shown to reduce the number of microemboli generated during coronary revascularization. Large scale retrospective studies demonstrate that the risk of stroke may be reduced in high risk patients. However prospective randomized trials examining neurocognitive outcome associated with OPCAB have shown conflicting results when compared with CABG (Hogue et al., 2008; Roach et al., 1996). This sets the basis for ongoing trials to identify potential risk and to further minimize neurologic complications associated with CABG.

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 Doppler ultrasound, as a technical strategy, to evaluate patients with carotid bruit was not implemented in this study. Patients identified with carotid artery disease are at increased risk for neurological outcomes during cardiac surgery and this lends itself to the possibility of patients having cerebrovascular disease. These patients fall into a higher risk category, therefore, indications for cerebral monitoring would be strongly supported.

Finally, patients undergoing CABG and OPCAB at Inkosi Albert Luthuli Central Hospital, Cardiothoracic unit, should undergo periodic neurodevelopmental surveillance for early detection of neurocognitive impairment so that rehabilitation could be instituted early. The cerebral oximeter was easy to use and provided reliable operation during the trial. Its role in clinical monitoring remains to be defined by additional trials. However, further investigations are necessary to develop diagnostic and therapeutic strategies to reduce mortality and morbidity and to conserve resources.

CHAPTER SEVEN: REFERENCES

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APPENDICES

APPENDIX A

FLOW CHART

APRIL – JUNE 2008 (3 MONTHS)

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

JULY – AUGUST 2008 (2 MONTHS)

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

SEPT 2008 – OCT 2008 (2 MONTHS)

Collection of blood samples from central venous lines.
Checking parameters
Measuring cerebral oximetry

NOV 2008 – NOV 2008 (1 MONTHS)

Analysing
Presentation of results

NOV 2008 – DEC 2008 (1 MONTHS)

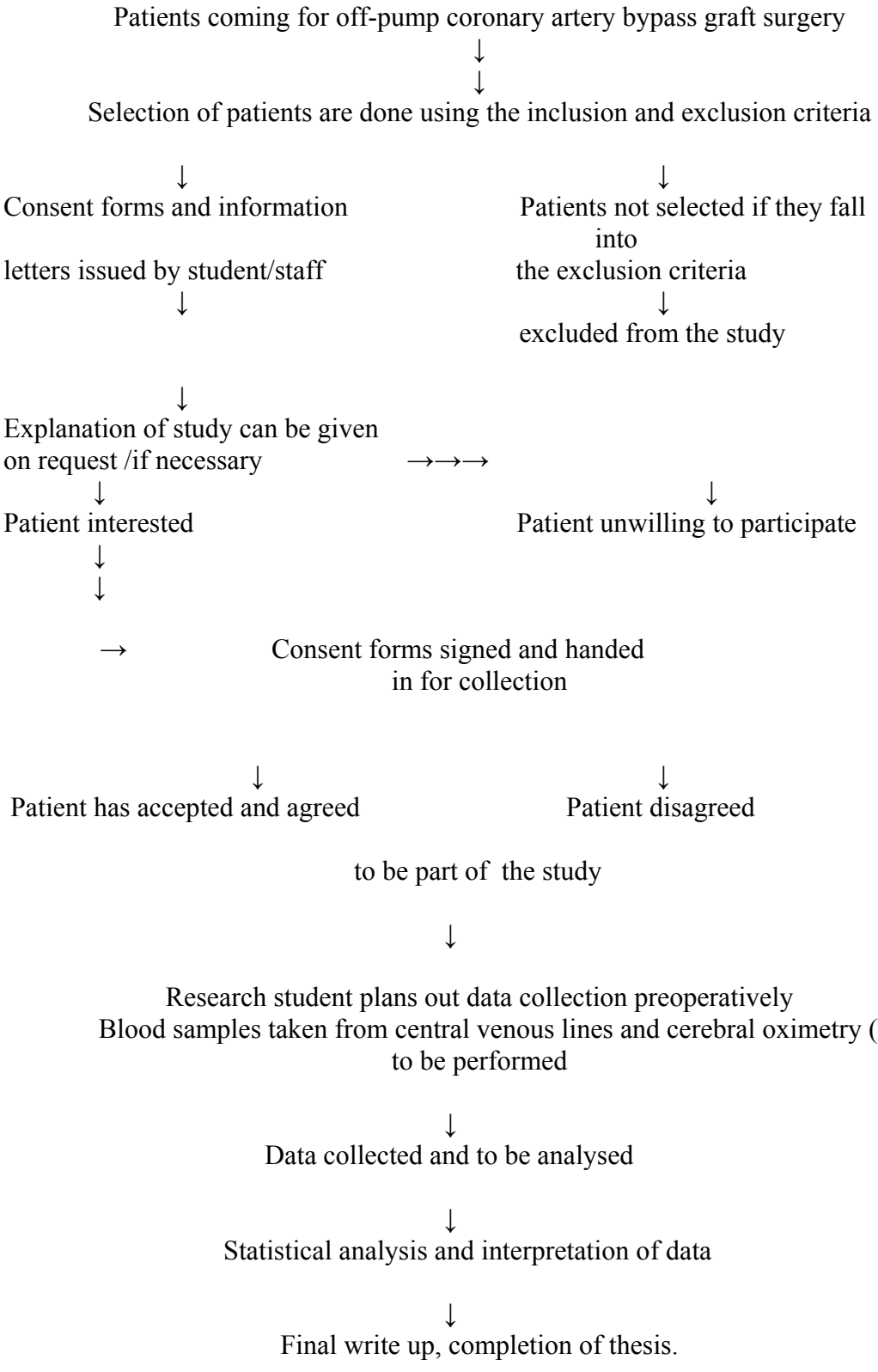
Bringing all information together

DEC 2008– FEB 2009 (3 MONTHS)

Final write up
Correction of all information

APPENDIX B

FLOW CHART- SUMMARISING THE RESEARCH PROCESS



APPENDIX C

DURBAN UNIVERSITY of TECHNOLOGY

BIOMEDICAL AND CLINICAL TECHNOLOGY

FACULTY OF HEALTH SCIENCES

Prof. A Reddi

DEPT OF CARDIOTHORACIC SURGERY
Inkosi Albert Luthuli Central Hospital

DATE:23/06/2008

RE: MASTERS: CLINICAL TECHNOLOGY - Mr Y Harilall (Student No. 20150784)

This serves to inform that MrY Harilall's proposal to conduct the Masters Degree in Clinical Technology (Perfusion) served the Faculty of Health Sciences Research Ethics Committee on the 2nd of June 2008.

Approval has been granted for him to continue with the research investigation.

Yours Sincerely,

Dr J.K. Adam
Chairperson: Faculty of Health Sciences Research Committee

APPENDIX D

DURBAN UNIVERSITY of TECHNOLOGY

04 September 2008
Student No: 20150784

Mr Y Harilall
1126 Quarry Road
Clare Estate
Durban
4091

Dear Mr Harilall

MASTER'S DEGREE IN TECHNOLOGY: CLINICAL TECHNOLOGY

We are pleased to advise that:

1. the Higher Degrees Committee at a meeting dated 28 August 2008 approved the following:

   (i) your research proposal and **dissertation title**, being:

Correlation between cerebral tissue oxygen saturation and central venous oxygen saturation during off-pump coronary artery bypass graft surgery.

Please note that ANY proposed changes in the dissertation title require the approval of your supervisor and the Faculty Research Committee.

   (ii) Supervisor - Dr J K Adam
   Joint Supervisor - Prof A Reddi

2. your request for funding totalling **R10 876,00** subject to:
   any literature referred to in Section H of the DUT186 form being accessioned by this University

NOTE:- **This funding is not paid directly to you but is controlled by your Head of Department. Any proposed changes to this funding allocation needs the approval of your supervisor, and the Faculty of Health Sciences Research Committee**

The Institution Research Committee has stipulated that:

(a) ownership of any patent registered in respect of the results of your Master's 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 Master's Degree in Technology studies, you will be required to repay pro rata, the **R10 876,00** investment which the Institution Research Committee has made in approving your request for funding;

(c) If the Durban University of Technology provided the equipment/materials for the creation of artefacts, this cost would be refunded to the University if such artefacts were sold and

(d) Durban University of Technology 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 **G24(2) (b)** which states:
If a student fails to obtain the Master's Diploma or Degree within four years after first registering for the qualification the Senate may refuse to renew the student's registration or may impose any conditions it deems fit. A student may apply to the Faculty Board for an extension. (Amended w.e.f. 2003/01).

Furthermore, if you experience any problems relating to your research studies, your supervisor must be informed as soon as possible. If the difficulty persists, you must then approach your Head of Department and thereafter the Executive Dean of the faculty.

I attach:

(a) **a duplicate** of this letter which **you are required to sign,** where indicated, acknowledging your acceptance of the above conditions. Please return it ***urgently.*** Failure to comply will necessitate the Faculty of Health Sciences Research Committee reviewing their decisions set out herein;

(b) a copy of the 2008 General Rules governing the submission of your dissertation;

Please do not hesitate to contact me if I can be of any assistance.

Yours sincerely

MR VIKESH SINGH
FACULTY OFFICER
FACULTY OF HEALTH SCIENCES

Student's signature accepting the conditions.

Date of accepting the conditions.

APPENDIX E

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

6th June 2008

Faculty Research Committee
Durban University of Technology
DURBAN

Re: STUDY PROPOSAL BY YAKEEN HARILALL

Topic : Correlation between Cerebral Tissue, Oxygen Saturation & Central Venous Oxygen Saturation during Off-pump 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

A. REDDI
HEAD
CARDIOTHORACIC SURGERY

c.c. Dr M Joshua
Medical Manager
IALCH

APPENDIX F

CONSENT FOR PARTICIPATION OF STUDY

TITLE

Correlation between cerebral tissue oxygen saturation and central venous oxygen saturation (ScvO2) during off-pump coronary artery bypass graft surgery.

INTRODUCTION

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 is any questions, which are not clearly explained in this letter, do not hesitate to ask the supervisor or investigator.

PURPOSE OF THIS STUDY

The purpose of this study is to determine if oxygen levels in the blood is the same as oxygen levels in the brain. If there is a large difference between the levels in the blood and brain, then this will highlight the need for continuous brain monitoring during cardiac surgery. This will help in the delivery of better service to South African Cardiac patients. We will be able to identify patients who are high risk and in the future change their management so that they may have a better outcome associated with surgery.

PROCEDURE

During surgery blood samples of approximately 1-2ml will be taken at different time periods by the investigator and will be analysed by a blood gas machine. Blood samples will be taken from a catheter which is routinely inserted during surgery therefore you will not endure any pain. Blood samples will be discarded after being analysed. Electrode patches will be placed on the forehead to measure brain oxygen levels.

REQUIREMENTS OF THE PATIENT

As a candidate in this research, you will undergo elective off pump coronary artery bypass surgery. It will be performed under general anaesthesia so it will not cause you any discomfort. To qualify to be in this research you must be over the age of 18 years.

PATIENTS RIGHT TO PARTICIPATE

Your participation in this trial is entirely voluntarily. Your withdrawal at any time will not affect your medical treatment. There are no risks involved.

CONFIDENTIALITY

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

Appendix F: Informed Consent

Title of research study : Correlation between cerebral tissue oxygen saturation and central venous oxygen saturation (ScvO2) during off-pump coronary artery bypass graft surgery.

Names of supervisors : Prof A. Reddi (031)2402128
Dr J.K Adam (031) 3735291

Name of research student : Mr Yakeen Harilall.
(031) 2693933 / 0832778586

PLEASE CIRCLE THE APPROPRIATE ANSWER:

1. Have you read the research information sheet?
YES/NO
2. Have you had the opportunity to ask questions regarding this study?
YES/NO
3. Have you received satisfactory answers to your questions?
YES/NO
4. Have you had the opportunity to discuss this study?
YES/NO
5. Have you received enough information about this study?
YES/NO
6. Do you understand the implications of your involvement in this study?
YES/NO
7. Do you understand that you are free to withdraw from this study?
a) At any time?
YES/NO
b) Without having to give a reason for withdrawing?
YES/NO
c) Without affecting your future health cares?
YES/NO
8. Do you agree to voluntarily participate in this study?
YES/NO
9. Whom have you spoken to? _____

Please ensure the researcher completes each section with you.
If you have answered NO to any of the above, please obtain the necessary information before signing.

Please print in block letters:

PATIENT Name_____Signature_____

WITNESS Name_____ Signature_____

APPENDIX G

Appendix G

Isivumelwano Sokungenela Ucwaningo

ISIHLOKO: Ucwaningo ngobudlelwane obukhona phakathi kobukhona bomoya (oxygen) owanele engqondweni nasemzimbeni wonke, ezigulini ezihlinzwa inhliziyo zingalekelelwa umshini. [OPCAB]

ISINGENISO
Niyamenywa ukuba yingxenye yocwaningo. Okubhalwe kulencwadi kozinisiza ukuqonda kahle ukuthi ucwaningo lolu olwani nokuthi luzokwenza kanjani ubungcono ezingeni lokuhlinzwa kwakho. Uma kunemibuzo, engachazekile kahle kulencwadi, ungabuza uMphathi Wohlelo noma i-Investigator.

INHLOSO YALOLUCWANINGO
Inhloso yalolucwaningo ukuthola ukuthi bukhona yini ubudlelwano phakathi komoya osegazini emzimbeni nomoya osengqondweni. Ngalokhu siyokwazi ukuthi iziguli siziphe yini isenezelo somoya (02) ozoya engqondweni (ekhanda) futhi sazi nokwenza umoya (02) ungeneli ngalokho siyosiza umphakathi wase (SA) ophethwe yinhliziyo. Siyokhona nokubona iziguli eziyingcuphe sizivikele ngesikhathi sokuhlinzwa.

OKUDINGEKAYO EZIGULINI
Njengomunye wabantu abazobamba iqhaza kulolucwaningo, kuzodingeka ukuthi uhlinzwe imithambo yenhliziyo. Lokho kuyokwenziwa ulalisiwe, ukuze ukhululeke. Ukuze wamukeleke kuloluhlelo, kumele ube ngaphezu kweminyaka eng-18.

ILUNGELO LOKUNGENELA KWEZIGULI

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

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

Appendix G

IFOMU LOKUZIVUMELA
Ucwaningo ngobudlelwane obukhona phakathi kobukhona bomoya (oxygen) owanele engqondweni nasemzimbeni wonke, ezigulini ezihlinzwa inhliziyo zingalekelelwa umshini. [OPCAB]

Isihloko socwaningo
Igama likaSuphavaza **:** Professor A.Reddi, Dr JK.Adam
Ucingo : (031) 240 2128 (031) 3735291
Igama lomfundi ocwaningayo : Yakeen Harilall
Ucingo : 0832778586

Ucelwa ukuba ufake isikokela empendulweni efanele:
1. Ulifundile iphepha elinolwazi locwaningo?
YEBO/CHA
2. Ubenako ukuneliseka ngethuba lokubuza imibuzo mayelana nalolucwaningo?
YEBO/CHA
3. Utholile ukuneliseka ezimpendulweni ozinikiwe?
YEBO/CHA
4. Ubenalo yini ithuba lokuthi niluxoxe lolucwaningo?
YEBO/CHA
5. Ulutholile ulwazi olwanele ngalolucwaningo?
YEBO/CHA
6. Uyayiqonda imiphumela yokuthi ungenele lolucwaningo?
YEBO/CHA
7. Uyaqonda ukuthi ukhululekile ukuthi ungaluyeka lolucwaningo:
a) Noma ngasiphi
YEBO/CHA
b) Ngaphandle kokuthi uthole isizathu
YEBO/CHA
c) Ngaphandle kokuthi ulahlekelwe amalungelo akho okulashwa
YEBO/CHA
8. Uyavumelana nokuthi uzivumele ukungenela lolucwaningo
YEBO/CHA
Uyacelwa ukuthi uqiniseke ukuthi unesi/umcwaningi uligcwalisa nawe lolucwaningo. Uma uphendule ngo Cha kulokhu okungenhla uyacelwa ukuthi uthole ulwazi olwanele ngaphambi kokuthi usayine.

Ucelwa ukuthi ubhale ngamagama amakhulu

UFAKAZI IGAMA _____SAYINA _____

ISIGULI IGAMA _____SAYINA _____

UMGWANINGI/UMFUND

APPENDIX H

CHART RECORDING

STUDY

Correlation between cerebral tissue oxygen saturation and central venous oxygen saturation during off-pump coronary artery bypass graft surgery

INVESTIGATOR: MR Y HARILALL

PATIENT NAME	DATE	KZ .NO	AGE	GENDER	HEIGHT / WEIGHT
				M I F	cm / Kg

BASELINE

MAP	HR	SpO2	rSo2(R)	rSo2(L)
		%	%	%

INDUCTION	Scvo2	rSo2(L)	rSo2(R)	SpO2	HR	MAP	PcvCo2	HCT	lact	fio2
Post induction	%	%	%	%		mmHg	%	%		
PRE STERNOTOMY										
PRE PLACEMENT SWABS										
POST PLACEMENT SWABS										
PRE OCTOPUS										
POST OCTUPUS										
PRE SNARING OF LAD										
POST SNARING										
PRE ANASTOMOSIS										
DURING ANASTOMOSIS (1)										
DURING ANASTOMOSIS (2)										
POST ANASTOMOSIS										
PRE SWAB REMOVAL										
POST SWAB REMOVAL										
PRE TRANSFER TO ICU BED										
POST TRANSFER TO ICU BED										