A STUDY INVESTIGATING THE RELATIONSHIP BETWEEN INTRAOPERATIVE BRAIN OXYGEN UTILISATION MEASUREMENTS, AND NEUROPSYCHOLOGICAL DAMAGE AFTER CARDIAC SURGERY

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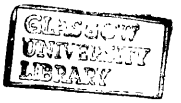

ABSTRACT

Cerebral damage can occur in association with cardiac surgery. This thesis relates to a study which attempted to determine predictors of cognitive impairment using a new technique, Near Infrared Spectroscopy (NIRS). The Critikon NIRS equipment was used to measure patients' cerebral oxygenation and oxygen utilisation, continuously and non-invasively, during cardiac surgery. To assess patients' cognitive function, a battery of neuropsychological tests was administered preoperatively as a baseline measurement, and repeated six days and six months after surgery. The study control consisted of 25 patients who underwent general surgery whose results were compared, retrospectively, with 50 patients who underwent elective cardiac surgery. Results of this stage were then tested prospectively in a further 70 patients. Thirty nine per cent of cardiac patients were found to have cognitive impairment at six days while 12% were impaired six months after surgery. No relationship was found between cognitively impaired cardiac patients and the NIRS measurements. Further development of the NIRS monitor is required to counteract the recently discovered problem of the light-piping effect of cerebrospinal fluid in the brain. This problem reduced the expected volume of brain tissue in which the oxygenation change is being measured from 80 to 20%.

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DECLARATION PAGE

This thesis described a large multidisciplinary team project in which the author set up and implemented the study, gathered the data, scored and documented the results of the tests, was involved in the interpretation and description of the data, and coordinated the complete investigation. The material herein was written solely by the named author.

Signature _____

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ABBREVIATIONS

ACT	Activated clotting time
CABS	Coronary artery bypass surgery
CAD	Coronary artery disease
CCOUM	Critikon Cerebral Oxygen Utilisation Monitor
NIR	Near Infrared
NIRS	Near Infrared Spectroscopy
PDGF	Platelet derived growth factor
RCBF	Regional cerebral blood flow
SD	Standard deviation

GLOSSARY

Aetiology: The cause of a specific disease.

Atherosclerosis: A disease of the arteries in which fatty plaques develop on the inner walls, with eventual obstruction of blood flow.

Atheromatous Plaque: Degeneration of the walls of the arteries due to fatty deposits and scar tissue which limits blood circulation and predisposes to thrombosis.

Cerebral Infarction: Death of a segment of brain tissue which follows an interruption of its blood supply.

Choroidretinitis: Any inflammatory process involving the choroid and the overlying retina of the eye.

Chromophore: When light enters tissue it is absorbed by compounds within the tissue known as chromophores.

Computed Tomography: Diagnostic radiology for the examination of the soft tissue of the body. The technique involves the recording of 'slices' of the body with an x-ray scanner; these records are then integrated by computer to give a cross-sectional image.

Cytochrome: A compound consisting of a protein linked to haem. Cytochromes act as electron transfer agents in biological oxidation-reduction reactions, particularly those associated with the mitochondria in cellular respiration.

Cognition: The mental process by which knowledge is acquired. These include perception, reasoning, acts of creativity, problem-solving and possibly intuition.

Demographic: Pertaining to the study of population on a national, regional or local basis in terms of age, sex and other variables.

Diabetic Retinopathy: A disease of small retinal blood vessels that causes blood leakage which may be confined to the retina or which may extend forward into the vitreous body with serious effects on vision.

Embolus: Material such as blood clot, fat, air or a foreign body, that is carried in the blood from one point in the circulation to lodge at another point.

Encephalopathy: Any degenerative or other non-inflammatory disorder affecting the brain in a widespread manner.

Epidemiological Studies:	Studies relating to the incidence and distribution of disease in a population.
Extracorporeal Circuit:	The apparatus through which blood is circulated outside the body, as through a heart-lung machine.
Fibrin:	The final process of blood coagulation - An insoluble protein produced by the action of the enzyme thrombin on fibrinogen (a substance present in the blood plasma).
Hypothermia:	Reduction of the body temperature below the normal range.
Intima of the blood vessels:	The inner layer of an artery or a vein. It is composed of a lining of epithelial cells.
Intra-aortic balloon:	Intra-aortic balloon assistance is a device which can provide mechanical circulatory assistance for the failing heart. The effect of the intra-aortic balloon assistance is to increase systemic arterial pressure and improve myocardial blood flow while reducing ventricular work and thus decrease the size of myocardial ischaemic injury.
Macroembolism:	Embolism which occludes flow in arteries 200 micrometres or greater in diameter.
Macrophages:	These are important cells in the immune system. Macrophages are scavenging cells, large phagocytes derived from blood monocytes, and are found all over the body especially in the liver, lymph nodes, spleen and bone marrow.
Media of the vessel wall:	Middle layer of the wall of a vein or artery. It is the thickest of the three layers, being composed of elastic fibres and smooth muscle fibres in alternating layers.
Microemboli:	Emboli which occlude flow in smaller arteries, arterioles and capillaries.
Model:	A model is a formalised expression of a theory or the causal situation which is regarded as having generated observed data. In statistical analysis the model is generally expressed in symbols, that is to say in a mathematical form, but diagrammatic models are also found.
Neuropsychological:	The psychiatric effects of disorders of neurological function or structure.

Neuropathies: Any disease of the peripheral nerves usually causing weakness and numbness.

Neurotransmission: Transmission of impulses from nerve endings across synapses to other nerves and across the minute gaps between the nerves and the muscles or glands that they supply.

Parkinson's disease: A degenerative disorder characterised by an insidious onset with slowing of emotional and voluntary movement, muscular rigidity, postural abnormality and tremor.

Pathophysiology: The discipline concerned with the effects of disease on body function.

Percutaneous transluminal coronary angioplasty: Is an effective therapy for some patients with coronary artery disease. Angioplasty may be used to dilate narrowed arteries. A catheter with a deflated balloon on its tip is passed into the narrowed part of the artery. Then the balloon is inflated, and the narrowed area widened.

Perfusion: The passage of blood or other fluids through the body or the effectiveness with which a part, such as the brain, is supplied with blood.

Pericardial sac: The membrane surrounding the heart.

Probability: A measure of the relative frequency or the likelihood of an occurrence of an event. Symbol: p. Values are derived from a theoretical distribution or from observations. Probability is a number from 0 and 1. Probability 0 means impossibility, 1 is certainty

Psychosis: One of a group of mental disorders that feature loss of contact with reality. Psychotic disorders manifest some of the following: delusions: hallucinations, severe thought disturbances, abnormal alteration of mood and grossly abnormal behaviour.

Rank: The position, when in order, of a member within a set. For most statistical tests involving ranks it does not matter if the rank starts with the highest or lowest number as rank1, so long as the test is consistent throughout.

Retinitis pigmentosa: Slow degenerative disorder of the rods and cones of the retinas of both eyes with migration of pigment from the retinal pigment layer.

Skew: (of a distribution) not having equal probabilities above and below the mean. In a skew distribution, the median and the mean are not coincident. If the median is less than the mean the distribution is said to be positively skewed, and vice versa.

Somatic: Relating to the body rather than the mind.

Stenosed: An abnormal narrowing of a duct, orifice or tubular organ such as a blood vessel.

Sternotomy: A surgical division of the sternum (breast bone) to allow access to the heart and its major vessels.

Vasopressors: Drugs which stimulate the contraction of blood vessels and therefore bring about a rise in blood pressure.

CHAPTER ONE

INTRODUCTION

Many cardiac surgery procedures are performed using a cardiopulmonary bypass (CPB) system. Blood is diverted through an extracorporeal system which oxygenates the blood and provides adequate perfusion of all body organs. This allows optimum surgical exposure for procedures such as heart valve replacements, coronary artery bypass grafts and heart transplants. Cerebral complications have been a recognised problem since the early days of cardiac surgery and many researchers recognised that the CPB circuit was a contributory factor to this adverse outcome (Javid, Tufo, Najafi, Dye, Hunter, Julian, 1969; Aberg, Kihlgren, 1974; Willner, 1993).

The close proximity of the heart to the source of the cerebral arterial blood supply makes the brain susceptible to damage by micro- or macroemboli which can enter the blood during cardiac surgery and are immediately swept up into the brain. The two major arteries which supply the brain (the brachiocephalic trunk and the left common carotid artery) originate in the arch of the aorta.

1.1 Review of the Structure and Function of the Heart

The heart is the centre of the cardiovascular system. The cardiovascular system provides the 'pump' for circulating constantly refreshed blood through the blood vessels. As blood flows through body tissue, nutrients and oxygen diffuse from the blood into the interstitial fluid and then into the cells. Blood also removes the waste products of cell metabolism.

Structure of the Heart

The heart is a hollow muscular organ, roughly conical in shape, situated in the anterior part of the lower thorax in close proximity to the lungs. It is composed of two halves, the left and right heart, which are separated by a dividing partition, the atrial and ventricular septum. The heart is responsible for two pathways of circulation which are in series with each other. The right side of the heart (right atrium, right ventricle and pulmonary artery) is responsible for delivering systemic venous blood to the lungs, where the blood releases carbon dioxide to the exhaled air and is replenished with oxygen. The left side of the heart (left atrium, left ventricle and aorta) is responsible for delivering oxygenated blood to the remainder of the body with the exception of the lungs. Each half of the heart is further subdivided into an upper atrial and lower ventricular chamber and between each atrium and ventricle is a valvular opening that allows blood to flow only in the direction of the ventricle. There are also valves at the outlet of the heart where the great vessels begin (Figure 1.1). The superior aspect of the heart is called the base and the extremity of the ventricles is called the apex.

The Heart Wall

The surface of the heart is covered by a thin membrane, the *epicardium*. The epicardium is the visceral layer of the serous pericardium.

The *pericardium* is a triple-layered bag which surrounds and protects the heart. It confines the heart in the mediastinum, yet allows it sufficient freedom of movement for vigorous and rapid contraction.

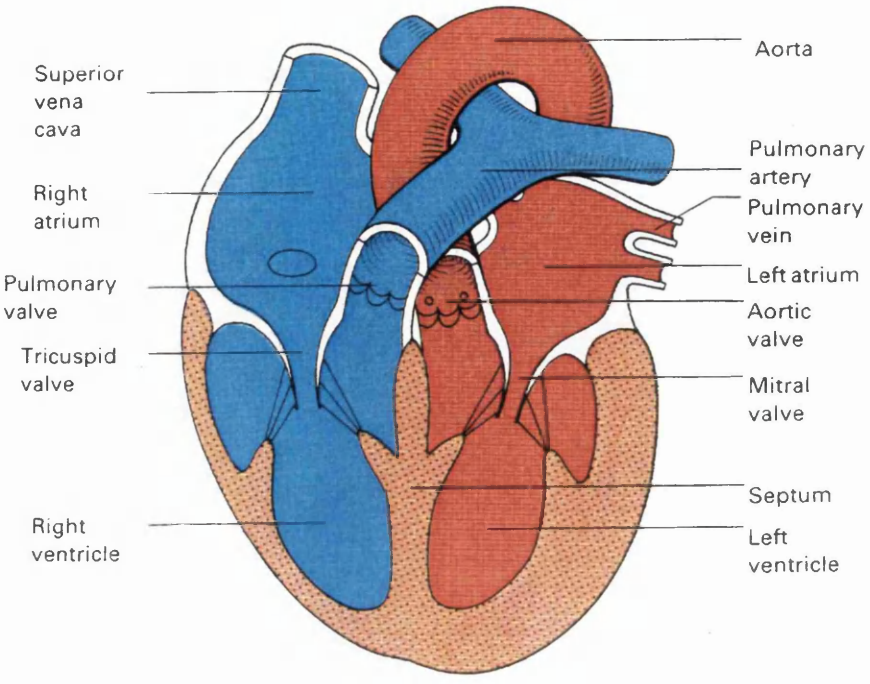

Figure 1.1 Atria and ventricles of the heart

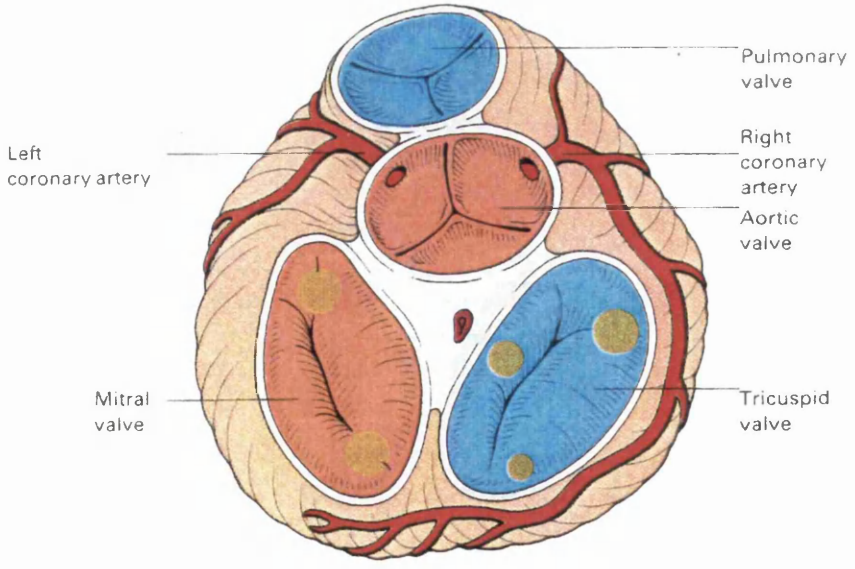

Figure 1.2 Heart valves

Illustration taken from Textbook and Colour Atlas of the Cardiovascular System, C. Thomas et al as authorised by Chapman and Hall, Medical Publishers.

The pericardium consists of two principal portions: the fibrous pericardium and the serous pericardium. The outer fibrous pericardium is composed of tough, inelastic, fibrous connective tissue. The inner serous pericardium is a thinner, more delicate membrane that forms a double layer around the heart. The outer parietal layer of the serous pericardium is fused to the fibrous pericardium while the inner visceral layer of the serous pericardium adheres tightly to the muscle of the heart. Between the parietal and visceral layers of the serous pericardium is a space where a thin film of serous fluid known as the parietal fluid is secreted by the parietal cells. This fluid reduces friction between the membranes as the heart contracts.

The *myocardium*, the middle layer, is composed of cardiac muscle tissue. The myocardium is thickest at the apex and thins out towards the base.

The *endocardium*, the innermost layer, is a thin layer of endothelium overlying a thin layer of connective tissue.

Valves of the Heart

Atrioventricular Valves

Atrioventricular valves separate the atria and ventricles. The right atrium and right ventricle are separated by the tricuspid valve. The left atrioventricular valve is called the bicuspid (mitral) valve and separates the left atrium from the left ventricle (Figure 1.2).

Semilunar Valves

Both arteries that emerge from the heart have a semilunar valve that prevents blood from flowing backwards into the heart. The pulmonary semilunar valve, at the origin of the pulmonary artery as it leaves the right ventricle has three leaflets or cusps. Similarly, the aortic semilunar valve at the origin of the aorta as it leaves the left ventricle has three leaflets. The description 'semilunar' valves refers to the three semilunar arcs of connective tissue, one corresponding to each of the valve leaflets called the valve annulus (Figure 1.2).

As each chamber of the heart contracts, it pushes a portion of blood into a ventricle or out of the heart through an artery. The valves prevent back flow as the blood flows through the heart. The valves open and close in response to pressure changes as the heart contracts and relaxes.

The Coronary Arteries

The right and left coronary arteries branch from the ascending aorta (Figures 1.3 and 1.4). The *right* coronary artery, arising from the right coronary sinus, gives off vessels which supply the right atrium and the right ventricle. The vessel continues as the posterior descending coronary artery and supplies the posterior part of the interventricular septum and the posterior left ventricular wall. The *left* coronary artery arises from the left coronary sinus, and is usually not more than 2.5 centimetres in length. It then divides into the left anterior descending and left circumflex arteries. The left anterior descending artery supplies the anterior septum and the anterior left ventricular

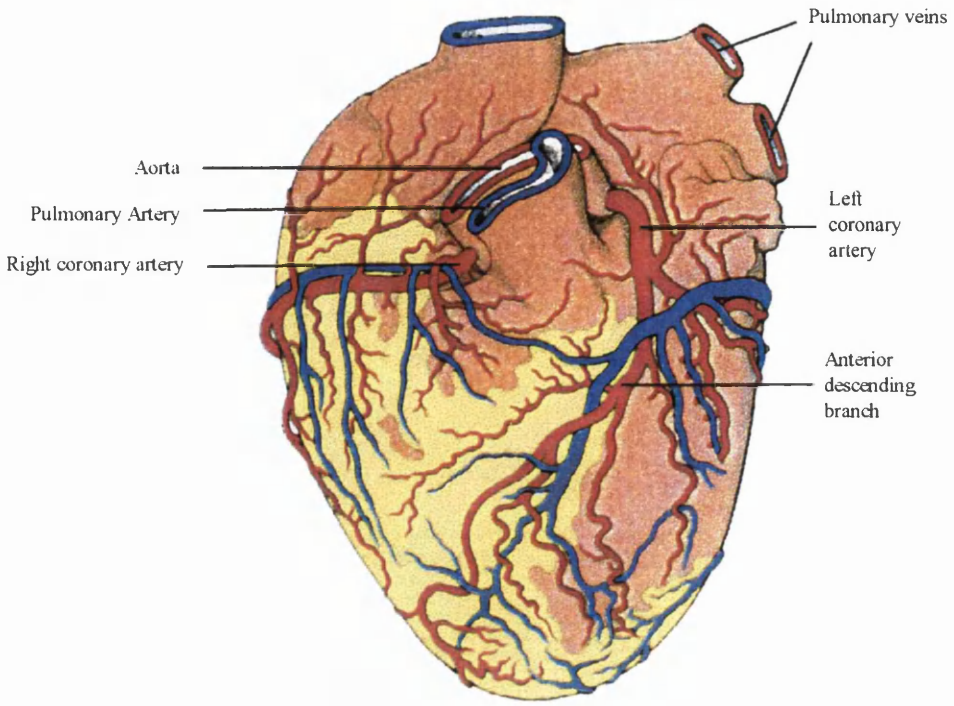

Figure 1.3 Coronary vessels - anterior surface of heart

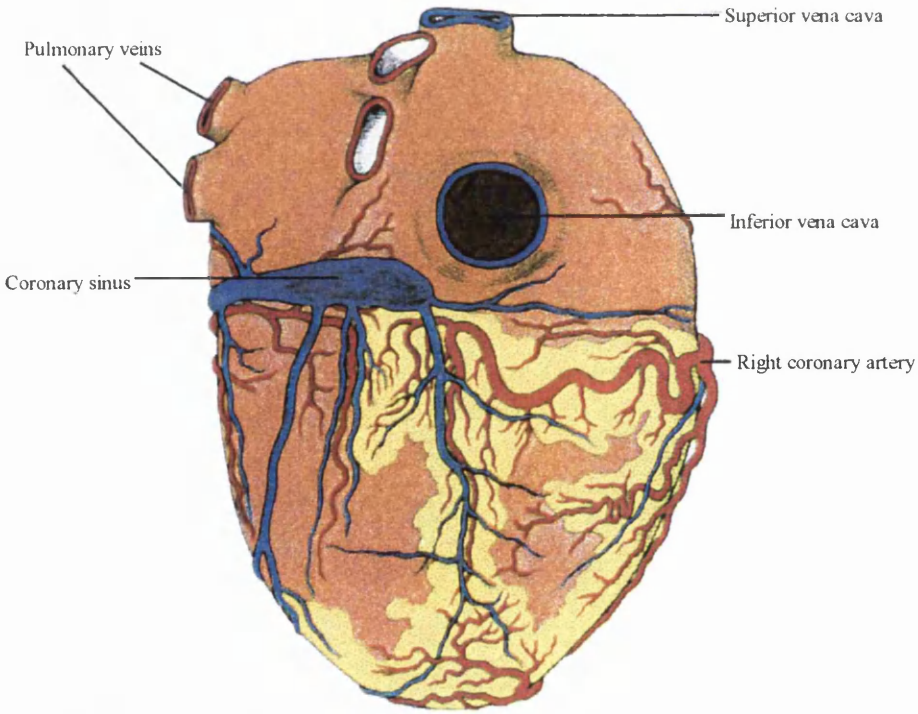

Figure 1.4 Coronary vessels - posterior surface of heart

Illustration taken from Textbook and Colour Atlas of the Cardiovascular System, C. Thomas et al as authorised by Chapman and Hall, Medical Publishers

wall. The left circumflex artery gives off branches to the left atrium and the left ventricle (marginal branches).

Coronary Veins

As the blood passes through the coronary circulation, it provides the tissue with oxygen and nutrients and collects carbon dioxide and waste products of cell metabolism. It then drains into a large vein on the posterior surface of the heart, called the coronary sinus which empties into the right atrium. The principal tributaries carrying blood into the coronary sinus are the great cardiac vein, which drains the anterior aspect of the heart, and the middle cardiac vein, which drains the posterior part of the heart.

Conduction System of the Heart

During embryonic development, a small fraction of the cardiac muscle fibres become autorhythmic (self-excitable), that is, able to repeatedly and rhythmically generate electrical impulses. The autorhythmic fibres have two important functions. They act as a pacemaker, setting the rhythm for the entire heart, and they form the conduction system, the route for conducting impulses throughout the heart muscle. The conduction system ensures that cardiac chambers contract in a coordinated manner, which makes the heart an effective pump. The components of the conduction system are:-

1 The sinoatrial node

2 The atrioventricular node

3 The atrioventricular bundle (the Bundle of His)

4 The right and left bundle branches

5 The conduction myofibres (Purkinje Fibres)

Cardiac Cycle

A single cardiac cycle includes all the events associated with one heart beat. In each cardiac cycle pressure changes occur as the atria and ventricles alternately contract and relax, and blood flows from areas of higher blood pressure to areas of lower blood pressure.

Systemic venous blood travels to the heart from all parts of the body except the lungs. The deoxygenated blood returns to the heart through the inferior vena cava and superior vena cava, each of which delivers blood to the right atrium. The coronary sinus also empties into the right atrium, delivering blood that has travelled through the coronary circulation and supplied the heart itself.

The cardiac cycle consists of diastole (ventricular filling) and systole (ventricular emptying). Diastole begins with the closure of the aortic and pulmonary valves, marking the end of the previous cardiac cycle and the beginning of the next. During diastole, blood flows from the right atrium across the tricuspid valve into the right ventricle and from the left atrium across the mitral valve into the left ventricle. When the ventricles are filled, systole begins, and the ventricular muscles begin to contract. The growing intraventricular pressure forces the mitral and tricuspid valve to close. When the ventricular pressure exceeds the resting pressure in the aorta and pulmonary artery, blood flows across the pulmonary and aortic valves, marking the beginning of a new cycle.

Systole and diastole are usually defined as the contraction or relaxation of ventricular muscle. At a late stage of diastole, the atria contract, helping to propel the blood from the atria to the ventricles (Mathers, Chase, Dolph, Glasgow, Gosling, 1996).

Nervous Control of the Heart

Nervous system control of the cardiovascular system stems from the cardiovascular centre in the medulla oblongata of the brain. This centre receives information from higher brain regions such as the cerebral cortex and limbic system, and from sensory receptors. The sensory receptors include: proprioceptors which monitor internal changes in the body brought about by movement and muscular activity, chemoreceptors that monitor chemical changes in the blood, and baroreceptors that monitor blood pressure in major arteries and veins. From the cardiovascular centre impulses propagate along sympathetic and parasympathetic nerves to the heart. These reflexes are important for regulation of blood pressure as well as heart rate.

Sympathetic fibres extend from the medulla into the spinal cord. From the thoracic region of the spinal cord, cardiac accelerator nerves extend out to the sinoatrial node, atrioventricular node, and most portions of the myocardium.

Parasympathetic impulses reach the heart via the right and left vagus nerves. These fibres innervate the sinoatrial node, the atrioventricular node, and atrial myocardium. Only a few vagal fibres extend to ventricular muscle.

There is always a balance between sympathetic and parasympathetic stimulation of the heart, but the parasympathetic effects predominate at rest (Tortora and Grabowski, 1993).

1. 2 Heart Disease

Like all body organs, the heart, despite its amazing capacity for work, is susceptible to disease. Many congenital heart defects can be resolved by surgical means. Acquired heart diseases such as valvular heart defects and coronary artery disease may be managed by medical treatment or ultimately by surgical intervention.

Valvular Heart Disease

The normal human heart can be considered as a two stage pump, each containing two valves. The right side of the heart receives deoxygenated blood from the superior and inferior venae cavae and pumps it through the lungs to be oxygenated. The re-oxygenated blood is then returned to the left side of the heart to be ejected into the aorta. If a heart valve is congenitally defective or degenerates in later life, the heart cannot pump blood as efficiently. It must work harder to maintain the same cardiac output, enlarges, and eventually fails. This degenerative process may take many years and as a consequence, the patient's quality of life diminishes. The defective valve may be surgically repaired, however, if this is not possible, the only alternative is replacement with an artificial or prosthetic valve.

Rheumatic heart disease is a condition in which the heart valves are damaged by an inflammatory disease process as a result of rheumatic fever. The incidence of rheumatic fever is now less common, consequently there has been a decrease in this type of cardiac lesion.

Coronary Artery Disease

The term coronary artery disease (CAD) refers to clinical features such as angina and myocardial infarction caused by atherosclerosis. Atherosclerosis causes thickening of the walls of the coronary arteries and loss of elasticity. The narrowing of a coronary artery can cause an imbalance between oxygen supply to and demand of the myocardium (the pathophysiology of CAD is detailed in the literature review).

The Incidence of Coronary Artery Disease

Coronary artery disease remains a major cause of premature death in industrialised countries of the world and is emerging as an increasing cause of death in developing countries. According to World Health Organisation statistics the CAD mortality rates for both men and women in Scotland continue to be among the highest in the world (Appendix 1).

Government concern about the high incidence of the disease in the United Kingdom has prompted the setting up of epidemiological studies to help identify the cause of CAD and to recognise the risks factors associated with the disease. Identification of the risk factors is important in the treatment, management and prevention of CAD. The Scottish

Office has set a target of reducing deaths from CAD among the under 65's in Scotland by 40% between 1990 and 2000 (The Scottish Office,1992).

Treatment of Coronary Artery Disease

Medical pharmacology has improved and many effective drugs are available to treat the symptoms of CAD and to prevent further clinical deterioration. Consideration is given to some form of mechanical revascularisation when medical management of the patient's symptoms becomes ineffective. One technique to improve perfusion of a stenosed coronary artery is called percutaneous transluminal coronary angioplasty where a stenosed artery is dilated by a balloon threaded through the lumen.

Since the 1970's surgical intervention has become an increasingly effective option when medical management of CAD fails and there is evidence of severe heart disease. Coronary artery bypass grafting was developed in the United States of America in the late 1960's but was not introduced into the United Kingdom until the early 1970's. Improved surgical and anaesthetic management of coronary artery bypass surgery (CABS) has prolonged many patients' lives and eased or eradicated the symptoms of CAD. However, adverse cerebral symptoms may be experienced by some patients as a result of cardiac surgery.

1.3 Cerebral Damage as a Result of Cardiac Surgery

Cardiac surgery can cause brain damage. Despite years of research, no single cause of the cerebral damage has yet been identified although gaseous bubbles and debris from the extracorporeal circuit are thought to be major contributory factors (Willner, 1993).

Alternative surgical techniques are constantly being explored, but cardiac surgery, using the cardiopulmonary bypass circuit, is still the technique currently used and is likely to be used for some time.

Advances in practice have reduced the severity of neurological damage experienced by some patients in the early days of cardiac surgery. As the incidence of neurological damage decreases, researchers in recent years have increasingly investigated the neuropsychological damage associated with cardiac surgery. World-wide interest in the problem provoked an international meeting, held in America in 1995, the Fort Lauderdale Conference. This brought together a group of professionals from different disciplines with an interest in the outcomes after cardiac operations, to try to find some consensus of opinion about the methods and tests used to investigate this problem.

1.4 Technological Development

A recent technological development provided some optimism in the search for the identification of moments during cardiac surgery at which the patient is vulnerable to neurological damage. By using the technique of Near Infrared Spectroscopy (NIRS), cerebral oxygenation and oxygen utilisation could potentially be measured. This information could be recorded continuously during the operative procedure using the Critikon cerebral monitor, and the measurements downloaded to a computer. Analysis of this data could be completed at a later stage. The NIRS technique had the added advantage of being a non-invasive method of measurement using a sensor which was placed on the patient's forehead.

The introduction of this new cerebral monitor could be a breakthrough in identifying impending problem moments during cardiac surgery when interventional measures could be taken. This prompted the research question, 'Is there a relationship between the results of NIRS findings and the occurrence of postoperative cognitive deficits?'

Implications

The patient's quality of life following cardiac surgery must be the primary concern of medical staff. Prevention of brain damage during surgery would be conducive to a quicker postoperative recovery and return to a reasonable quality of life.

The economic implications are important in today's cost-conscious National Health Service. Considerable savings could be made if cerebral damage as a result of cardiac surgery could be explained and prevented. Elucidation of this problem could for example, reduce the time required by patients in the intensive therapy unit. Intensive care is expensive care due to the high staff/patient ratio such a unit requires. Minimum recovery time would be required in the general ward, and less clinical support would be necessary while in hospital and during the postoperative recovery period at home.

CHAPTER TWO

LITERATURE REVIEW

2.1 Coronary Artery Disease and Its Incidence in Scotland

Introduction

Mortality from coronary artery disease (CAD) varies widely in different countries. Male mortality rates from CAD are much greater than female mortality rates in the young and in early middle age, but the difference narrows in the elderly (Appendix 1). There may be marked regional variations, for example the English-Scottish difference is part of an increasing gradient from the south east to north west of the United Kingdom. Within Scotland itself, Watt (1993) identified a considerable difference in coronary mortality between Glasgow and Edinburgh.

Incidence of Coronary Artery Disease

According to the CAD mortality figures calculated from World Health Organisation (WHO) data in 1977 (Appendix 1), Finland followed by Northern Ireland then Scotland had the highest mortality figures. Japan, at the opposite end of the scale, had the lowest mortality rate.

Although there has been a slight reduction in the mortality rate of CAD, Northern Ireland, Finland and Scotland continue to have the highest rates according to the 1994 WHO statistics (Appendix 1). In 1993, coronary artery disease accounted for 25% of deaths in the United Kingdom and cost the National Health Service £1,420 million (British Heart Foundation,1996).

These alarming statistics have stimulated much research to review the factors predisposing to CAD and to determine the reasons for the geographical differences in coronary mortality rates (Crombie, Smith, Kenicer, Tunstall-Pedoe, 1986; Tunstall-Pedoe, Smith, Crombie, 1986; Tunstall-Pedoe, Smith, Crombie, Tavendale, 1989; Watt, 1993; Macintyre, 1994). The results of these studies have raised an awareness of the need for health authorities to set up CAD prevention programmes.

Geographical differences in Mortality Rates

Japan has one of the lowest rates of heart disease in the world. The long life expectancy in Japan is, according to a study by Marmot and Smith (1989), unlikely to be due simply to the fact that the Japanese have some intrinsic biological advantage. Changes in mortality patterns have occurred among Japanese migrants to America. Among men of Japanese descent living in Japan, Honolulu and the San Francisco Bay area, the prevalence of coronary artery disease is 2.5%, 3.5% and 4.5% respectively. These changes are thought to be due to differences in environment or lifestyle. Diet seems to play an important part in their health and it may make a major contribution towards the lower rates of coronary artery disease.

Finland in 1977 had the highest coronary mortality rate in the world (Appendix 1) and almost twenty years later, only a slight reduction in the death rate has occurred (Appendix 1). In a recent study, Pekkanen, Juha, Tuomilehto, Uutela, Vartiainen and Nissinen, (1995) sought to evaluate the associations between social class as defined by occupation, health behaviour and mortality from all causes and coronary artery disease

among middle-aged men and women in eastern Finland. They concluded that unfavourable risk factors and high mortality are concentrated among lower social classes in Finland, although in women this association was found to be smaller.

In Scotland there is a large difference in the coronary death rate between Edinburgh in the east of the country and Glasgow in the west. Crombie, Kenicer, Smith, Tunstall-Pedoe, (1989) described this contrasting pattern and noted some inconsistencies. Within a cluster of very high mortality districts in the Clydeside conurbation are two districts (Bearsden and Milngavie, and Eastwood) with very low rates. This geographical pattern poses a question about the underlying factors responsible for this distribution; the geographical based analysis, however, does not in itself provide evidence for the aetiology of coronary artery disease.

As a result of the high coronary mortality rate and regional variation within Scotland a government sponsored Cardiovascular Epidemiological Unit was formed in Dundee in 1981. Two projects exist at present: the Scottish Heart Health Study and the Scottish Monica Project in collaboration with Glasgow University Medical School (Macintyre, 1994). These studies are part of a large international project coordinated by the World Health Organisation.

2.2 Pathophysiology of Coronary Artery Disease

Coronary artery disease is a common condition in industrialised countries (Thomas, Gebert, Hombach, 1992) and occurs when the coronary arteries which supply blood to the heart become diseased. This results in narrowing of the vessels (atherosclerosis) so

that there is an insufficient blood supply to the heart muscle. The term CAD when used clinically refers to the spectrum of disease covering angina, myocardial infarction, cardiac failure and sudden cardiac death.

Theories about the aetiology of atherosclerosis have developed since the middle of the last century. In 1852, Robitonsky suggested that the thickening of the intima of the blood vessels was the result of fibrin formation, the end product of the coagulation process, with secondary lipid accumulation. In 1856, Virchow suggested that lipid accumulation in the wall of the arterial tree came from the blood, and overwhelmed the mechanism present in the arterial walls for removing lipid.

A more recent theory is that of injury to the vessel wall. The response of the wall and the circulating blood to that injury, appear to be crucial to the origin and progression of atherosclerosis. The endothelium plays a fundamental role in maintaining the tone of the vessel by continuously producing chemicals in very small amounts e.g. prostacyclin, endothelium derived relaxing factor - now known to be the gas, nitric oxide. These chemicals prevent the formation of clots and the adhesion of platelets and create the correct environment for normal responses of the vascular tree to various situations.

If the endothelium is breached either physically or chemically, e.g. by the chemicals in tobacco smoke, the function of the whole vessel is compromised. The breaching of the wall leads to the accumulation of macrophages and lipids, and this is the initial feature of an atheromatous plaque. Platelets also recognise the endothelial damage and are 'activated' causing aggregation and clumping of these cells. The macrophages, platelets

and endothelium release various factors for example, platelet derived growth factor (PDGF), that lead to the proliferation of smooth muscle cells. This can form an outer muscle capsule that surrounds the lipid interior, and starts to infiltrate the media of the vessel wall. If this lesion is disrupted, thrombus formation is stimulated. Initially these thrombi are small, but they can organise and add to the growth of the atheromatous lesion. If the thrombi become large, they can occlude a vessel resulting in myocardial infarction.

2.3 Clinical Manifestations of Coronary Artery Disease

Angina Pectoris

Angina pectoris is a symptom caused by an imbalance between myocardial oxygen supply and demand which results in myocardial oxygen deficiency. This is expressed via vagal and sympathetic nerve fibres as a retrosternal pain or discomfort which can radiate to the arms, back or throat. It is usually due to coronary artery disease but can be caused by other clinical conditions such as anaemia and aortic valve disease.

Myocardial Infarction

Coronary artery disease is the most common cause of myocardial infarction. Myocardial ischaemia occurs as a result of inadequate blood supply to the heart muscle caused by constriction or blockage of its coronary arterial blood supply. Blood supply to the area distal to the obstruction is compromised and tissue damage occurs. Recovery depends on the severity of deterioration of the blood flow and injury can vary from being potentially reversible to irreversible cell death.

Cardiac Failure

Cardiac failure may be defined as 'a pathological state in which the tissues are insufficiently perfused in relation to their metabolic needs due to inadequate cardiovascular function' (Sedwick, Green, 1994). Cardiac failure may result from primary myocardial dysfunction such as coronary artery disease or valvular disease, or secondary to other disease processes such as sepsis or chronic lung disease. Symptoms associated with this condition include dyspnoea, fatigue and fluid retention such as ankle oedema.

Sudden Death

Lindsay and Gaw (1997), noted that in sudden cardiac death, 75% of subjects have evidence of coronary artery disease. Other causes include cardiomyopathy, valvular disease and hypokalaemia.

2.4 Risk Factors Associated With Coronary Artery Disease

Certain risk factors have been associated with the development of coronary artery disease and these include modifiable factors such as cigarette smoking, hyperlipidaemia and hypertension. Other factors include increasing age, a family history of CAD, obesity and diabetes. Identification of risk factors can contribute to interventional preventative programmes in an effort to decrease the risk of developing coronary artery disease or to slow down the progress of the disease.

2.5 Coronary Artery Disease Prevention

In 1992 the Government produced a White Paper (Department of Health, 1992) recognising the need for a disease prevention programme to be introduced in an effort to reduce the high incidence of CAD in Britain. A programme of health education was proposed so that people could make informed decisions about their own health. Health information is readily available in many forms e.g. health information leaflets available in hospitals, clinics and GP surgeries, newspapers, magazines, television and telephone helpline. It is too early to assess the effect of this campaign, but hopefully future generations will reap the benefit of today's efforts to reduce the incidence of CAD.

2.6 Medical and Surgical Management of Coronary Artery Disease

Medical Management

Medical management of CAD includes the use of nitrates, beta-adrenoceptor blocking agents (beta blockers), and calcium channel blockers which are effective drugs for the treatment of angina. Nitrates are drugs which cause venous dilatation resulting in reduction of preload (cardiac filling pressure) and reduced myocardial oxygen consumption. At higher doses arterial dilatation can be produced. They can be prescribed in various forms such as tablet, spray or transdermal patch and are effective for rapid relief of angina. Beta blockers were initially developed to treat exertional angina and have proved extremely effective in treating this disorder. They reduce myocardial oxygen consumption by slowing the heart rate and reducing the force of contraction of the myocardium. This group of drugs is also prescribed for the treatment of other conditions such as, hypertension, arrhythmias and for its cardioprotective effect

following myocardial infarction. Calcium channel blockers are also used as a treatment of angina hypertension and arrhythmias. Calcium ions are present in relatively high concentrations in the extracellular fluid, whereas the intracellular fluid contains much less. Activation of muscle contraction requires the movement of calcium ions from the exracellular fluid via calcium channels in the cell membrane, to the intracellular fluid. Calcium channel blockers are a group of drugs which act by restricting the movement of calcium ions in the calcium channels, therefore reducing the sensitivity of cardiac muscle to stimulation, lowering the heart rate and reducing myocardial oxygen demand.

Percutaneous Transluminal Coronary Angioplasty

Angioplasty is used to dilate stenosed coronary arteries. A catheter with a deflated balloon on its tip is passed into the diseased coronary artery. The balloon is inflated and an attempt made to pass it through the narrowed portion of the artery to widen the lumen. This is an effective treatment for some patients with CAD.

Laser Angioplasty

Laser angioplasty is also a procedure used in an attempt to unblock a coronary artery damaged by atherosclerosis. A catheter with a laser tip is passed into the diseased artery, the laser emitting pulsating beams of light that vaporise the plaque.

The decision to use balloon or laser angioplasty depends on certain criteria such as the position of the blockage in the artery, the number of blockages present, and the extent of the blockage. If both methods prove unsuitable, coronary artery bypass surgery would then be considered.

Coronary Artery Bypass Graft

Surgical intervention for CAD is indicated when the patient develops severe angina, disease of the left main coronary artery, triple vessel disease or when complications occur during cardiac catheterisation or angioplasty.

A coronary artery bypass graft is a surgical procedure in which a blood vessel such as the saphenous vein or the internal mammary artery is used to bypass the stenosed area of a coronary artery. This revascularisation procedure is effective in improving the myocardial blood supply giving the patient symptomatic relief, but is not a solution to the underlying disease process.

The heart is exposed through a median sternotomy and pericardotomy. The internal mammary artery is then harvested from the chest wall. It is frequently the vessel of choice for grafting because it has a lower rate of plaque formation than the saphenous veins.

If multiple grafts are required, another surgeon prepares the saphenous vein. Heparin is administered intravenously prior to cannulation of the great vessels and then followed by commencement of cardiopulmonary bypass (CPB). The CPB machine oxygenates and maintains the required temperature of the blood which is pumped through the system during the surgical procedure. The patient's body temperature is lowered to 28°C-32°C. Reduction of the body temperature lowers the metabolic rate therefore reducing the oxygen demand during surgery. The aorta is then cross-clamped which isolates the heart from the circulating blood supply. Myocardial protection is important at this stage and

an infusion of cold cardioplegic solution is administered into the aortic root to fill the coronary arteries. Cardioplegia contains a high potassium content therefore the heart arrests allowing anastomosis of the grafts to commence. When the distal anastomoses are completed, the patient is then rewarmed and the cross-clamp removed.

As warm blood now perfuses the coronary arteries, the heart usually begins to beat spontaneously. The proximal ends of the vein grafts are then anastomosed to the ascending aorta after applying a partial occlusion clamp. Mechanical ventilation is recommenced and the patient is gradually weaned off the CPB machine. Decannulation takes place and reversal of the effect of heparin by administration of intravenous protamine sulphate. Following the positioning of mediastinal and pleural drains the sternum is closed using wires and thoracic incision sutured.

2.7 Cardiopulmonary Bypass

Cardiopulmonary bypass is a technique employed to maintain haemodynamic and metabolic conditions in an anaesthetised patient in the absence of cardiac and pulmonary function. By using artificial pumps and artificial gas exchange devices, the vital functions of such a patient can be successfully maintained (Figure 2.1).

For all but the simplest of cardiac surgical procedures it is necessary to have a still, bloodless heart. By using CPB, the heart may be isolated for surgery in such a way that little or no blood passes through it (Illustration 2.1).

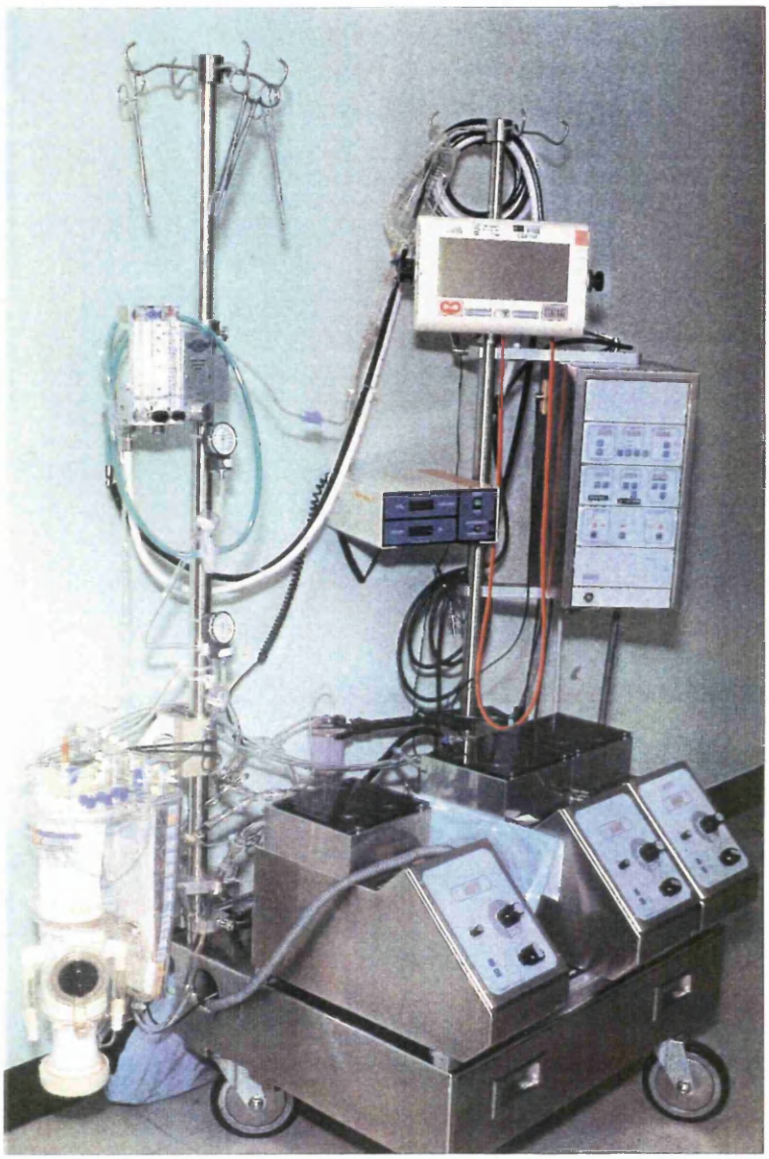

Illustration 2.1 Cardiopulmonary Bypass Machine

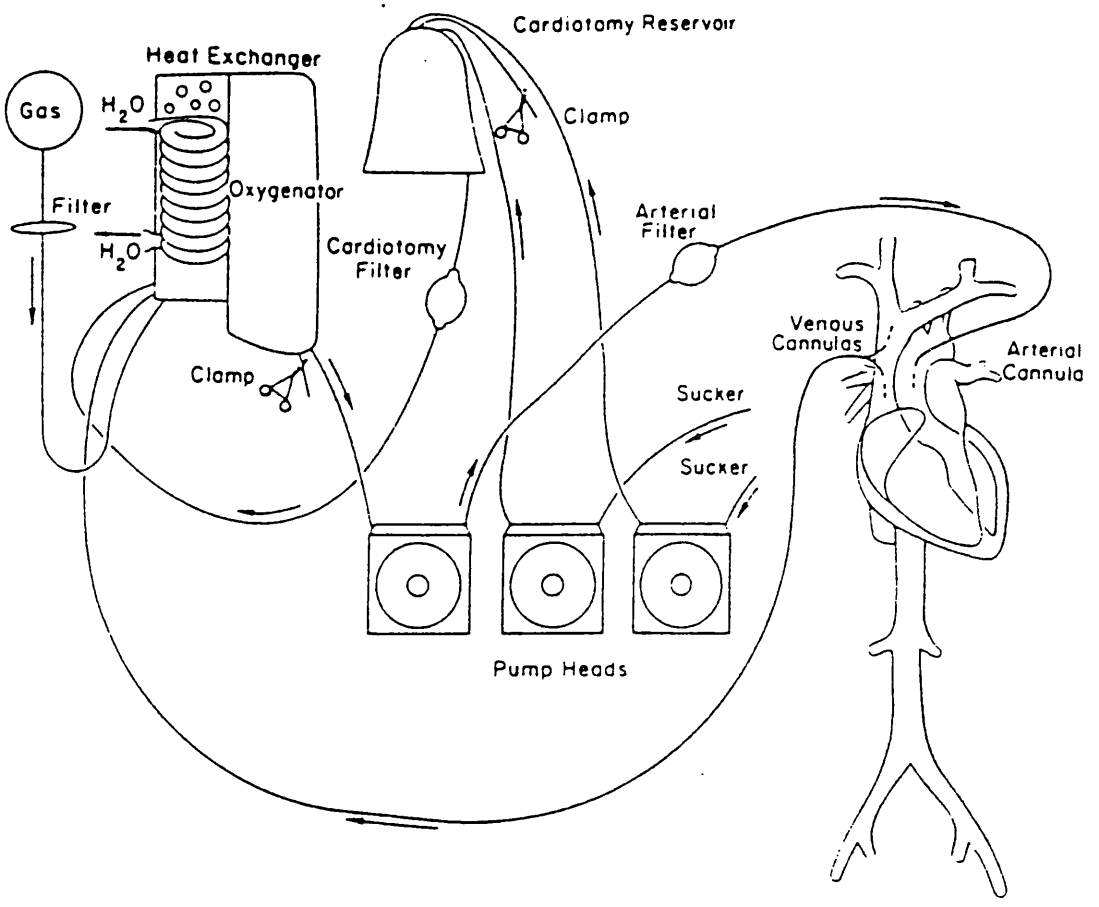

Figure 2.1 Cardiopulmonary Bypass Circuit

From Management of Cardiopulmonary Bypass Anaesthesia for Cardiac Surgery

J A DiNardo

The first proposal of an 'artificial circulation' was by Le Gallous (Bigi, Ghelli, Menghini, Panzani, date unknown) in 1812 when he perfused rabbit brains through the carotid arteries. In 1882 Shroder assembled the first bubble oxygenator and two years later Van Frey and Gruber created the first membrane oxygenator. The true beginning of extracorporeal circulation occurred in 1953 when Gibbon performed the first open heart operation at the Massachusetts General Hospital. He realised that the key to the extracorporeal circulation was the oxygenator and since then the technology of the extracorporeal circulation has rapidly evolved.

Research since the early days of cardiac surgery has identified the fact that cerebral damage following cardiac surgery could be attributed to aspects of the use of the extracorporeal circuit such as, the type of oxygenator and non-pulsatile blood flow. Appropriate modifications have been made. Perfusionists, skilfully trained in the use of this technology, are very aware of the long term adverse problems which can occur postoperatively. The perfusionists and anaesthetists work in close collaboration during CPB.

2.8 Damaging Effects of Cardiopulmonary Bypass and The Neurological and Neuropsychological Changes as a Result of Cardiac Surgery

Introduction

In the early years of cardiac surgery severe central nervous system (CNS) damage was a common occurrence, resulting in complications such as stroke and death. It was apparent at this early stage that use of a cardiopulmonary bypass system contributed to organ dysfunction and resulted in significant mortality and morbidity following surgery.

Developments in technology, surgical techniques, and anaesthetic management have enormously diminished the incidence of severe neurological complications (Shaw, Bates, Cartlidge, Heaviside, Julian, Shaw, 1985), however, postoperative morbidity persists.

Neurological and Neuropsychological Changes

A variety of neurological disturbances have been encountered after cardiac surgery including: motor and/or sensory disorders of varying degree, the presence of primitive reflexes, visual field defects, cranial and peripheral neuropathies, and in some instances spinal injury. Cognitive and psychiatric signs have also been reported (Smith, 1993).

A considerable amount of literature has accumulated about the cerebral complications of cardiac surgery and the consequent modifications made to technology, surgery and anaesthetic techniques (Fox, Rizzo, Gifford, 1954; Javid et al, 1969; Savageau, 1979; Shaw et al, 1985; Newman, Smith, Treasure, Joseph, Ell, Harrison, 1987; Smith, 1993). Although progress has been made as a result of research, brain function during cardiac surgery remains an area of interest in cardiac research.

Causes of Neurological/Neuropsychological Damage

Emboli

Embolism from the heart or CPB apparatus is one of the most commonly suggested causes of cerebral damage and it is thought to be the most probable cause of severe stroke related to cardiac surgery (Willner, 1993).

Macroembolism

Macroembolism may be caused by air or particulate matter such as valve fragments, calcified debris, fat dislodged during manipulation of the heart, or cross-clamping of the aorta, and embolisation of the cerebral arteries. Fat may be released during sternotomy or during excision of the mediastinal tissues; it may drain into the pericardial sac and then be sucked into the extracorporeal system. Macroembolisation may occur when air is trapped in the heart in the proximal parts of the great vessels and is pushed forward when the ventricles begin to contract. Gaseous emboli may also occur from air trapped in stored cold blood which bubbles when blood is rewarmed.

Microembolism

Microemboli in the cerebral arteries may consist of aggregated blood elements, fibres from cotton swabs or small bubbles of air generated in the oxygenator. Normally microemboli are trapped in the lungs, but during CPB they are distributed throughout the arterial system because the lungs are bypassed. Aggregates of leukocytes, platelets and fibrin which may accumulate in stored blood, develop when blood is exposed to artificial surfaces or form in blood vessels during episodes of hypotension and circulatory arrest.

Microemboli are considered to be the most common cause of cerebral complications resulting in cerebral infarction or hypoperfusion. The number of microemboli reaching the cerebral vessels can be reduced by developing more and more effective microfilters for the exracorporeal circuit. Membrane oxygenators release considerably fewer microbubbles than the bubble oxygenators used earlier (Smith and Taylor, 1993).

Cerebral Hypoperfusion

Cerebral hypoperfusion resulting in disturbed neuronal metabolism and transmission may be caused by embolisation, hypotension, low flow rate on CPB, and malposition or obstruction of the aortic or venous cannula which are inserted before establishment of CPB. Among the most common causes of cerebral hypoperfusion are pre-existing carotid or cerebrovascular disease. Cerebral blood flow decreases at the onset of CPB when induced hypothermia reduces metabolic demand and therefore a smaller blood flow is required.

Cerebral Blood Flow

The cerebral blood flow is provided by the internal carotid and vertebral arteries. These systems converge on the circle of Willis. Blood supply to the cerebral hemispheres is provided from the circle of Willis by the perforating vessels and the anterior, middle, and posterior cerebral arteries. Some overlap and anastomosis between the terminal branches of these cortical vessels do occur, but these regions are the most vulnerable to reduced flow states (the watershed zones). If cerebral perfusion is reduced below the lower limit of autoregulation (60mm Hg), the watershed zones will be the most susceptible to ischaemia and ultimately infarction of the brain tissue.

The normal blood flow is 50 millilitres/100 grams of brain tissue per minute and it is maintained at this constant rate over a wide range of cerebral perfusion pressures by a phenomenon called autoregulation. Using sensors in the carotid sinus and other parts of the cerebral arterial tree, the central nervous system can influence the heart rate and muscle tone in the vascular system to maintain a consistent flow of blood to the brain.

The cerebral arteries constrict as the systemic arterial pressure increases, and dilate as it decreases. Autoregulation normally exists between mean arterial pressures of 60-130 mm Hg.

The use of hypothermia during CPB was thought to be a protective measure as reduction in core temperature progressively reduces tissue oxygen requirements. However, recent controversy about the correct acid-base management during CPB have raised doubts about this theory (Smith and Taylor, 1993). Acid-base balance, in relation to a normal core temperature, was defined as an arterial pH of 7.40 and an arterial $PaCO_2$ of 40 mm Hg. During the hypothermic phase of CPB, as the core temperature decreases carbon dioxide solubility increases therefore the blood $PaCO_2$ decreases with temperature. Until recently, blood pH and $PaCO_2$ levels were maintained at the normal levels by addition of CO_2 to the bypass circuit during the period of hypothermia. This resulted in elevation of the $PaCO_2$ and a decrease of the pH. A temperature-corrected method of assessment of blood gases was used known as the pH stat method and remains the method of preference by many anaesthetists. An alternative method of acid-base management using a regime where temperature correction is not applied, is the alpha-stat method. It is claimed that the latter method allows cerebral autoregulation to be maintained more effectively than the former (Stephen, Weyland, Kazmaier, Henze, Menck and Sonntag, 1992).

Hypotension

The role of arterial blood pressure, perfusion pressure and hypotension during heart operations, and particularly where CPB is employed, have remained controversial.

Intraoperative hypotension has been considered one of the most important causes of cerebral complications by some researchers (Branthwaite, 1972; Kornfield, Heller, Frank, Edie, Barsa, 1978) but less important by others (Heller, Frank, Malm, Bowman, Harris, Charlton, Kornfield, 1970; Kolkka, Hilberman, 1980, Shaw et al, 1985).

Other Potentially Harmful Factors

In addition to the most common causes of cerebral dysfunction described above, there are other factors potentially harmful to the brain during heart surgery. Anaesthesia may cause disturbances in neurotransmission. There is also a continuous threat of unexpected technical incidents, errors in surgical technique, toxins may be liberated or generated during the procedure, haematological and immunological disturbances may occur and currently unrecognised causes of cerebral damage may exist.

Often overlooked is the contribution of the post-operative period to the incidence of cerebral injury. In a study by Bruer, Furlan and Hanson, (1983) it was noted that the use of vasopressors and the need for an intra-aortic balloon assist device, were associated with a higher incidence of post-operative encephalopathy.

Conclusion

Major neurological morbidity has been reduced to 5% or less (Willner, 1993). Whether there has been a corresponding reduction in postoperative neuropsychological impairment however, remains controversial. Willner (1993) reported some disparity in the criteria used for the identification of cerebral impairment following cardiac surgery.

He suggested that the reasons for such discrepancies in findings are inconsistencies in the tests and measuring techniques used, and differences in experimental design.

2.9 Quality of Life After Coronary Artery Bypass and The Effect on The Family

Mayou and Bryant (1987), psychiatrists from Warnerford Hospital, Oxford, realised that CABS was usually successful in its main aim, the relief of angina. However, while many patients experienced an improved quality of life, concern still existed about the incidence of neuropsychological complications and subsequent employment difficulties as a result of surgery.

They conducted a study in 1986 to determine patients' quality of life following coronary artery bypass surgery (CABS). Seventy nine men, aged not more than 65 years, entered the study. Using standard interview procedures, they were assessed preoperatively, and at three and twelve months after surgery. The principal psychosocial measures assessed were mental state and expectations, social activities and satisfaction, and a self-report questionnaire indicating performance of everyday activities. Details of the patients' medical history were obtained from the case notes.

Mental state was measured using the Present State Examination method. This was a widely used standard mental state interview where a wide range of symptoms are rated and a computer generates a severity score (Index of Definitions). Mood state was determined using a self-report questionnaire (Lorr-McNair Assessment) and cognition was assessed using two sub-tests from the Wechsler Adult Intelligence Scale (Digit Symbol and Digit Span).

Social activities and satisfaction were measured using a detailed semi-structured interview at the three designated stages, for interviewer ratings on four-point scales of behaviour, satisfaction at work, leisure, and family relationships.

A self-report questionnaire to identify difficulty in performing everyday activities was developed for the study.

Seventy one patients were assessed one year after surgery (two patients had died and six were lost to the study). Eighty six per cent of the patients described relief of angina. Mental state had not significantly changed as measured by the Present State Examination, but significant improvement was found in the Lorr-McNair sub-scales of tension, anxiety and vigour. Six per cent of the patients received psychiatric care during the year. At the preoperative interview 46% of the 79 patients were working (55% of these at a reduced level) while one year after surgery 56% of the 71 patients interviewed were at work (45% of these at a reduced level or in a lighter occupation). Nine per cent of patients were markedly dissatisfied and 14% were moderately dissatisfied with their general level of recovery.

Mayou and Bryant (1987) suggest that doctors have often been unrealistic in expecting the quality of life benefits of CABS to be evident in crude measures such as return to work or physical activity. They expressed the opinion that increased happiness and satisfaction are equally important.

The researchers concluded that all patients require routine preoperative information, but that more could be done to counteract their unrealistic expectations and to provide extra help to those most 'at risk' of psychosocial difficulties after surgery. They suggest that individually planned care for the rehabilitation period would be beneficial.

Basia, Tack and Gilliss (1990) carried out a nurse-monitored cardiac recovery project for the purpose of providing professional support to cardiac surgery patients during their early recovery period at home. Seventy five patients undergoing cardiac surgery received telephone calls weekly for the first four weeks, then fortnightly until eight weeks following discharge from hospital. The purpose of this project was to assist early recovery at home, by providing information or advice as required, monitor recovery for early detection of problems and to provide emotional support for both the patient and carer. Following each call, the nurses recorded detailed notes on the patients' progress and concerns. Analysis of the contents of the nursing notes progressed in three phases:

1 Documentation of the process of interaction between the nurse and patient

2 A description of the frequency and timing of patient problems

3 Identification of the work accomplished in the recovery period

Eighty four nursing diagnoses approved by the North American Nursing Association (NANDA) represented the preset codes for problem categorisation. The analysis of the documentation was based on the information from 72 patients and carers (three patients did not receive the telephone call intervention).

During the phone calls the principal nursing actions were assessment, support, referrals, and education. Assessment of physical and psychological response during the recovery

phase included aspects such as pain control, wound healing, nutrition, exercise compliance and individual and family coping. If a nursing diagnosis was made, the nurse intervened, but if the problem was medical in nature, the nurse would provide reassurance and refer the patient to his or her general practitioner. Psychological support was important at this early postoperative stage to provide reassurance and alleviate any anxieties experienced by the patient or carer. If the nurse was unable to help the patient or carer, then they were referred to the appropriate personnel, e.g. medical staff, dietician, physiotherapist or social worker. A significant amount of teaching was undertaken during the eight week monitoring period focusing in particular on problems such as pain control during this phase of recovery and aspects such as fatigue and nutritional problems. Common problems identified by the nursing team included difficulties encountered by the patient or carer in coping with this extremely stressful period of recovery from cardiac surgery, persistent wound pain and activity intolerance.

Basia et al (1990) recognised the benefits of monitoring patients and carers during the early postoperative recovery period. They suggested that improvements could be made in preparing the patients for recovery at home and in educating nurses to identify and respond to common recovery problems. Limitations of this study were also recognised by the investigators. Although the study highlighted the need for professional support during the early postoperative period, limitations such as the subjective data collection method and the omission of a control group were recognised by the investigators.

The study by Basia et al (1990) indicates that the carers of patients who have undergone cardiac surgery benefit from reassurance and emotional support during the early stressful postoperative period. This is supported by Artinian (1993) who reported that cardiac surgery affects the spouse more than any other member of the family. Documentation of symptoms such as anxiety, depression, low self-esteem, marital disharmony and psychosomatic symptoms have been experienced by spouses for up to one year after the cardiac event.

2.10 Cognitive Dysfunction in The Early Days of Cardiac Surgery

During the early days of cardiac surgery, postoperative cerebral complications were a recognised problem. In a report by Fox and Gifford (1954), it was stated that psychiatrists had first been attracted to the problem when frequent requests were made by surgeons to review patients who had developed depressive reactions following cardiac surgery.

Thirty two patients undergoing mitral valve surgery in the Peter Bent Brigham Hospital in Boston, Massachusetts were interviewed by psychiatrists pre- and postoperatively. This method of assessment focused mainly on the patient psychological coping mechanism to an increasingly debilitating physical condition, their reaction to the impending life-threatening operation, and assessment of their postoperative psychological state.

Three psychiatrists were involved in interviewing the patients pre- and postoperatively. They noted that six of the patients had obvious emotional disturbances after cardiac

surgery which had not been present preoperatively. Although the psychiatrists were aware of the physiological upheaval experienced by the patients, there was no indication that these disturbances could be attributed to the operation.

Progress as a Result of Research

By the late 1960s considerable research into the problem of cerebral complications following cardiac surgery had taken place and resulted in modifications to the technology, surgical technique and anaesthetic management.

In 1969 Javid et al (1969) of Chicago Illinois realised that in spite of technological and clinical progress, central nervous system (CNS) abnormalities continued to occur. Reports had identified psychological problems following cardiac surgery but had related these to insufficient preoperative counselling to allay anxieties, patient personality, and inability to cope with stress. Neurological complications, however, had been linked to emboli, calcium debris, and fat or air emboli during cardiopulmonary bypass. The cause of the problem remained unknown and the incidence varied from 13% - 70% according to various authors (Egerton, Kay, 1964; Blackly, Starr, 1964; Kornfield, Zimberg and Malm, 1965; Gilberstadt, Sako, 1967).

In an attempt to determine the incidence, extent and the reversibility of CNS damage in patients undergoing cardiothoracic surgery, Javid et al (1969) studied 100 adult patients undergoing surgery which included mitral, aortic and multiple valve replacements, congenital heart surgery and resection of aortic aneurysm.

Preoperative measurements involved neurological examination, visual acuity, and an assessment of mental status. Physiological information was collected by interview and the results of cardiac investigations retrieved from case records. During the intraoperative period haemodynamic measurements were made and continuous electrocardiogram (ECG) and electroencephalogram (EEG) data were recorded. A daily postoperative neurological examination and standardised assessment of mental status was performed. Independent judgements on behavioural changes were made from observation of the patient by a neurologist and the intensive care unit physicians. The study patients were re-assessed many times (no specific time periods were stated) during a two year follow-up period.

Results showed that 15 patients died within two weeks of surgery and in 41 patients clinical neurological signs were noted immediately following recovery from anaesthetic. These signs disappeared in most patients during the first two weeks following surgery. However, 16 of these patients had persistent neurological abnormalities. Behavioural disorders were observed in 35 patients in the first 24 hours after surgery and all of these patients had some degree of intellectual deficit. In 15 of these 35 patients, behavioural disturbances were mild and presented as intermittent confusion and lethargy. Mental status was abnormal in all 35 patients with loss of orientation and loss of memory (degree of memory loss was not stated) being the most prevalent problems. Both behaviour and mental status returned to the preoperative state two weeks following surgery. On follow-up at various stages of recovery from surgery, it was noted that 12 patients were discharged with residual neurological abnormalities. They were re-assessed at various stages throughout the two year follow-up period. Two individuals

from this group died from myocardial infarction. Another patient died 15 months after surgery from congestive heart failure. Three patients had minimal memory disturbance (according to their families they had not returned to their preoperative state) and the remaining six made a full recovery.

The incidence of neurological deficit following cardiac surgery had proved higher than expected by Javid et al (1969). Although the exact cause of brain damage could not be defined, the researchers believed that cerebral damage following cardiac surgery appeared to be related to inadequate blood flow to the brain during CPB. Assessment of risk factors revealed that advanced age, low mean arterial pressure during perfusion and prolonged CPB were significant causes of central nervous system damage during cardiac surgery.

Introduction of Coronary Artery Bypass Surgery

The surgical procedure, coronary artery bypass surgery for ischaemic heart disease, was introduced in the early 1970s. The successful results of this surgery as measured by relief of angina and improved quality of life, led to increasing use of this palliative surgical technique.

Despite continuing developments of technology and clinical advancements, a research team from America (Savageau, Stanton, Jenkins, Klien, 1985) reported that the incidence of behavioural disturbances and neurological impairment following cardiac surgery varied between 20% - 80%. In an attempt to achieve a better understanding of the extent of CNS dysfunction, Savageau et al (1982) conducted a two-year study. Data

were obtained from four centres, three in Massachusetts and one in New York. The study group comprised 227 patients (early assessment) and the aim of the investigation was to determine the cause of neuropsychological dysfunction following elective cardiac surgery.

Demographic details including medical and social history were obtained by standardised patient interview and questionnaire. Further medical details were retrieved from hospital records. Neuropsychological tests were administered at the preoperative and postoperative stages. The difference between scores on pre- and postoperative neuropsychological tests was analysed statistically. Patients were later classified as showing deterioration in function on a particular test if postoperative scores were more than one standard deviation (SD) lower than the preoperative score. Postoperative changes of more than 1SD were observed in each of the four scores derived from the testings in 11- 17% of patients

Savageau et al (1982) noted that other perioperative factors associated with reduced test performance seemed to be related to severity of trauma associated with operation. Factors which they identified included: time on bypass, cross-clamp time, duration of anaesthesia, length of operation time, blood loss, difficult intubation and hypotension. A follow up of this study was carried out at the six month postoperative stage. Of the 28% of 245 (study cohort stated in six month assessment) patients who showed deterioration in one or more tests at nine days following surgery, over 80% of these patients had returned to normal at the six month assessment. Savageau et al (1982) observed strong correlations between concurrent emotional and physical state and performance of

neuropsychological tests. Therefore, because of the lability of neuropsychological dysfunction, the investigators stated that repeated study measures should be well spaced out in time.

Criticism could be levelled at this study because of the discrepancy in the number of patients participating in the study. During the early assessment it was stated that the study cohort consisted of 227 patients while at the six month assessment, 245 patients were studied. Data were collected from four centres. Surgical technique in these centres probably differed and the neuropsychological tests would have been administered by different personnel. Although all staff involved were trained to administer the tests as accurately as possible, individual differences may exist.

By the mid 1980's adverse effects of cardiac surgery on the brain were being assessed using radiological methods such as computed tomography (Aberg, Ronquist, Tyden, Brunnkvist, Hultman, Bergstrom, Lilja, 1984). The use of a cerebral function analysing monitor was also well established (Bolsin,1986).

The Newcastle Experience

Shaw et al (1985) recognised the need to describe the grades of neurological complications after coronary artery bypass surgery (CABS). With the support of colleagues from the Newcastle University Department of Neurology, Cardiology and the Cardiothoracic Unit of Freeman Hospital, a prospective study took place between September 1983 and August 1984. The study investigated a cohort of 312 patients who underwent elective coronary artery bypass surgery. The study was designed to identify

the incidence, extent and clinical course of neurological and neuropsychological abnormalities after coronary artery bypass surgery. Another aspect researched was identification of pre-, intra-, and postoperative factors that may predispose to these complications. It was the first large-scale study in which patients undergoing coronary artery bypass surgery were assessed prospectively using clinical neurological and neuropsychological methods.

A consistent anaesthetic method and surgical technique was used on each patient. Two days before surgery a detailed clinical neurological assessment was undertaken to identify any neurological abnormalities, any previous neurological illnesses, and any potential risk factors for cerebrovascular disease. Cognitive evaluation, using a battery of ten standard neuropsychological tests, was also undertaken.

Neurological abnormality	*Results*
Peripheral nerve disorders Abnormalities of tendons Presence of primitive reflexes	Present in 30% of patients
Residual signs of stroke Retinal vascular occlusion	Present in 3% of patients
Ophthalmological abnormalities - e.g. Diabetic retinopathy Choroidoretinitis Retinitis Pigmentosa Glaucomatous changes	Present in 6% of patients
Parkinson's disease	Present in 3 patients
Amnesic syndrome	Present in 1 patient resulting from previous cardiac surgery

Table 2.1 Neurological Abnormalities Detected on Preoperative Examination (Shaw et al 1985)

Of the 312 patients, 35% had detectable neurological abnormalities on preoperative examination as shown in Table 2.1. Shaw et al (1985) recognised that identification of

such preoperative abnormalities emphasised the importance of prospective evaluation of patients.

Postoperative Neurological Assessment

Postoperatively, the patients' neurological state was assessed daily. Some neurological investigations were also performed when clinically indicated and these included computed tomography and electroencephalography. Neuropsychological tests were repeated on the seventh day.

At this early postoperative stage four patients died. Three of the deaths were due to cardiac disorders and one patient died from cerebral hypoxic damage. Sixty one per cent (191) of the patients developed new clinical abnormalities. These included prolonged depression of conscious level, stroke, ophthalmological abnormalities, primitive reflexes, psychosis, and peripheral nervous system abnormalities as shown in Table 2.2.

Neurological abnormality	*Results*
Prolonged depression of conscious level unrelated to drugs	Occurred in 3% of patients
Stroke	Occurred in 5% of patients
Ophthalmological abnormalities	Occurred in 25% of patients
Unilateral and bilateral retinal infarction	Occurred in 17% of patients
Symptomatic visual disturbances e.g. Blurring of vison Difficulty in reading Blurring or haziness of peripheral vision	Occurred in 46% of patients
Primitive reflexes	Developed by 39% of patients
Postoperative psychosis	Occurred in 1% of patients
Peripheral nervous system complications	Occurred in 12% of patients

Table 2.2 New Clinical Abnormalities Developed as Noted During Postoperative Assessment (Shaw et al 1985)

The 61% reported neurological abnormalities represent a high incidence, but it needs to be remembered that all severities of abnormality have been shown. Many of these abnormalities were asymptomatic or produced only mild disability.

Postoperative Neuropsychological Assessment

Early neuropsychological assessment of the patients in this study was performed seven days after surgery on 298 (95%) patients. Fourteen patients could not be evaluated because four had died, seven had been discharged early from hospital, and three declined to complete the study. Detailed neuropsychological testing was performed on patients using a battery of ten standard tests of cognitive function (Table 2.3).

Test	*Measurement of :-*
Halstead-Reitan trail making test	Reaction time Mental flexibility Visuo-spatial organisation
Wechsler Memory Scale Tests (WMS)	
WMS - Information	Six questions to assess patient's memory of personal and current information
WMS - Orientation	Five questions to test the patient's immediate orientation
WMS - Mental control	Consists of three subtests: Counting backwards from 20 to one Repeating the alphabet Counting in threes to 40
WMS - Logical memory	This test measures immediate recall of logical material
WMS - Digits total	Attention span Audioverbal immediate memory
WMS - Visual reproduction	Visual memory Visuo-spatial ability
WMS - Associate learning	Auditory memory New learning ability
Wechsler Adult Intelligence Scale (WAIS)	
WAIS - Block Design Test	Non-verbal reasoning Visuo-constructive ability
WAIS - Vocabulary	General intelligence

Table 2.3 Neuropsychological Tests (Shaw et al 1985)

Two hundred and thirty five (79%) of the 298 patients showed impairment in some aspect of cognitive function on the seventh postoperative day. Ninety two patients in this impaired group were impaired on one test only and 143 were impaired on several tests. The cognitive abilities which were compromised included psychomotor speed, attention and concentration, new learning ability and auditory short-term memory. Of the 235 patients whose neuropsychological assessment scores deteriorated after surgery, 123 of these patients were not aware of any cognitive disability while in hospital. Eighty nine patients were aware of a deterioration of their intellectual abilities, often complaining of memory impairment, difficulty concentrating and mental slowness. Although the incidence of cerebral impairment detected by psychometric testing following CABS is high, Shaw et al (1985) recognised that often this is not sufficiently severe to interfere with the patient's everyday activities in the hospital environment.

The difference between the pre- and postoperative score was the variable used in the statistical analysis of the data. Preoperatively, the mean and standard deviation for each test was calculated. Patients were considered to show significant deterioration on a particular test if the score after operation decreased more than one standard deviation below their preoperative score.

Shaw et al (1985) remarked that an important factor which should be taken into account when interpreting these findings is whether the neuropsychological deterioration could be due to general tiredness, depression, or lack of motivation following major surgery rather than the deleterious effects of cardiopulmonary bypass on the brain.

Cerebral Impairment after Cardiac Surgery - Psychologists' Viewpoint

Another major study by a research team (Newman et al 1987) from the Academic Department of Psychiatry, University College and Middlesex School of Medicine in London, examined patients undergoing CABS. Neuropsychological tests, used to assess cognitive function and regional cerebral blood flow (RCBF) measurements, were recorded preoperatively and at eight days and eight weeks following surgery.

Newman et al (1987) recognised the difficulty of finding a control group of patients with similar demographic characteristics, preoperative states and durations of surgery, but who did not require CPB. This resulted in some difficulty in trying to differentiate the effects of the surgical procedure from the specific effects of the extracorporeal circulation.

Sixty seven patients entered the study over one year. The control group comprised twenty four patients undergoing either major vascular surgery or major thoracic surgery. Standardised anaesthetic and surgical procedures were used. The Bentley Bubble Oxygenator was used in the extracorporeal circuit with a 'prime' of 1.5 litres of electrolyte solution. Pulsatile, hypothermic (28^0C) cardiopulmonary bypass was commenced at a flow of 2.5 litres/m^2/minute. The mean arterial pressure was maintained in the range of 50-100 mm Hg by the use of drugs.

The neuropsychological assessments were completed two days before surgery and eight days and eight weeks postoperatively. A battery of 10 tests was completed and the tests were similar to those used in other studies in order that a comparison might be made

(Table 2.4). Assessments of anxiety and mood state were made at each stage with an assessment of personality carried out preoperatively. The patient's physiological state was recorded throughout the course of surgery.

Test	*Measurement of :-*
Halstead -Reitan trail making test versions A and B	Reaction time Mental flexibility Visuo-spatial organisation
Rey Auditory Verbal Learning Test	Verbal memory
Purdoe Pegboard Test	Motor coordination
Wechsler Adult Intelligence Scale (WAIS)	
WAIS - Picture completion	General intelligence
WAIS - Vocabulary	General intelligence
WAIS - Block design test	Non-verbal reasoning Visuo- constructive ability
Computer applications	
Symbol digit replacement	Eye coordination
Choice reaction time	Reaction time
Non-verbal recognition memory test	Short term memory recall

Table 2.4 Neuropsychological Tests (Newman et al 1987)

Cerebral blood flow was measured at each stage after an intravenous injection of 12-15 mC1 Xenon-133 with a 10 detector system (Novocerebrograph 10a).

Neuropsychological impairment was measured by the change in performance from preoperative score to the eight-day and eight-week assessments. For each test a standard deviation of performance was calculated from all the preoperative scores. A patient showing a decrease of one standard deviation or more from his or her preoperative score, was considered to have a deficit in that test. Neuropsychological state was then classified according to the number of tests showing a deficit (Table 2.5).

Analysis of the data revealed that 73% of patients had a neuropsychological deficit at eight days following surgery (24% severe and 49% moderate) and 37% had

neuropsychological deficits at the eight weeks postoperative stage (1% severe and 36% moderate).

Level of deficit	Classification
Severe deficit	Patients showing a deficit in more than three tests.
Moderate deficit	Patients showing a decrease of at least one standard deviation in two or three tests.
No deficit	Patients showing a deterioration in one test or no deterioration noted in any test.

Table 2.5 Classification of Neuropsychological State (Newman et al 1987)

An association was sought between duration of cardiopulmonary bypass and the neuropsychological outcome eight days following surgery. Although Savageau et al (1982) had reported a relationship between duration of surgery (greater than seven hours) and neuropsychological outcome, Newman et al (1987) could find no association between these variables at the eight day postoperative stage.

Neuropsychological measures reflect cerebral dysfunction whereas measurement of regional cerebral blood flow (RCBF) provides some indication of how such cerebral damage occurs. In Newman et al's (1987) study RCBF showed a significant decrease eight days after cardiac surgery although this usually reverted to preoperative levels by eight weeks. In contrast, no overall change was noted in the RCBF of the control group at each of the three assessments.

According to Newman et al (1987), these results infer that RCBF in the early postoperative period is different when CPB is used. The extent of change in RCBF did not correlate with the neuropsychological deficits in CABS patients.

2.11 The Fort Lauderdale Conference

The cause of neuropsychological dysfunction remains unresolved. Cognitive assessment remains a complex issue and lack of consensus on the neuropsychological test battery to be used, definition of cognitive impairment, and in the methods of scoring and analyses of the test results, still exist. Although interest in researching this area continues, differences of opinion persist. For the first time, a meeting was held in Fort Lauderdale, America which offered an opportunity to attempt to achieve a consensus of opinion among the investigators present.

The conference entitled Central Nervous System (CNS) Dysfunction After Cardiac Surgery: Defining the Problem, brought together a multidisciplinary group, from all over the world, with an interest in cerebral physiology and outcomes after cardiac operations. The conference, held in Fort Lauderdale, Florida on December 10-11th 1995, included a review of cerebral changes during cardiopulmonary bypass, an exploration of the pathophysiology of postoperative cerebral dysfunction and a discussion of the methods used to assess neuropsychological outcome.

The assembled group at the conference in Fort Lauderdale brought together experts from disciplines as varied as psychology, neuropsychology, neurology, anaesthesia, cardiovascular surgery, epidemiology and biostatistics. A structured discussion, to find some consensus of opinion on the methods used to assess neuropsychological outcome,

was attempted at the concluding stage of the conference. A Consensus Statement was achieved which included issues such as:

1 Recognition that a spectrum of postoperative CNS dysfunction both acute and persistent occurs in a proportion of patients following cardiac surgery.

2 The necessity to assess the patient's preoperative neurological and neuropsychological state to elucidate any pre-existing CNS abnormalities.

3 Change in performance from preoperative (baseline) assessment to an assessment performed at a designated time after operation is essential to evaluate the impact of the operation.

4 Designs should incorporate the use of a control or comparison group.

5 Time constraints and physical limitations of the patient should be taken into account when selecting neuropsychological tests.

6 Care must be taken in performing the assessments, as neuropsychological performance can be influenced by environmental, psychiatric, physiological and pharmaceutical factors.

7 Mood state assessments should be performed concurrently with neuropsychological assessments.

8 Tests should be performed in a standardised manner.

9 As the incidence of neuropsychological dysfunction is highest in the immediate postoperative period and then declines, care must be taken to perform at least one assessment when the patient's performance is more stable. Ideally this should be at least three months postoperatively.

10 'Practice effect' must be taken into account. Repeated testing can improve performance.

Participants of this conference were encouraged that this important first step was taken in an attempt to standardise the approach to this complex problem.

2. 12 Modern Techniques To Reduce Cerebral Complications Following Cardiac Surgery

Anaesthetic Technique

Improved anaesthetic technique over the years has helped to reduce neurological and neuropsychological morbidity. More sophisticated monitoring systems have been devised and developments within the pharmaceutical industry have resulted in the availability of more effective drugs for the anaesthetic management of patients and treatment of cardiac disease (Smith and Aitkenhead, 1985). Senior anaesthetic staff specially trained in cardiac anaesthetic technique ensure an environment of optimum safety for patients undergoing cardiac surgery.

No single anaesthetic technique is preferred for cardiac surgery. Careful, accurate monitoring allows the anaesthetist to ensure that an adequate cardiac output and myocardial blood supply is maintained perioperatively.

Sufficient premedication is necessary on the evening before operation and on the morning of surgery. It is important that induction of anaesthesia can progress smoothly on a relaxed patient. Two anaesthetists and all supporting staff should be present during induction of anaesthesia, the theatre should be prepared and the extracorporeal circuit 'primed' ready for use. Following induction of anaesthesia all required cannulae should be inserted such as an arterial line into the radial artery and a central venous pressure line

into the internal jugular vein. A urinary catheter is inserted to monitor the patient's urine output. This is a measure of adequacy of renal function intraoperatively and during early stages of postoperative recovery.

During the period leading up to bypass the anaesthetist ensures that the patient's heart rate and arterial pressure remain stable. Additional intravenous analgesic drugs or inhalational anaesthesia may be required at this stage. Close monitoring of arterial blood gases, coagulation by measuring the activated clotting time, and observation of serum potassium levels are important before cannulation of the major vessels.

Two factors must be taken into account when considering anaesthesia during cardiopulmonary bypass. First, the haemodilution by the priming solution from the extracorporeal circuit which dilutes the effect of the drugs. Second, cardiopulmonary bypass prevents the use of inhalational anaesthesia because the circuit bypasses the lungs. Anaesthesia is usually maintained by intravenous administration of opioids such as morphine, and muscle relaxants such as pancuronium. Often a continuous intravenous infusion of a short-acting anaesthetic will be administered throughout the cardiopulmonary bypass stage.

Cross-clamping of the aorta usually precedes surgery on the heart; this prevents backflow of blood into the left ventricle and the coronary arteries. The aorta is clamped between the aortic cannula and the aortic valve thus depriving the heart of oxygenated blood supply. During this phase the myocardium is at risk of ischaemic damage unless measures are taken to reduce myocardial oxygen consumption. Myocardial preservation

is achieved by administration of cardioplegic solution, which is high in potassium content, around the coronary arteries to arrest the heart. There is also a concurrent filling of the pericardial sac with cold saline. Hypothermia is also induced to reduce the basal metabolic rate, usually to a temperature of 28^0C - 32^0C as requested by the surgeon. Further administration of cardioplegic solution is repeated if myocardial activity becomes evident.

Perfusion during cardiopulmonary bypass is dependent on the extracorporeal pump's flow rate and the patient's systemic vascular resistance. It is difficult to assess clinically under hypothermic conditions and often anaesthetists assess perfusion by measurement of the patient's urine output reflecting adequate organ perfusion.

Anticoagulation must be maintained during CPB. Therefore, the activated clotting time (ACT) is measured at regular intervals to ensure the recording remains greater than 400 seconds otherwise further dosage of heparin would be required.

Oxygen delivery is assessed regularly throughout surgery by measurements of arterial blood gases. Oxygen carriage is dependent on haemoglobin concentration, therefore packed cell volume is also assessed regularly and should not be allowed to decrease below 20%. Further reduction can be prevented by administration of concentrated packed cells.

Serum potassium should be maintained at approximately 4.5 m.mols/litre by administration of intravenous potassium chloride.

Restoration of the heart beat occurs when the cross-clamp is removed and oxygenated blood is allowed to flow through coronary arteries once again, flushing out any residual cardioplegic solution. Occasionally the heart beat will commence spontaneously in sinus rhythm, but often ventricular fibrillation occurs. Internal defibrillation is required to convert to sinus rhythm. Rewarming commences at this stage. When the body temperature reaches 36°C and heart is in sinus rhythm, an attempt is made to assess the ability of the heart to maintain an adequate cardiac output. Mechanical ventilation will then be resumed. When the bypass cannulae have been removed, residual effects of heparin will be counteracted with intravenous protamine sulphate. Inotropic support may be required when CPB is discontinued, either by administration of a small dose of calcium chloride or intravenous dopamine.

Following CPB circulation is maintained by use of drugs to maintain cardiac function and oxygen supply to the tissues. Temperature control, biochemical monitoring and maintenance of cardiac rhythm are important at this stage. The patient is then transferred to the cardiac intensive therapy unit and maintained on intermittent positive pressure ventilation until his or her condition stabilises.

Surgical Technique

Results of cardiac research have made surgeons aware of the neurological and neuropsychological problems which can occur postoperatively. Although the mortality rate from cardiac surgery has decreased to a figure as low as 2%, the existence of neuropsychological problems still persist in varying degrees. 'Surgical success may no

longer be assessed by survival alone - it is the quality and duration of life which has become important' (Smith and Taylor, 1993).

Vulnerable stages of cardiac surgery well recognised as potential risk events are: cannulation of the major vessels which may be plaque-lined, cross-clamping the aorta to isolate the heart from the CPB circuit, myocardial protection during arrest of the heart, sudden effects of haemodilution and cooling during CPB. Commencement of rewarming, also venous and aortic decannulation are known risk events. Great care is taken by surgeons at all stages throughout the procedure to minimise the associated risks.

Near Infrared Spectrometry

The maintenance of an adequate and continuous supply of oxygen is a fundamental requirement for the survival of all tissue cells. The situation is particularly acute in the brain where cessation of the blood flow to the cerebral cortex can result in loss of function within 4-6 seconds, loss of consciousness in 10-20 seconds, and irreversible cell damage in 3-5 minutes.

Near infrared spectrometry is a technique used to measure cerebral oxygenation and oxygen utilisation. This non-invasive method of measurement is based on the principles of pulse oximetry in which infra red light is used to detect changes of oxygenation.

Blood Oxygenation

It has been known for many years that oxygenated blood appears a bright red colour whereas deoxygenated blood is a dark bluish red. This observation which is due to the

different absorption properties of oxy- and deoxyhaemoglobin, has led to several optical techniques being developed to monitor blood oxygen levels.

In 1935 Matthes (1935) showed that the ratio of detected light at two wavelengths shone through the skin was related to the oxygen status of the blood contained within it. He built a device which was able to follow trends in oxygenation but could not produce quantitative data due to other background absorbing substances within the tissue sample volume. Further refinements were made to this technique over the years.

Nakajima (1975) recognised that the pulsatile component of the light absorption trace was due to change in the blood volume associated with each heart beat and therefore originated in arterial blood. In 1980 Yoshida (1980) reported an instrument that measured the arterial oxygen saturation using the pulsatile component of the absorption signal. This was the start of pulse oximetry, a technique that is now in widespread use throughout the world.

Blood Oxygen Utilisation

Cytochromes are proteins with an iron-containing group (haem) capable of existing alternately in a reduced form or an oxidised form. They form part of the electron transport chain, transferring electrons from flavoproteins to molecular oxygen. There are at least five cytochromes in the mitochondria (a structure found in the cytoplasm of all cells): cytochromes b, c, c1, a and a3. The terminal two cytochromes in the chain (a and a3) form a copper-containing complex, cytochrome oxidase which is the only component of the chain capable of reducing molecular oxygen.

The last cytochrome in the electron transport chain cytochrome a3, passes its electrons to one-half of a molecule of oxygen (0_2). This becomes negatively charged, then picks up two hydrogen molecules (2H+) from the surrounding medium to form water (H_20). This is the point in aerobic cellular respiration where oxygen is consumed.

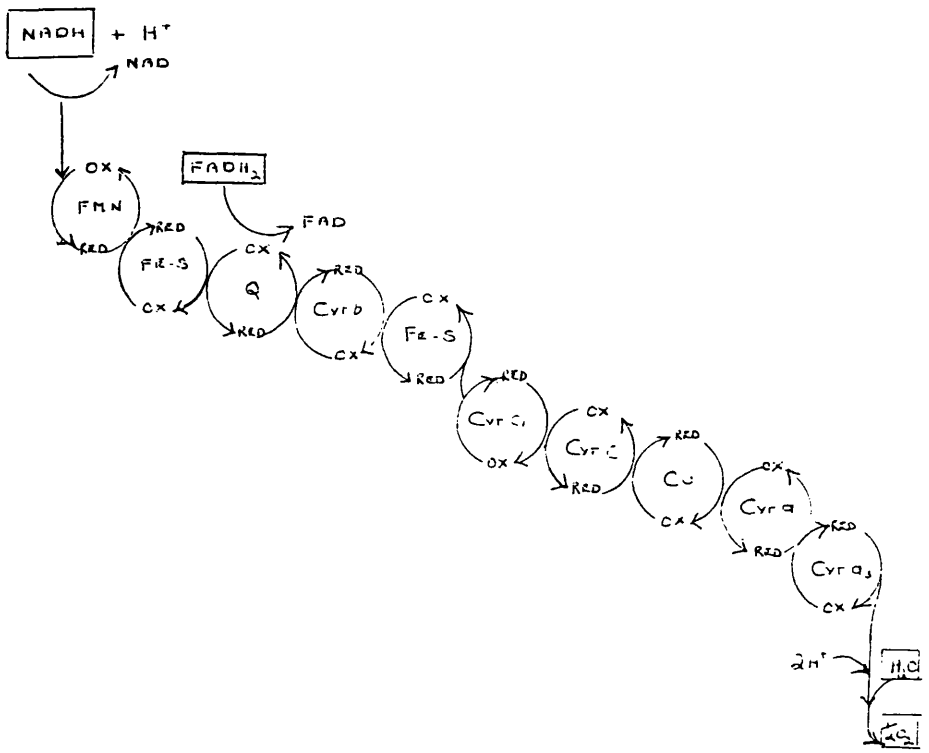

Figure 2.2 **Electron Transport Chain** (Adapted from Figure 25.6 Principles of Anatomy and Physiology Tortora and Grabowski, 1993)

Cytochrome aa3

Keilin (1925) was the first to report changes in the absorption spectra of cytochrome aa3. This observation was used by Chance (1951) who further developed the technique and produced an instrument for measuring cytochrome absorption *in vitro* using visible light.

Haemoglobin and Cytochrome aa3 Oxidase

The application of Near Infrared Spectroscopy (NIRS) for monitoring tissue concentration of haemoglobin and cytochrome oxidase was first proposed by Jobsis (1977). Since that time several groups have developed research instrumentation mainly for application in neonatal cerebral monitoring.

The first NIRS devices were only capable of monitoring trends which were proportional to changes in cerebral oxygenation. To enable changes to be quantified the optical pathlength of the light had to be calculated. This was achieved in 1988 by Delpy (1988) who demonstrated that pathlength could be calculated by measuring the 'time of flight' of picosecond pulses of photons through the tissue. However apparatus required for 'time of flight' measurements is large and expensive so it is not feasible to build into a clinical monitor.

Knowing the average optical pathlength has enabled NIRS devices to monitor quantified changes in chromophore concentration from a predefined baseline but the goal of absolute quantification has remained elusive.

2.13 The Study Concept

The development of the new Critikon research monitor with the facility to measure cerebral oxygenation and oxygen utilisation non-invasively, was the motivating factor for the study described in this thesis.

Clinical application of this monitor relies on the theory that first, while the skull, tissue and skin are opaque to visible light, they are transparent to near infrared light (700-1300nm). Second, within biological tissue few compounds absorb near infrared light (NIR), and only haemoglobin and cytochrome aa3 change their NIR absorbence. The advantage over previous methods of measuring brain metabolism was that it non-invasively and continuously measured the concentrations of oxygenated and deoxygenated haemoglobin and Cytochrome aa3 (Caa3), also known as cytochrome oxidase.

Cerebral Monitoring During Cardiac surgery

Such a technique for early detection of cerebral hypoxia stimulated the idea of its potential value as a monitoring tool to detect impending brain damage during cardiac surgery. Could this technology be used as a clinical tool to identify the moment of cerebral damage intraoperatively in patients undergoing cardiac surgery? If it proved successful in identifying the occurrence of such a problem, anaesthetists could perhaps use interventional measures e.g. neuroprotective drugs, to reduce the incidence and severity of cerebral damage associated with cardiac surgery. Discussion with colleagues from various academic specialties appropriate to the problem area, about the feasibility of this research project, led to a positive response.

Clinical aspects of the project were supervised by a consultant anaesthetist. To define the incidence and severity of cognitive impairment caused by cardiac surgery, the patients required neuropsychological assessment pre- and postoperatively. This involved the application of a battery of neuropsychological tests. To select the appropriate tests,

educate the research nurse on the application of these tests, and advise on the analyses of the neuropsychological data, the expertise of a behavioural scientist was deemed necessary. The organisation, implementation and management of the complete study was the responsibility of the author, as research nurse.

Consideration was then given to the various dimensions of the study. It was agreed, to achieve reliable results, a large study population would be required. The involvement of statisticians was therefore necessary to help analyse the large volume of study data.

From a practical viewpoint, the logistics of such a study were carefully considered before a timescale of two years was decided. Some thought was also given to the experimental environment i.e. cardiac theatre and cardiothoracic ward, and approval of the study by the appropriate personnel from these departments was pursued.

The study hypothesis was defined, study design and method considered, consent form devised (Appendix 3), and a research proposal written. Application for financial support for this research project, submitted to the Scottish Home and Health Department, was successful. Ethical approval for this proposed research project was then sought and received from the local Ethics Committee.

CHAPTER THREE

STUDY METHOD

3.1 The Study Hypothesis

The primary objective of the study was to ascertain the cause of the intraoperative problem with a long-term desire to reduce the incidence and severity of brain damage after cardiac surgery. The hypothesis was that there is a relationship between Near Infrared Spectroscopy findings and the occurrence of postoperative cognitive deficits. The null hypothesis was therefore that there is no relationship between Near Infra Red Spectroscopy findings and the occurrence of postoperative cognitive defects.

Stages of the Study

Testing the hypothesis involved the following stages:-

1 ***The Control Phase*** - To determine the 'normal' patterns of cerebral oxygenation and oxygen utilisation changes in patients undergoing anaesthesia for non-cardiac operations in 50 patients.

2 ***The Retrospective Phase*** - To identify patterns of cerebral oxygenation and oxygen utilisation in 50 cardiac patients which relate to the measurements of cognitive deficits detected after operation.

If this part of the study revealed indicators of impending cognitive impairment in the groups of patients, the next stage would be to investigate whether such damage could be predicted in individual patients and possibly prevented by interventional measures (e.g. neuroprotective drugs) during the operation.

3 ***The Prospective Phase*** - To test prospectively the relationships discovered in the Retrospective Phase in a further 100 patients undergoing cardiac surgery.

A two-point analysis approach was preferred as it leads to stronger conclusions. It was recognised that any detailed analysis of any large volume of data would produce associations by chance that are unimportant. Such associations can be distracting; however, if two completely separate groups i.e. retrospective and prospective, are analysed and the same associations turn up, then one can be confident that they represent a true relationship.

3.2 Design and Planning Phase

To achieve a degree of consensus with researchers who had recently undertaken major studies of the cerebral problems caused by cardiac surgery, the methods and outcome measures of these studies were closely scrutinised. The study design was therefore partly influenced by the work of two research teams: the Newcastle Group whose chief investigator was a clinician (Shaw et al, 1985), and the Middlesex Group headed by a psychologist (Newman et al, 1987).

The Research Team

The Investigators of this study included an anaesthetist, a behavioural scientist and a senior statistician. Co-workers in the study included an assistant statistician and a research nurse (Appendix 2).

The research nurse's responsibilities included careful planning and effective management of the complete project. Efficient organisation while setting up the study, and completion of a pilot study were necessary for the smooth running of the project. Patient recruitment to the study was followed by the commencement of the data collection phase. This involved the administration of neuropsychological tests at three different stages, preoperatively, and at six days and six months after surgery. Continuous measurement of patients' cerebral oxygenation and oxygen utilisation was logged on to computer during surgery. The neuropsychological tests were scored and results entered into patients' case record files before submission to the statisticians to complete the preliminary analysis.

To maintain effective communication throughout the project, it was the research nurse's responsibility to organise regular meetings with the aim of updating team members of study progress and to resolve any problems encountered at each stage. During each phase of data analysis, the results were assessed by the team and decisions made about the next stage of the analytical procedure.

Communication with 'Critikon' Personnel

Regular communication with the personnel from 'Critikon', the company who supplied the cerebral monitor, was thought important and of mutual benefit. The Critikon Cerebral Oxygen Utilisation Monitor (CCOUM) was a new technical development and training in the use of this device was essential. The training was provided by a company training manager. A 'Helpline' facility was available and this proved to be useful, particularly at the early stage of the study. Up-to-date literature relating to the use of

this technology was regularly provided by the company. An informative description of the study was presented to company personnel by the study group at an early stage. This had the effect of not only creating interest in the clinical application of the CCOUM, but also conveyed the magnitude of the project. The company then became aware of the potential value of this project as a test of the validity of this device.

Study Population

During the retrospective stage of the study, 25 patients chosen randomly from the general surgery list, were entered into the study as a control. This was followed by the entry of a further 50 patients, randomly chosen from the operation lists of two cardiac surgeons. These patients were undergoing elective cardiac surgery. A further 70 patients undergoing elective cardiac surgery, were then selected randomly from the cardiac operation lists during the prospective stage of the study.

Exclusion factors included: patients with existing neurological disease; those receiving drugs affecting the brain; patients with impaired vision or impaired limb movements; and those with inaccessible home location, due to the difficulty accessing patients for the six month follow up appointment.

Timescale of the Research Project

It was envisaged that the project would take two years to complete. Practical difficulties such as the time constraints when assessing patients preoperatively, the clinical condition of the patients at six days, and continued cooperation of the patients at the six month assessment, were considered. The six month assessment would often be completed in

the patient's home. Intraoprerative monitoring involving long periods in the cardiac theatre (approximately three to four hours per patient) was also taken into consideration.

Setting of the research

The research study was conducted in the general and cardiothoracic wards and theatres of the Western Infirmary Glasgow.

Neuropsychological data collection entailed the assessment of patients pre- and postoperatively at six days and six months. The neuropsychological tests were administered by the author at the appropriate stages. Clinical data collection involved intraoperative cerebral monitoring of patients using the CCOUM. Recording operation events, anaesthetic and cardiopulmonary bypass details, and retrieval of the patient's medical history from the Case Records were also the author's responsibility.

Neuropsychological Assessment

Application of a battery of neuropsychological tests to determine evidence of cerebral impairment in patients pre- and postoperatively at six days, was completed in the ward. To avoid distraction during the administration of the tests, it was essential that the neuropsychological assessment was performed in as quiet an environment as possible. Therefore, a room adjacent to the ward was used for this purpose. Occasionally the six month neuropsychological assessment was also performed in the ward, if requested by the patient. Alternatively, assessments were administered in the patient's home environment.

Clinical Data Collection

Using the CCOUM, cerebral oxygenation and oxygen utilisation were measured continuously throughout the course of surgery. Ideally, cerebral monitoring should have been commenced in the anaesthetic room prior to induction of anaesthesia, however, this was impractical. The bulky nature of the cerebral monitor and computer, very fragile sensor cable, and the amount of equipment already sited in theatre, excluded this as an option.

Communication with ward and theatre personnel

Cooperation of the medical and nursing staff was necessary for the smooth running of the project. Therefore, prior to the commencement of the study, details of the proposed research project were distributed to the appropriate personnel. A meeting with the cardiac surgeons resulted in agreement of two consultants to include their patients in the study. Meetings were also arranged with the nursing staff in the general and cardiothoracic wards, Cardiac Intensive Care Unit and general and cardiac theatres, to discuss the forthcoming research study. Such topics as patient access, the requirement of a suitable room for application of the study tests, and possible practical difficulties which could be encountered in theatre were discussed. The study generated considerable interest as the nursing staff often observe the difficulties some patients experience postoperatively as a result of neurological impairment.

Ethical Considerations

It is essential that the rights of all patients who participate in research studies are protected. Therefore, each institution involved in research must submit research

proposals to an ethics committee for review. Investigators must comply with all recommendations by the committee before approval of the study is given.

The research proposal and copy of a consent form was submitted to the Western Infirmary Ethics Committee by the investigators of the study and approval was granted.

Informed Consent

The consent form (Appendix 3) provided a comprehensive account of the research project which made it easily understood by the patient. The title, objectives and patient's involvement in the study were clearly defined. Patients were assured of confidentiality throughout the study process, particularly pertaining to data storage. Case Record Files were stored in a locked filing cabinet which could be accessed only by study personnel.

Patient consent was preceded by a detailed verbal description of the project and discussion about the patient's expected participation in the study. Although it was important that the patient understood their commitment to the project, they were assured that they could withdraw from the study at any time. On agreeing to participate in the project, the patient and a witness (the research nurse) signed the consent form. The form was then retained in the patient's Case Record File.

Data Collection Methods

Data Requirements for the Study

Identification of the necessary variables required for data analysis of this study was carefully completed by the research nurse at this stage. This information was used for

the compilation of Case Record Files and by the statisticians to set up a database. Clinical and neuropsychological variables were considered.

Clinical Variables

Initially, the relevant demographic data were defined. Appropriate variables concerning the patient's medical and cardiac history were then selected. The anaesthetic data included all the drugs used for premedication, induction and maintenance of anaesthesia throughout the operative procedure. Intraoperative measurements of arterial blood gases and activated clotting time, during cardiac surgery, were also noted. It was hoped that haemodynamic measurements, recorded by the cardiac monitor, would be downloaded continuously to the computer via an Interface Pod (Figure 3.1). The relevant details about the functioning of the extracorporeal circuit during the cardiopulmonary bypass phase of cardiac surgery were described. Postoperative observations including any sudden change of the patient's condition, and data relating to the patient's recovery during this phase, were recorded.

Neuropsychological Assessments

The neuropsychological assessment for each patient involved the application a battery of 10 tests. Individual and total scores for each test were recorded using standardised methods. These results were documented at three stages during the study: preoperatively, six days postoperatively and six months after surgery.

Methods used to log the study data

Case Record Files

A manageable data recording system and effective filing system was a priority to prevent loss of such a large volume of data and to ease accessibility. Using the 'Tables' facility of the Microsoft Word computer software, the Case Record Files were designed. Separate files were compiled for the general and cardiac patients (example in Appendix 3). The design and compilation of the Case Record Files were based on the requisite variables at the appropriate stage of data collection.

Filename

Individual patient files were numbered in chronological order. Each patient also required a computer filename. The construction of each filename included the patients' initials, age, gender, indication of stage of study, and a file number.

Operation History

It was important that the patient's operation history was recorded. Reference could then be made not only to the normal stages of surgery but also the adverse events. A chart was designed to record these events (Appendix 3) and entered into the appropriate Case Record File on completion

Operation events could also be logged on the computer. This facility was useful, particularly during cardiac surgery. Vulnerable moments for the patient such as cannulation of major vessels, commencement and discontinuation of cardiopulmonary

bypass and rewarming were recorded in real time. Any adverse events were also noted using this method.

Components of the Critikon Cerebral Monitoring System

The cerebral monitoring system included the Cerebral Oxygen Utilisation Monitor (CCOUM) and the Interface Pod which were both linked to a personal computer (Illustration 3.1) and a Sensor (Illustration 3.2).

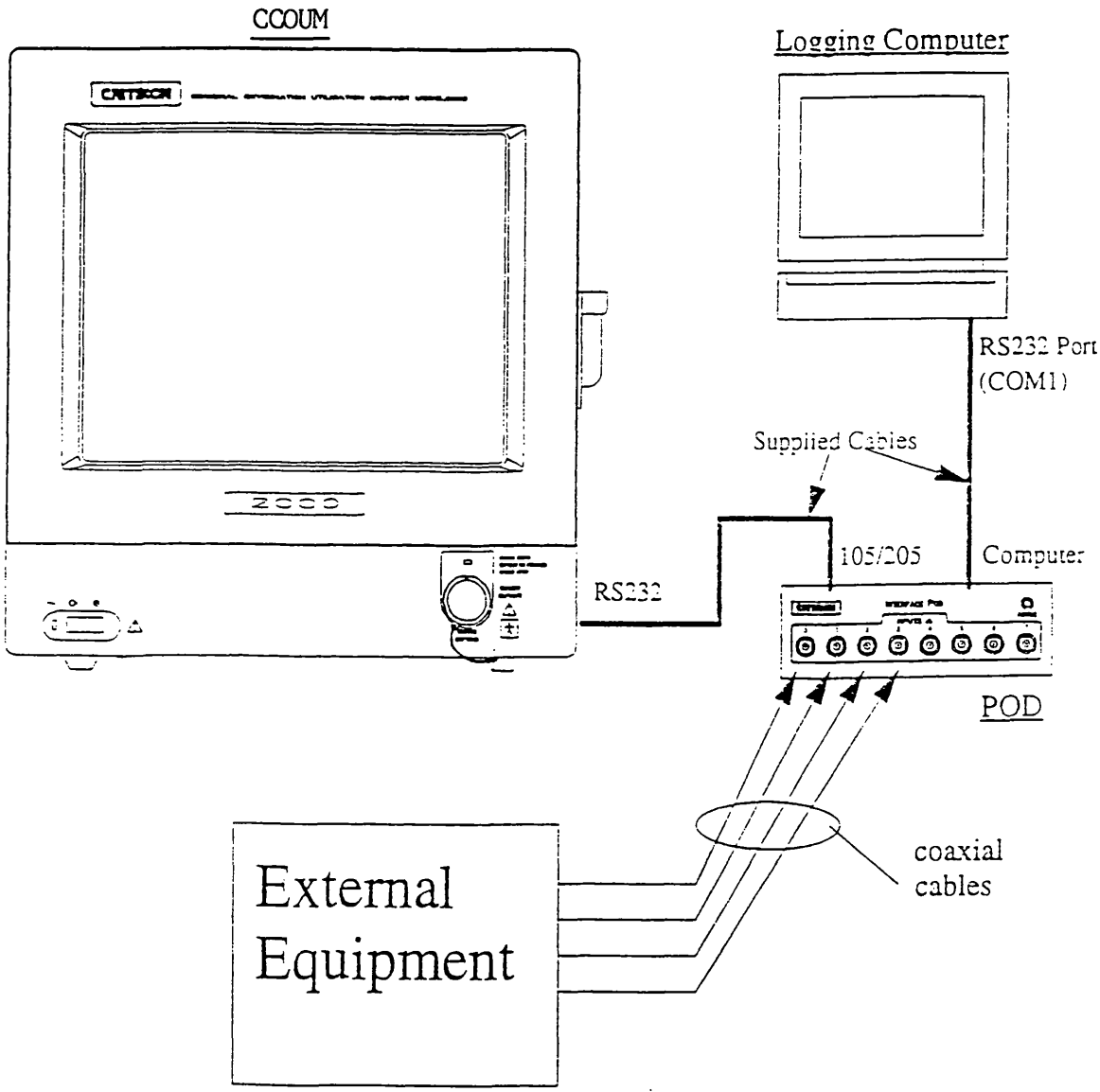

Figure 3.1 Diagram of the Cerebral Monitoring System

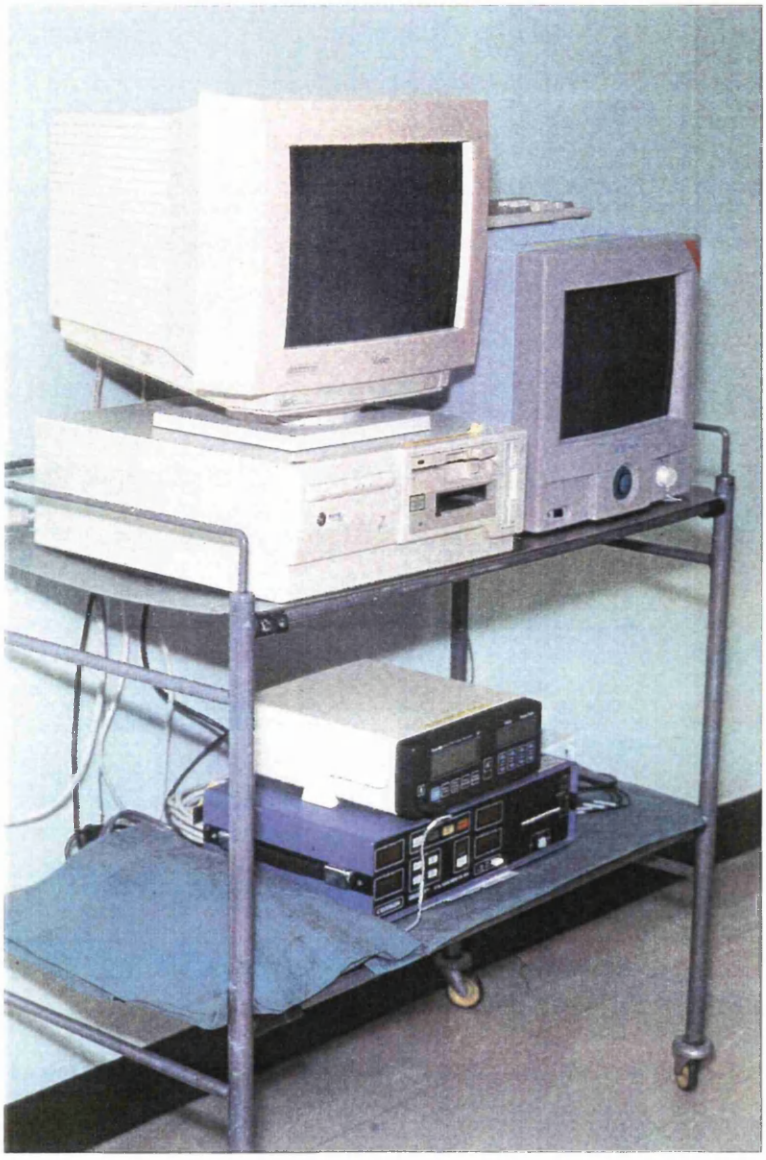

Illustration 3.1 Critikon Cerebral Oxygen Utilisation Monitor, PC, Interface POD, Dinamap Monitor and Pulse Oximeter.

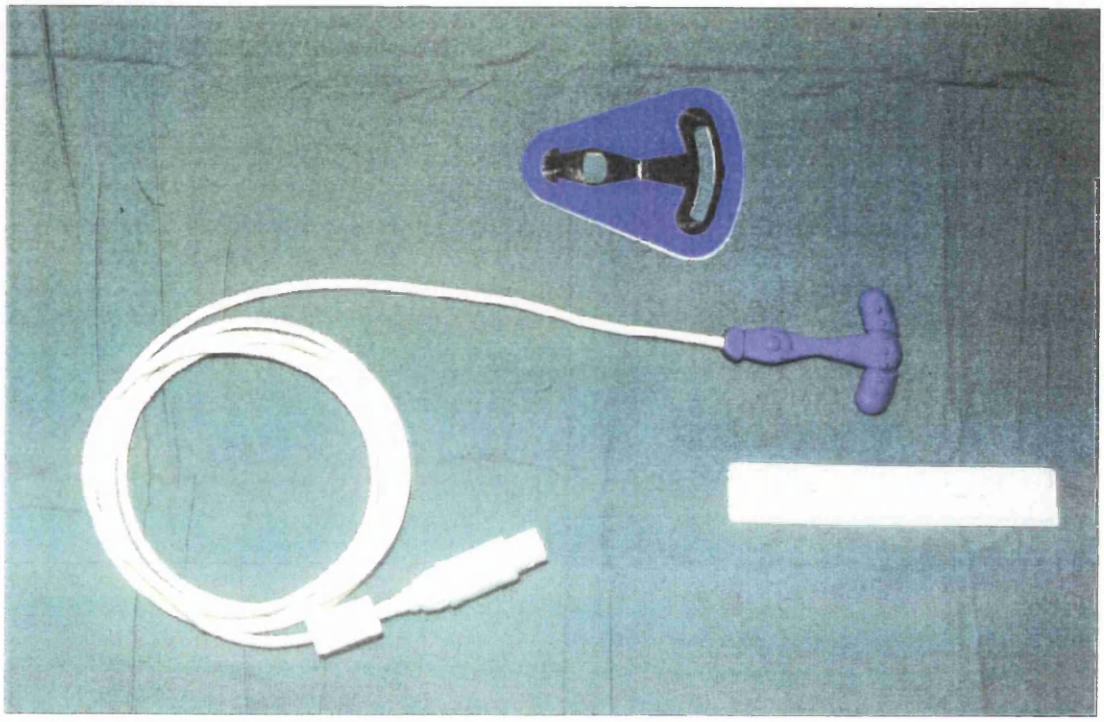

Illustration 3.2 **CCOUM -** Sensor and Fibre-optic Cable

The software used to record the results of the cerebral monitoring, the Critikon PC Data Logger/Review software was provided by 'Critikon'. This allowed the user to log on to the hard disk and view in real time on the PC screen, the data produced by the cerebral monitor. Operation events were also recorded using the Data Logger.

Neuropsychological Assessment

Detection of cognitive impairment involved the application of a battery of neuropsychological tests as a diagnostic measurement. These tests assessed various aspects of cognition such as memory, attention and concentration, mental flexibility and psychomotor ability.

A similar set of neuropsychological tests to those used in previous major studies by Shaw et al (1985) and Newman et al (1987) were chosen for this study. Tests of memory, attention and concentration, and mental flexibility involved several paper tests while those for psychomotor evaluation used a computer programme. They were applied at three different stages during the research study period: preoperatively, six days postoperatively and six months postoperatively. Four questionnaires were also completed by the patients, three of which were repeated at each stage of the study.

Tests Used for Neuropsychological Evaluation

The Eysenck Personality Inventory (Eysenck and Eysenck, 1984) was the chosen method of assessing personality as it evaluates the various dimensions which were of interest in the study. These include extroversion, neuroticism and a lie-scale which measures any

tendency in the respondent to put himself or herself in an unrealistically positive light. The questionnaire was completed by the patients at the preoperative stage. The other questionnaires included: the Beck's Depression Inventory (Beck and Steer, 1987) which was used to determine mood state; the State-Trait Anxiety Inventory (Spielberger, Gorsuch, Lushene, Vagg, Jacobs, 1983) measuring the level of anxiety experienced by the patient in response to their situation (state anxiety), and proneness to anxiety in stressful situations (trait anxiety); and a Subjective Assessment Scale, a self assessment of memory, which was compiled by the behavioural scientist. The National Adult Reading Test (Nelson and Willison, 1991) was the first of 12 tests applied during the neuropsychological assessment. The patients were asked to read aloud a list of 50 words which were printed in order of increasing difficulty. The recognition and pronunciation of the words were recorded by the examiner. This test is frequently used by clinical psychologists and psychiatrists as an assessment of intelligence. The Benton Visual Retention Test (Benton, 1992) was applied as a measure of visual perception and memory. This is a figure-drawing task and to reduce practice effects, was presented at each assessment in a different form. Tests of memory, attention span, concentration and new learning ability were measured using subtests from the Wechsler Memory Scale - Revised (WMS-R) version (Wechsler, 1987). Included in this group were tests of attention span and audioverbal memory, Digit Span Forward and Digit Span Backward. Visual memory, concentration and new learning ability were measured using the subtests Verbal Paired Associates and Visual Paired Associates. Both these subtests had versions measuring delayed recall which were applied after a delay of at least 30 minutes. The Digit Symbol Substitution Task, a subtest of the Wechsler Adult Intelligence Scale - Revised (WAIS-R) version (Wechsler, 1981), was used to assess visual-motor speed.

The Stroop Test (Trenerry, Crosson, DeBoe, Leber, 1989) which has been used by psychologists since 1935, is a reliable measurement of cerebral damage, particularly frontal lobe damage. Psychomotor evaluation was completed using a computer programme called PsychE (Hope, Woolman, Gray, Asbury, Millar, 1998). Two tests were used from this computer programme. These included Numeric Vigilance which is a test measuring speed of motor response and Dual Task: Tracking (primary) and Visual Reaction Time measuring fine motor coordination and reaction time. The time involved for the administration of the neuropsychological tests was approximately one hour. Details of all the neuropsychological tests can be found in Appendix 4 and copies of the neuropsychological test record forms can be located in Appendix 5.

Factors Influencing Selection and Application of Neuropsychological Tests

Reliability of the test results of neuropsychological evaluation was dependent on several factors such as the patient's physical condition, anxiety or mood state, time limitation, size of test battery, complexity of tests, environment and learning effect. The time available to apply the battery of tests was limited because of clinical demands, therefore, this was a prime consideration when the number of tests to be included was selected. The number and complexity of tests should not be too demanding for patients recovering from cardiac surgery. Prior to application of the tests it was important for the examiner to build up a rapport with the patients to help them relax. Application of the tests was carried out in a quiet environment to avoid distraction. A room situated outwith the ward was used for this purpose. To avoid the learning effect which can occur when tests are repeated, a different form of the test was applied at each assessment

CHAPTER FOUR

DATA ANALYSIS

(Flowchart in Appendix 6 highlighting the various stages of the data analysis)

4.1 Retrospective Phase of Analysis

The study attempted to answer the following questions:-

1. Do the neuropsychological results differ between the patients undergoing general surgery and those undergoing cardiac surgery?
2. In the cardiac group alone, do any patients' neuropsychological assessment results indicate impairment, and could this be identified by the Critikon monitor?

Analysis of 50 Cardiac Patients vs 25 General Surgery Patients

Neuropsychological tests were administered before surgery, six days postoperatively and six months after surgery. Analysis was carried out on the differences for each patient between their preoperative (baseline) and postoperative scores. The research team decided to use this method as the variability is reduced by considering differences and it is therefore a more sensitive way of analysing the data. The differences of the 50 cardiac surgery patients were then compared with the 25 general patients.

Differences Between Pre- and Postoperative Six Day Scores

The differences between the pre- and postoperative six day scores were calculated for each patient. A comparison was then made between the groups using non-parametric analyses as the normality assumptions for the majority of outcomes was not valid. Using the Mann-Whitney test and Chi-Squared test, a statistically significant difference between the cardiac and general surgery patients occurred on twelve occasions (probability of less

than 0.05). Three neuropsychological tests which distinguished between the two groups consistently were, the WMS-R subtest Verbal Paired Associates, the WAIS-R subtest Digit Symbol Substitution Task, and the Stroop Colour-Word Task.

Differences Between Pre- and Postoperative Six Month Scores

The differences were calculated for each patient between their pre- and postoperative six month scores. Non-parametric comparisons of the two groups were then made using the Mann-Whitney test and Chi-Squared test. A statistically significant difference between the cardiac and general surgery patients occurred on eight occasions (probability of less than 0.05). The neuropsychological tests which distinguished between these two groups were the WMS-R subtest Verbal Paired Associates and the WAIS-R subtest Digit Symbol Substitution Task.

The results of the six day and six month differences therefore indicated that the tests which distinguished consistently between the two groups were WMS-R subtest Verbal Paired Associates and WAIS-R subtest Digit Symbol Substitution Task.

Defining Impairment in Cardiac Surgery Patients

A method of differentiating between impaired and unimpaired cardiac patients had to be defined before further analyses could continue. The definition of neuropsychological impairment varied in previous studies due to disparity in the test methods and number of neuropsychological tests applied. Therefore, no ideal method of defining impairment has yet been identified.

Professor K Millar (behavioural scientist), basing his interpretation of the neuropsychological test results on experience, identified a group of patients he considered to be impaired. This was determined by their postoperative test results at six days and six months after surgery. Although this was a subjective method, it was a first step in an attempt to define cognitive impairment.

In comparison, a scoring system was devised by the statisticians to identify objectively, impaired and unpaired patients. The results of each test were standardised (i.e. the mean was subtracted and divided by the standard deviation) if the data were considered to be normally distributed. As a good response could be indicated by either a positive or negative result depending on the test, all variables were converted so that good responses were positive.

The variables were ranked into five groups and weighted, depending on their real life relevance and importance, as specified by the behavioural scientist. A total score for each patient was calculated as 5 x rank1 + 4 x rank2 + 3 x rank3 + 2 x rank4+ 1 x rank5. A list of the normally distributed tests and their ranks is given on page 92.

The total score could not be calculated if even a single test score was missing. If any of the ranks were missing then a Maximum Likelihood Estimation of the missing data was carried out, based on the other values attained for that individual. This was calculated using the computer statistical package BMDP (Biomedical Package). If however too

many values were missing and it was not possible to estimate missing data, a standardised value of zero was used.

The variables considered to be normally distributed were ranked into five groups as follows (rank one is most important):-

Rank	Test
1	Verbal Paired Associates- Maximum Easy
1	Verbal Paired Associates- Maximum Hard
1	Verbal paired Associates- Maximum Total
1	Delayed Verbal Paired Associates- Maximum Hard
1	Delayed Verbal Paired Associates- Maximum Total
1	Visual Paired Associates - Sets 1-111
2	Digits Forward
2	Digits Backward
2	Digits Total
3	DSST - Total Number of Symbols Copied
3	DSST - Total Copied Correct
3	DSST - Total Time to Copy 3 Rows
3	Stroop Colour Word Task - Correct
4	PsychE Test - Mean Reaction Time
4	PsychE Test - On Target
4	PsychE Test - Vigilance Hits
5	Benton Visual Retention Test - Number Correct
5	Benton Visual Retention Test - Number of Errors

Table 4.1 Ranking of Variables Into Five Groups, Depending on Their Real Life Relevance and Importance

The patients' test results were reassessed by the behavioural scientist in light of the statistical impairment results. On reassessment there were only a few patients whose impairment assessment differed using the two strategies. However, following comparison of the two systems it was decided to use the statistical method of defining impairment as this method was more reproducible and less open to bias.

The statistical method led to a score for each patient which could be analysed in two ways. The binary definition of impairment catagorised the patients into either impaired or unimpaired state according to a predefined score. The continuous definition, or actual level of impairment according to the ranked score, was the alternative and more sensitive method. Both methods were used to analyse the study data.

Identifying Impaired Cardiac Surgery Patients Using Near Infrared Spectroscopy

The Critikon data monitor produces four sets of data: oxygenated haemoglobin (O_2Hb), deoxyhaemoglobin (HHb), total haemoglobin (tHb) and cytochrome aa3 (Caa3). These variables are displayed continuously during the operation and recorded once per second (Figure 4.1). For analysis, the CCOUM data was exported into Excel and imported into Minitab (computer statistical packages).

Cardiac surgery is lengthy surgery lasting several hours. Because of the volume of data produced, the study team decided that the amount of data required should be reduced in some way. The two stages of operation thought to be most relevant to the patient were commencement of cardiopulmonary bypass, and rewarming to discontinuation of cardiopulmonary bypass. Therefore, these two stages were considered in detail.

Graphs were produced for each patient detailing the behaviour of the four measurements at the two relevant stages of their operation (Appendix 7). Much variation was seen on viewing the graphs, but there appeared to be no consistent difference between impaired and unimpaired patients. Despite reducing the volume of NIRS data to consider the

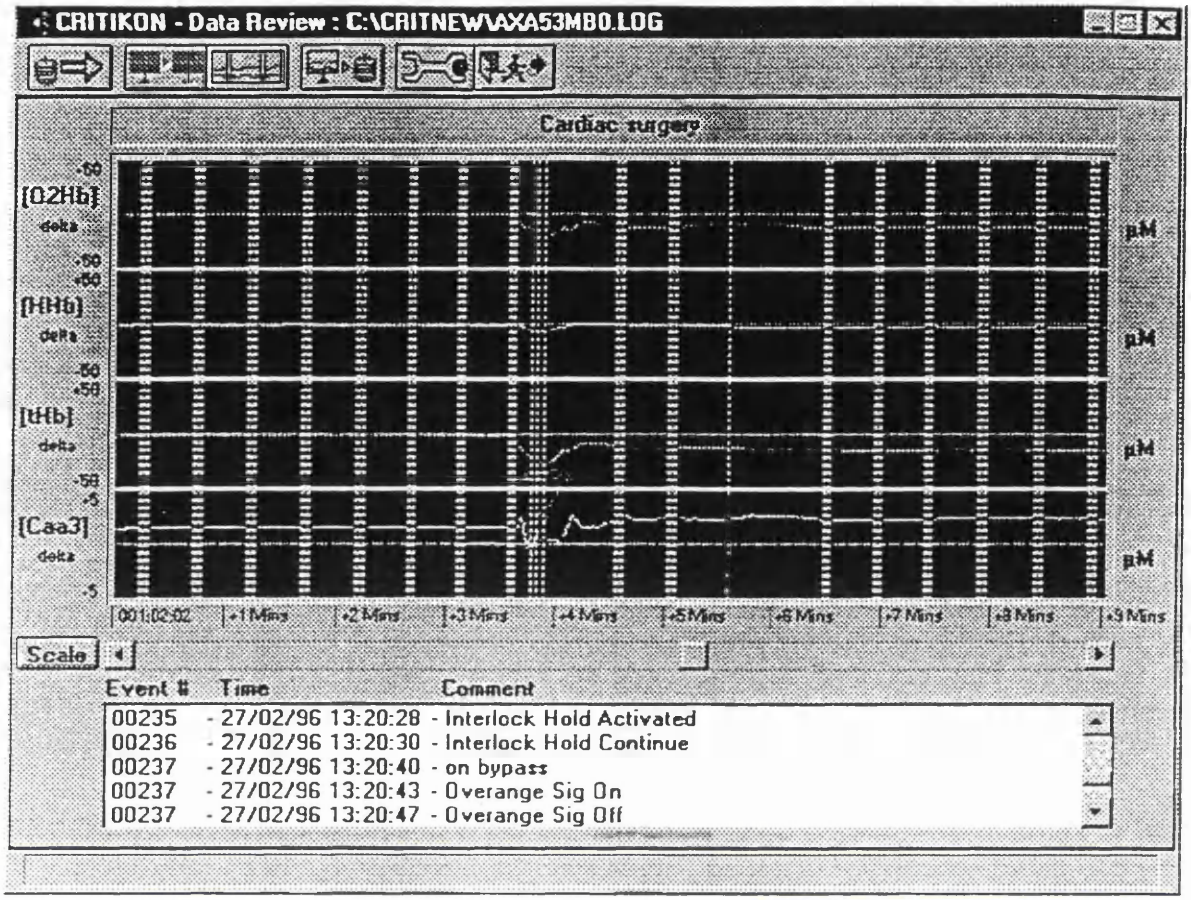

Figure 4.1 NIRS Datalogger

stages of surgery most relevant to cardiac patients, the CCOUM monitor had so far proved ineffective in identifying impaired cardiac patients.

Review of NIRS Measurements

It was at this stage of the study that notification of recent research findings by the staff of the Medical Physics Department, University College London, was provided by Critikon, the company who devised the cerebral monitor. Although Near Infrared Spectroscopy was increasingly used as a method of measuring cerebral oxygenation, concern was being expressed about the effect of the clear cerebrospinal fluid (CSF) on the distribution of

light in the head (Firbank, Arridge, Schweiger, Delpy, 1996). Previous studies had considered only the scattering effect of light on the layers of tissues; however, Firbank et al (1996) studied the effect of non-scattering (clear) layers on the distribution of light in the head while using NIRS technology. Calculations and comparisons were made using experimental and theoretical models of light transport and the investigators concluded that a thin non-scattering layer, (cerebrospinal fluid), between two scattering regions (scalp and skull, and the brain), had a significant effect on the light distribution. The light-piping effect of the cerebrospinal fluid layer considerably reduced the amount of cerebral tissue being measured. Measurements indicated that in NIRS, the brain may only contribute 10-20% of the total optical pathlength instead of the expected 80%. The implications of this finding were that further technological development would be necessary if Near Infrared Spectroscopy was to be used as a valid method of measuring cerebral function. Future analysis of the study data had also to be carefully considered.

Pseudo - Regional Saturation Measurement

The advantages of cerebral regional oxygen saturation measurement were given consideration at this stage for two reasons. Firstly, because of the detrimental effect of CSF on the measurement of cerebral oxygenation using NIRS, regional oxygen saturation may provide a more accurate measurement. Second, reduction of the two data streams which determine cerebral oxygenation (oxyhaemoglobin and deoxyhaemoglobin) to one measurement (regional oxygen saturation) would facilitate data analysis. Unfortunately the Cerebral Oxygen Utilisation Monitor type 2001 used in the study did not allow this parameter to be measured directly.

Realising the benefit of a cerebral regional oxygen saturation measurement to future analysis, the research team devised a mathematical method of calculating this parameter. Because it was not a direct measurement of cerebral oxygen saturation, the term pseudo-regional saturation was developed for this calculated measurement.

Calculation of pseudo-regional saturation

Pseudo-regional saturation is an artificial measure. In constructing such a measure, some scaling was required to convert the raw NIRS data to pseudo-regional saturation. The formula used to calculate a pseudo-regional saturation measurement was:

$$\text{Pseudo-Regional Saturation (\%)} = 100 \times \left(\frac{A + O_2Hb}{B + tHb} \right)$$

Measurements available in the equation were oxyhaemoglobin (O_2Hb) and total haemoglobin (tHb), A and B were initially unknown. Critikon advised that the normal range for cerebral regional oxygen saturation was between 65% and 75% during the early stable period of anaesthesia. Using the patient data in this period, and first guess values for A and B, a pseudo-regional saturation was calculated for each patient. The range of the pseudo-regional saturations were checked, and the calculation repeated with different volumes of A and B until all the pseudo-regional saturations lay in the range 65-75%. The final values obtained for A and B were 7900 and 12000 micromoles per litre (of tissue), respectively. Using these values for A and B, the pseudo-regional calculation was then applied to the rest of the data.

Using this calculation of pseudo-regional saturation, graphs of the whole operation (smoothed data) were produced for all patients who showed impairment at six days and

six months. Rewarming to time off bypass was another phase of the operation which was of interest, and therefore graphs of this period were also produced.

There was some indication by visual inspection of the graphs that the impaired patients had lower pseudo-regional saturation values at rewarming to time off bypass (Appendix 7). To investigate the probability of this observation, means and gradients were used to summarise the data on the following periods:-

1. Mean rewarming time plus five minutes
2. Mean off bypass time plus five minutes
3. Gradient rewarming time plus five minutes (a summary measure reflecting the rapidity of rewarming during this phase. A graph was formed and a regression line was drawn through the plotted data collected during this specified time period. The greater the gradient, the more rapid the rewarming phase.)
4. Gradient off bypass time plus five minutes
5. Mean off bypass time plus five minutes minus mean rewarming time plus five minutes

Impaired and Unimpaired

For each of the summary measures, the two states impaired and unimpaired (impaired if patient's impairment score was below zero) were compared using two sample t-tests. Comparisons were carried out using both six days and six month postoperative measurements. No statistically significant difference was found between the impaired and unimpaired patients (Table 4.2).

Continuous Impairment

The actual level of impairment score, as a continuous measurement, was also used to investigate any relationship with the summary measures of regional saturation. Using Pearson's correlation coefficient, correlations were sought between each of the summary measures and the level of impairment at six days and six months. No statistically significant correlation was found between the summary measures and actual level of impairment (Table 4.2).

Comparisons made with Summary Measures of Pseudo-Regional Saturation	**Statistical Method**	**Conclusion**
Impaired/Unimpaired patients (impaired if the patient's impairment score was below zero)	Two sample t-tests	No significant difference was found between impaired and unimpaired patients.
Continuous definition of impairment (actual level of impairment)	Pearson's correlation coefficient (Parametric distribution)	No significant relationship was found between summary measures and actual level of impairment.
Individual neuropsychological tests	Spearman's correlation coefficient (Non-parametric distribution)	No variable appeared to be a suitable predictor of the summary value of pseudo-regional saturation.

Table 4.2 Summary of Results - Comparisons Made With Summary Measures of Pseudo-Regional Saturation

Individual Neuropsychological Tests

Correlations were then sought between the individual test results and the summary measures of pseudo-regional saturation. In all the cases the data (six days or six months 'differences') were converted so that a positive value indicated an improvement. Spearman's correlation coefficient was used as the data were not all normally distributed. Significant correlations were found in a number of cases, but this was sometimes due to a test having only one or two outlying values. Although a trend could be observed, either

negative or positive, no variable appeared to be a suitable predictor of the summary value of pseudo-regional saturation (Table 4.2).

Summary Measures for Oxygenated Haemoglobin

As with summary measures of pseudo-regional saturation, attention was focused on the period of surgery from rewarming plus five minutes to off bypass plus five minutes. The summary measures calculated included: mean rewarming time plus five minutes, mean off bypass time plus five minutes, gradient rewarming time plus five minutes, gradient off bypass time plus five minutes, and mean off bypass time plus five minutes minus mean rewarming time plus five minutes.

Impaired and Unimpaired

Using a two sample t-test the impaired and unimpaired results were compared with the summary measures for oxygenated haemoglobin. Comparison was carried out using both six day and six month postoperative measurements. No significant difference was found for either impaired or unimpaired patients for any summary scores (Table 4.3).

Continuous Impairment

Because of the parametric distribution of data, Pearson's correlation coefficient was the method used to compare actual level of impairment and summary measures of oxygenated haemoglobin. Both six day and six month postoperative data were tested, but no significant correlation was found (Table 4.3).

Individual Neuropsychological Tests

A correlation was sought between individual test results at six days and six months and summary measures of oxygenated haemoglobin. Spearman's correlation coefficient was used because of the non-parametric distribution of the data. No variable was found to be a suitable predictor of the summary value of oxygenated haemoglobin (Table 4.3).

Comparisons made with Summary Measures for Oxygenated Haemoglobin	**Statistical Method**	**Conclusion**
Impaired/Unimpaired patients (Impaired if the patient's impairment score was less than zero)	Two sample t-tests	No significant difference was found between the impaired and unimpaired patients for any summary scores.
Continuous definition of impairment (actual level of impairment)	Pearson's correlation coefficient (Parametric distribution)	No significant correlation could be found.
Individual neuropsychological tests for both methods	Spearman's Correlation coefficient (Non-parametric distribution)	No variable appears to be a suitable predictor of the summary value of oxygenated haemoglobin.

Table 4.3 Summary of Results - Comparisons Made With Summary Measures for Oxygenated Haemoglobin

Temperatures and Mean Arterial Pressure During Cardiac Operations and Total Time On Bypass

Attention was now directed towards the clinical measurements recorded throughout the course of surgery. These operation details were compared with impaired and unimpaired patients at the six day and six month postoperative stage. Because of the non-parametric distribution of the data, the Mann-Whitney Test was used. The continuous level of impairment was also used to test for any relationship with the clinical measurements using Spearman's Correlation coefficient. Core temperatures, mean arterial pressure and

length of time on bypass were considered to be the most relevant variables to assess (Summary of results in Table 4.4 and detailed results in Appendix 8).

No statistically significant difference was found between impaired and unimpaired patients or actual level of impairment for any temperature, pressure or time.

Comparisons made with Operation Details	**Statistical Method**	**Conclusion**
Impaired/Unimpaired patients (impaired if patient's impairment score was less than zero)	Mann-Whitney Tests (Non-parametric distribution)	No statistically significant difference was found between the impaired and unimpaired patients for any temperature, pressure or time.
Continuous definition of impairment (actual level of impairment)	Spearman's Correlation coefficient (Non-parametric distribution)	No significant correlation was found between the temperatures, pressure or time and actual level of impairment **Closest to significance being total time on bypass at six months with a probability of 0. 061.**

Table 4.4 Summary of Results - Comparisons Made With Operation Details

Neuroticism Score at Baseline

The neuroticism score at baseline was analysed to detect if any differences could be observed between the impaired and unimpaired patients at the postoperative six day or six month stage using the two sample t-test. The actual level of impairment was then used to test for any relationship with the neuroticism score at baseline using Pearson's correlation coefficient

Although no statistically significant difference could be found in the impaired and unimpaired patients, the impaired group were noted to have higher neuroticism scores

than the unimpaired group. The neuroticism score at baseline was highly negatively correlated with the actual level of impairment at six days (probability of 0.005). (Summary of results in Table 4.5 and detailed results in Appendix 8).

Comparison with neuroticism score at baseline	**Statistical Method**	**Conclusion**
Impaired/Unimpaired patients (impaired if patient's impairment score was less than zero)	Two sample t-tests	Although no statistically significant difference could be found, the values at six days had a probability of 0.08. The impaired group had higher neuroticism scores than the unimpaired group.
Continuous level of impairment (actual level of impairment)	Pearson's correlation coefficient (Parametric distribution)	**The neuroticism score at baseline was highly negatively correlated with the actual level of impairment at six days (p=0.005). As before the higher the neuroticism score, the more impaired the patient.**

Table 4.5 Summary of Results - Comparisons With Neuroticism Score at Baseline

The strong correlation between neuroticism and impairment at six days suggested a potential predictor of impairment during the prospective stage of analysis.

Multivariate analyses

The objective of this analysis was to determine independently useful predictors of impairment at six days and six months. Before carrying out any multivariate analyses, univariate tests were performed on the State and Trait Anxiety, Sex and Age to determine whether there were any differences between the impaired and unimpaired patients.

Univariate Tests

1- State and Trait Anxiety at Baseline

Using two sample t-tests, impaired and unimpaired postoperative results at six days and six months were compared with state and trait anxiety results at baseline. No statistically significant differences were noted although the impaired group had higher trait anxiety scores than the unimpaired group. A comparison was then made between the continuous level of impairment postoperative results at six days and six months, and state and trait anxiety results at baseline. Pearson's correlation coefficient was the method used as the data were normally distributed. Neither state or trait anxiety scores were correlated with impairment at six days or six months (Table 4.6).

Comparison with State and Trait Anxiety at Baseline	**Statistical Method**	**Conclusion**
Impaired/Unimpaired patients (impaired if patient's impairment score was less than zero)	Two sample t-tests	No differences were significant at the 5% level, although the comparison of trait anxiety at baseline between the impaired and unimpaired patients at six months was close to the borderline (p= 0.07). The impaired group had higher trait anxiety scores than the unimpaired group.
Continuous level of impairment (actual level of impairment)	Pearson's correlation coefficient	Neither the state or trait anxiety score were correlated with impairment at six days or six months.

Table 4.6 Summary of Results of Univariate Tests - Comparisons With State and Trait Anxiety Scores at Baseline

2 - Age

Using a two sample t-test, a correlation was sought between impaired and unimpaired patients' results and age. A statistically significant difference in ages at the postoperative six day stage was noted (probability of 0.02). Older patients were more likely to be impaired. A significant correlation was also noted (probability of 0.008) when a

comparison was made between continuous level of impairment results and age. Because the data were normally distributed, Pearson's correlation was the statistical method used (Table 4.7).

Comparison with Age	Statistical Method	Conclusion
Impaired/ Unimpaired patients (impaired if patient's impairment score was less than zero)	Two sample t-test	**There was a statistically significant difference in ages at six days (P=0.02). Older patients were more likely to be impaired.**
Continuous level of impairment (actual level of impairment)	Pearson's correlation coefficient	**A significant correlation exists between impairment at six days and age (P=0.008). The higher levels of impairment are for older patients.**

Table 4.7 Summary of Results of Univariate Tests - Comparison With Age

3 - Sex

A comparison between impaired and unimpaired patients' results, and sex of patient was made using the chi-squared test. There was no statistically significant difference between impaired patients and sex of patient although at six days, a higher proportion of females than males were impaired. A correlation was then sought between continuous level of impairment results and sex of patient using the two sample t-test. No statistically significant difference was found at either six days or six months (Table 4.8).

Comparison with sex of patient	Statistical Method	Conclusion
Impaired/Unimpaired patients (impaired if patient's impairment score was less than zero)	Chi-squared test	There was no statistically significant difference in impaired patients between the males and females, although at six days a higher proportion of females than males were impaired ($p = 0.09$).
Continuous level of impairment (actual level of impairment)	Two sample t-tests	No statistically significant difference was found between males and females at either six days or six months.

Table 4.8 Summary of Results of Univariate Tests - Comparison With Sex of Patient

Multivariate Analyses: Stepwise Logistic Regression

Multivariate analysis was carried out to determine which factors at baseline were independently useful predictors of outcome. Outcome was defined as either impaired or unimpaired states or by the actual level of impairment. Stepwise logistic regression was the method used by which all potential predictors of impairment were considered and through which the combination of variables providing the most predictive power were chosen. Stepwise regression operates in a sequential manner. It begins with NO variables in the predictive model for outcome, then the most useful predictor of outcome (i.e. that with the smallest probability value) is brought into the predictive model of outcome. This is equivalent to finding the variable that is most highly correlated with the dependent variable. The significance of every other variable, adjusting for the most useful variable is then calculated. If any of the remaining terms can add a significant amount of additional predictive information, the most significant of these is added into the predictive model at the next step. This process is repeated until none of the terms excluded from the model can add significantly to the predictive power of those variables included in the model. At this stage the process halts and a set of independently useful predictors of outcome is obtained.

A value which is obtained from the regression model is R^2, the coefficient of determination. This measures the percentage of variability explained by the model. The closer this value is to 100% the stronger the linear relationship between impairment and the explanatory variable.

The factors allowed to enter the model were:

Pseudo-regional saturation:

- mean rewarming time
- mean off bypass time
- gradient rewarming time
- gradient off bypass time
- mean rewarming time-off bypass time

Neuroticism - at baseline

State anxiety - at baseline

Trait anxiety - at baseline

Sex

Age

The operation details (temperature, blood pressure and duration of operation) were not included in the model as the data did not follow a normal distribution and no normalising transformation could be found. (Summary of multivariate test results in Table 4.9)

Although the following operation details were not included in the above models because of non-parametric distributions, it was still necessary to evaluate whether they added any significant information when considered individually. The five variables were: core temperature at rewarming (during CPB), core temperature at off bypass, lowest mean arterial pressure during bypass, lowest core temperature during bypass, and total time on bypass

Due to the non-normality of the data, the data were converted to binary variables, either above or below the median value. The variables were then allowed to enter the previous

models. In each case none of the above variables added any information to the final models.

Predictors of Outcome	Statistical Method	Conclusion
Impaired/Unimpaired patients (Impaired if patient's impairment score was less than zero)	Stepwise logistic regression	*Six day analysis* **Age was entered into the model first. Once this factor was in the model no other variable adds a significant amount of information, and therefore the final model is age alone** *Six month analysis* No model was fitted here as no factor added any significant information
Continuous level of impairment (actual level of impairment)	Stepwise regression	*Six day analysis* **Neuroticism was entered into the model first, and allowing for this effect, Regional Saturation Average Off Bypass was still contributing a considerable amount to be included into the model. Once this factor was included no other variable was needed. For this model the value of $R^2 = 32\%$, therefore this is not a very good predictive model (a minimum of $R^2 = 70\%$ variance would be required to be termed a good result).** Six month analysis No model was fitted here as no factor added any significance

Table 4.9 Summary of the Results of Multivariate Analysis - Predictors of Outcome

Summary of Retrospective Phase of Analysis

A statistical method of defining cognitive impairment was used, and the cardiac group was subdivided into impaired and unimpaired sub-groups. Difficulties were experienced when trying to identify impaired cardiac patients using Near Infrared Spectroscopy and

an attempt was made to overcome this by devising a pseudo-regional saturation measurement. Graphs of the pseudo-regional saturation measurements - postoperative results at six days and six months (whole operation-smoothed), illustrated a slight separation of impaired and unimpaired patients at this stage. This would be tested again during the prospective stage of analysis. Variables with parametric and non-parametric distributions were analysed to determine potential predictors of impairment. Despite close scrutiny of this large volume of data and allowing for slight variations in anaesthetic and surgical techniques, only three factors were identified as possible predictors of impairment: pseudo-regional saturation, age and neuroticism. Their significance would again be examined during the prospective stage of analysis.

4.2 Prospective Stage of Analysis

Introduction

This stage involved analysis of the data for the remaining 70 cardiac patients. The same statistical methods used in the retrospective analysis, were applied during the prospective stage of analysis.

NIRS monitoring

As with the retrospective stage of analysis, the data from the Critikon Cerebral Oxygen Utilisation Monitor was exported into Excel and imported into Minitab (computer statistical packages).

Of the 70 cardiac patients, relevant data were available for 63 patients. Four patients had invalid NIRS data due to technical difficulties, one patient had a corrupted NIRS file, one

patient had no data recorded due to resuscitative measures being administered from the time of induction of anaesthesia, and one patient's surgery was abandoned due to evidence of pericardial infection.

Pseudo-Regional Saturation

The same formula was used as in the retrospective stage of the study and the pseudo-regional saturation was calculated for the whole operation. The pseudo-regional saturation formula was:-

$$\text{Regional Saturation (\%)} = 100x((7900 + O_2Hb)/(12000 + tHb))$$

Graphs of the whole operation (smoothed using a three minute averaging interval) were produced, for impairment at six days and six months. As for the retrospective stage the time period of most interest was the rewarming to off bypass phase of the operation; graphs were also produced for this period. No separation of the results between impaired and unimpaired patients were noted on these graphs.

Prospective Analysis - Summary Measures for Pseudo-Regional Saturation

Impaired/Unimpaired Patients and Continuous Level of Impairment

Summary measures were repeated on the prospective group data to test the difference between impaired and unimpaired patients for pseudo-regional saturation. Identical time periods and selection of summary measures were calculated using corresponding methods of analyses. No statistically significant difference was found between impaired and unimpaired patients or actual level of impairment for any summary measure.

Individual Neuropsychological Tests

As the overall level of impairment was not found to correlate with summary measures for pseudo-regional saturation, the individual neuropsychological test results were used instead. Although significant correlations were seen in nine variables (Appendix 8), the relationships were weak and inconclusive.

Comparison with Retrospective Group of Cardiac Patients

As for the retrospective group of cardiac patients, no statistically significant results were noted for pseudo-regional saturation, defining impairment as both a binary and continuous measurement.

When analysing the individual neuropsychological test results the significant test results for the prospective group of patients were completely different from the significant test results for the retrospective group of cardiac patients. This was probably a chance finding.

Prospective Analysis - Summary Measures for Oxygenated Haemoglobin

Impaired/Unimpaired Patients and Continuous level of Impairment

Again corresponding time periods, selection of summary measures and methods of analyses were used to calculate summary statistics for the prospective group of patients. A significant difference was found between the impaired and unimpaired patients for the gradient rewarming, at six months, with a probability of 0.04. No significant correlation was found between the summary measures and the actual level of impairment.

Individual Neuropsychological Tests

As before, the individual test results were analysed. Significant correlation was found in nine of the variables (Appendix 8). Again, some of the significant correlations are due to a test having only one or two outlying values. In the other tests although a trend could be observed, no variable appeared to be a suitable predictor of the summary value of oxygenated haemoglobin.

Comparison with Retrospective Group of Cardiac Patients

For the retrospective group of cardiac patients, no significant results were noted for oxygenated haemoglobin, defining impairment as either a binary or a continuous measurement. For the prospective group of patients a significant result was noted for gradient rewarming at six months, between the impaired and unimpaired patients. However if the continuous level of impairment was used no significant correlation was noted.

When analysing the individual neuropsychological test results, the significant test results for the prospective group of patients were completely different from the significant test results for the retrospective group of cardiac patients. This was probably a chance finding.

Prospective Analysis - Temperatures and Mean Arterial Pressure During Cardiac Operations and Total Time On Bypass

Corresponding time periods, intraoperative measurements and methods of analyses were used to analyse the prospective group data.

Impaired/Unimpaired Patients

Significant differences were found between the impaired and unimpaired patients for Lowest Core Temperature, at six days and Total Time On Bypass, at six days (Appendix 8). The impaired patients, at six days, had a lower core temperature and had a longer time on bypass. This difference is not apparent between the impaired and unimpaired patients at six months.

Continuous level of impairment

A significant correlation was found between the Total Time on Bypass and the level of impairment at six days (Appendix 8). As with the previous definition of impairment, the higher the level of impairment the longer the time on bypass.

Comparison with Retrospective Group of Cardiac Patients

No significant results were noted for the retrospective cardiac patients, however a significant relationship was noted for the lowest core temperature during bypass (impaired vs unimpaired) and for the Total Time on Bypass (impaired vs unimpaired and continuous level of impairment), both at six days.

Neuroticism Score at Baseline

The neuroticism score at baseline was again analysed using the same time periods and corresponding analytical methods.

Impaired/Unimpaired Patients and Continuous Level of Impairment

No statistically significant difference was found between the impaired and unimpaired patients and the neuroticism score at baseline. Similarly no correlation was found using the actual level of impairment.

Comparison with Retrospective Group of Cardiac Patients

For the retrospective set of cardiac patients the only significant relationship noted was between neuroticism at baseline and the level of impairment at six days. For the prospective group this was not noted.

Prospective Phase - Multivariate Analyses

As at the retrospective stage of analyses of cardiac patients' data, there was an interest in finding independently useful predictors of impairment at six days and six months. Before performing the multivariate analyses, univariate tests were performed on the State and Trait Anxiety, Sex and Age to detect any differences between impaired and unimpaired patients.

Prospective Phase - Univariate Analyses

The same time points and analytical methods were applied as for the retrospective group of cardiac patients.

Impaired and Unimpaired Patients

No significant differences were found for State and Trait Anxiety at Baseline or Sex. A statistically significant difference in Ages at the postoperative six days and six months stages was noted (Appendix 8). Older patients were more likely to be impaired.

Continuous level of impairment

Neither the State or Trait anxiety scores, Sex or Age was correlated with impairment at six days or six months.

Comparison with Retrospective Group of Cardiac Patients

During the retrospective analysis of cardiac patients using the continuous definition of impairment, there was a negative correlation with Neuroticism at six days. A correlation also existed between impairment and age and the older the patient, the more likely they were to be impaired. No such correlation between impairment and Neuroticism was noted at the prospective stage of analysis.

Prospective Phase - Multivariate Analyses: Logistic and Stepwise Regression

Stepwise logistic regression was performed to determine which factors at baseline are independently useful predictors of outcome. This was achieved using the same method as for the retrospective group of cardiac patients. The factors allowed to enter the model were: pseudo-regional saturation (mean rewarming time, mean off bypass time, gradient rewarming, gradient off bypass and mean off bypass-rewarming time), Neuroticism, State anxiety and Trait anxiety all at baseline, Sex and Age. The operation details (temperature, mean arterial pressure and duration of operation) were not included

in the model as the data did not follow a normal distribution and no normalising transformation could be found.

Impaired/Unimpaired and Continuous Level of Impairment

Analysing both definitions of impairment, no model was fitted as no factor added any significant information at six days or six months.

Operation Details

Although the operation details were not allowed to enter the above models, it was still necessary to evaluate if they added any significant information. Due to the non-normality of the data, the variables were converted to binary variables, either above or below the median value. The variables were then allowed to enter the previous models.

Impaired/Unimpaired Patients

Six Days Analysis

Time On Bypass was entered into the model first. Once this factor was in the model no other variable added a significant amount of information. Therefore, the final model was Time On Bypass alone.

Six Month Analysis

Again, Time On Bypass was entered into the model first. Once this factor was in the model no other variable added a significant amount of information. Therefore, the final model was Time On Bypass alone.

Continuous Level of Impairment

No model was fitted either at the six day or six month analysis as no factor added any significant information.

Comparison with Retrospective Group of Cardiac Patients

For the retrospective group of cardiac patients, Age was entered into the model as was Neuroticism and Pseudo-Regional Saturation Average Off Bypass at six days. These factors were not entered into the model during the prospective stage of analysis. Only Total Time On Bypass was entered into the models for impaired and unimpaired patients at six days and six months.

Summary of the Prospective Stage of Analysis

Statistical Analysis for the retrospective group explored a wide range of possible associations between cerebral state and NIRS data. In the prospective group we sought the same positive associations as we had seen in the retrospective group.

Corresponding time periods, analytical methods, and definitions of impairment were used for the prospective analysis. The prospective stage included the remaining 70 cardiac patients of the 120 cardiac patients in the study but analysed the data of only 63 patients.

Again, the Critikon Cerebral Oxygen Utilisation Monitor did not provide reproducible results. Using this technology, no separation could be made between the impaired and unimpaired patients. Despite a comprehensive analysis of the study data, the only positive comparison between the retrospective and prospective stage, was Age. Age is a

predictor of cerebral impairment after cardiac surgery. This is a well documented finding by researchers of similar studies.

CHAPTER FIVE

DISCUSSION

5.1 Hypothesis and Summary of Results

The original hypothesis was that there is a relationship between Near Infrared Spectroscopy findings and the occurrence of postoperative cognitive deficits. On studying the results of the data analyses of this project, the immediate conclusion was that no obvious association between the Critikon Cerebral Oxygen Utilisation Monitor (CCOUM) measurements and neuropsychological damage after cardiac surgery could be found. Results of neuropsychological tests indicated that 39% of the cardiac patients were cognitively impaired six days postoperatively, and 12% were impaired six months after surgery; five per cent of whom were impaired at six months only. However, these impaired patients could not be identified using the NIRS equipment due to a technical difficulty which was revealed during the final stages of the investigation.

5.2 Power Calculation

During the design phase of the research project, important factors such as cost, method, analysis of the data, study personnel and sample size were considered by the investigators. It was proposed that the study population would consist of 50 patients undergoing general surgery (control patients) and 50 plus 100 patients undergoing elective cardiac surgery (cardiac group). The control patients were to be studied to identify 'normal 'features such as the steadiness of the CCOUM data over time, the effects of movement, and the practicalities of probe siting.

Fifty cardiac patients (the retrospective group) were then to be studied to express the relationship between the CCOUM data and cognitive deficits in terms of five working rules (hypotheses) which would be prospectively tested in a further 100 patients. These 100 patients would give an 85% power to detect a correlation of 0.35 at a 1% significance level.

Funding for one research assistant was made available instead of an anaesthetist and study nurse as suggested in the grant application. This had practical implications relating to the logistics of the study and resulted in a reduction of patient entry. Despite careful planning the proposed sample size was not achieved (a total of 25 control patients and 50 plus 70 cardiac patients were entered into the study), therefore, the study power was reduced. The power calculations were also affected by the inability of the CCOUM to provide the expected measurements of brain tissue, therefore, no relationship could be identified in the 50 cardiac patients of the retrospective group or the 70 cardiac patients of the prospective group.

5.3 Study Limitations

Technical problems and time constraints experienced during the study, not only caused missing data, but contributed significantly to a reduction of patient entry into the study.

Technical Problems Experienced During the Study

CCOUM Monitoring

The major difficulty encountered during the project was reduced sensitivity of the CCOUM. Analysis of the patient monitoring data had persistently shown no separation between impaired and unimpaired cardiac patients. At a very late stage of the study the

research team learned of the light-piping effect of the fluid layer of the brain resulting in invalid measurements of cerebral function when using NIRS. The light-piping effect of cerebrospinal fluid caused a reduction in the expected measurement of brain tissue in the optical pathlength, from 80% to 10-20% (Illustration 5.1).

Measurement of regional oxygen saturation of the brain may have given more accurate results. However, the version of cerebral monitor used in the study did not provide this measurement. Despite promising results in the retrospective stage of analyses using a pseudo-regional saturation calculation, no separation of impaired and unimpaired cardiac patients was achieved during the prospective stage of analysis.

Approximately midway through the project, Critikon's offer to update the CCOUM 2001, the version of monitor used in the study, was declined. It was the concerted opinion of the study team that the updated monitor, the CCOUM 2020, would not produce data compatible with the previous version.

Datalogger

Considerable problems were experienced by the statistician at the early stage of data analysis when converting the results from the Datalogger (computer software provided by Critikon) in the PC to Microsoft Excel. These time-consuming, software problems were eventually resolved by Critikon personnel.

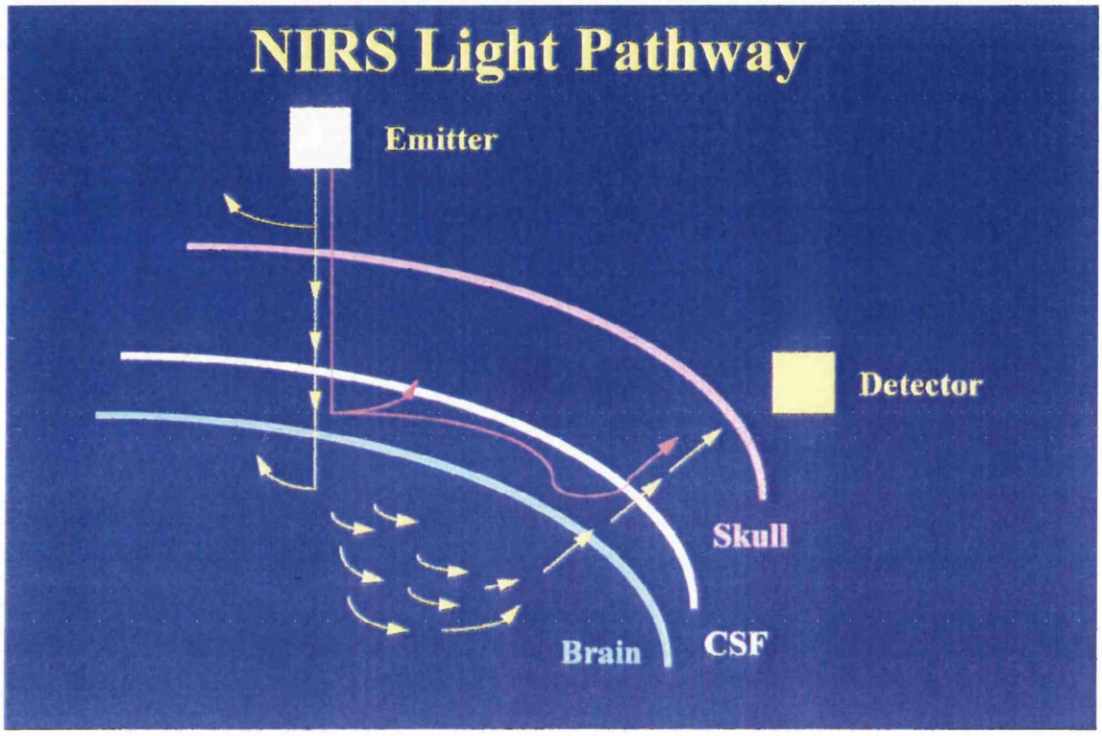

Illustration 5.1 Light-piping Effect of the Cerebrospinal Fluid of the Brain

Sensor

This fragile component of the cerebral monitoring system needed to be repaired or replaced on several occasions. Deterioration of sensor function caused a poor signal resulting in a bizarre random waveform and incomprehensible data.

Interface Pod

The Interface Pod, used to link the PC to the cardiac monitoring system, automatically measured haemodynamic parameters. Despite discussion with the manufacturer of the theatre cardiac monitoring system, cables required to link this system to the Interface Pod could not be provided. This problem was not helped by the manufacturer's reticence to give details of their monitor. The required parameters were therefore logged manually at five minute intervals throughout the operation.

Computer Application of Neuropsychological Tests

Many of the study population were unfamiliar with computer usage. Reassurance was given and patients were allowed to practice tests. Most patients complied and completed the required tests; however, some refused and this resulted in lost data. Refusal could be seen as an extreme variant of psychological damage.

Lost Data

Lost data was a troublesome and sometimes inevitable feature of the study. As well as the technical difficulties already stated, missing data resulted from intraoperative problems, inability to complete tests due to physical or neurological complications, and non-compliance or death of the patient.

Intraoperative Problems

Intraoperative incidents resulted in missing NIRS data of two patients. In the first instance, surgery was postponed at an early stage of the procedure. Emergency resuscitation prevented cerebral monitoring of another patient.

Other Factors Resulting in Lost Data

Fifteen patients refused or were unable to complete the study, twelve of whom were cardiac patients and three were general patients.

Eight cardiac patients requested to withdraw from the study at the postoperative six day stage; five due to their compromised physical state, two were anxious and slightly aggressive, and one was unwilling to complete the neuropsychological assessment. Physical complications such as cardiac tamponade and renal dysfunction which occurred in one patient, and extreme tiredness in another, were factors which led to refusal or inability to complete the study at the early postoperative stage. Neurological deterioration occurred in one patient who experienced a cerebral vascular accident on his second day following cardiac surgery. He became extremely distressed by the resulting physical problems and memory deterioration. Neuropsychological symptoms such as anxiety, agitation and aggressiveness were experienced by two cardiac patients within the first six days following surgery and refusal to continue in the study ensued.

Four cardiac patients withdrew from the study at the six month stage. Three of these patients developed serious physical complications; one developed a myocardial

infarction, and re-stenosis of grafts resulting in deterioration of cardiac function occurred in two patients. One cardiac patient did not provide a reason for refusal.

One general surgery patient, who appeared to be anxious preoperatively, refused to complete the six day assessment. Two general patients were unwilling to complete the neuropsychological assessment six months after surgery.

Nine patients did not reply to a request to complete the six month assessment when contacted either by correspondence or by telephone. Persistent non-attendance for appointment by four patients who had undergone general surgery resulted in much time-wasting.

Seven patients (4.6%) died following cardiac surgery. Five of these patients developed severe complications during the perioperative phase resulting in: multi-organ failure in two patients, cardiac arrest in two patients, and cerebral vascular accident in one patient. A further two patients died as a result of myocardial infarction at a later stage of recovery-one at three months and the other four months postoperatively.

If a test result was missing, the statisticians estimated the missing value using Maximum Likelihood Estimation. This was achieved using BMDP (biomedical package), a computer statistical package.

Cardiac Theatre - Limitation of Working Area

Cardiac surgery involves the use of numerous items of bulky equipment positioned around the theatre table, in a relatively small area. This created some difficulty accommodating the research equipment in theatre and considerably reduced the working area. The research equipment was not ideally positioned as it was outwith the direct vision of the cardiac monitor. The length and fragility of the fibre optic cable was also a limiting factor and careful handling and positioning of this cable was required. Illustration 5.2 effectively demonstrates the limitation of space in cardiac theatre

Time Constraints

The time to obtain patient consent to enter the study and complete preoperative neuropsychological assessment was limited to approximately 75 minutes due to clinical demands taking priority and restrictions of the ward routine (e.g. meal times and visiting times). These constraints again applied at the six day assessment stage.

Some unforeseen factors caused delay to the study schedule. Factors such as patient cancellation, or a sudden change of the planned theatre list occurred on a few occasions. Patients would sometimes request a change of appointment for the six month neuropsychological assessment and the travelling time varied according to their home location. The cardiac surgeons' annual leave caused a sudden decrease in recruitment of patients to the study. Likewise, theatre upgrading during the project resulted in a further reduction in patient recruitment.

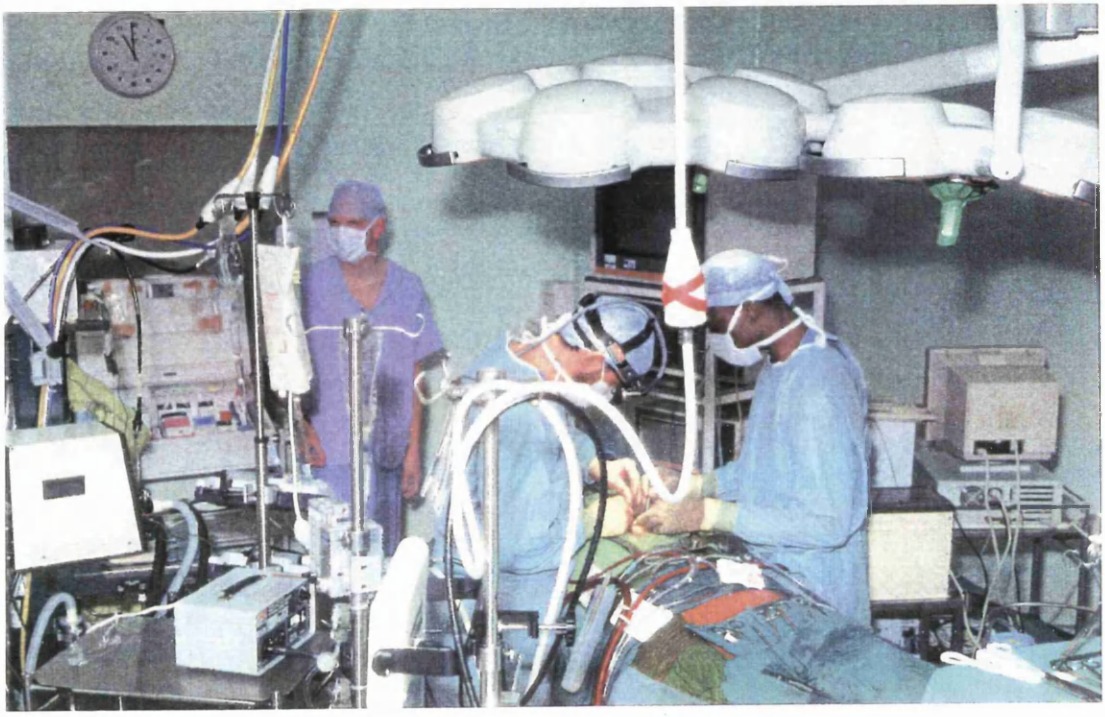

Illustration 5.2 Cardiac Theatre

To allow for the delays to the study schedule and to recruit as many patients as possible, the timescale of the study was extended by six months and totalled two and a half years. A total of 120 cardiac and 30 general patients were recruited to this study. This figure includes an extra five general surgery patients who were recruited at the terminal phase of the study. These patients were included to increase the statistical power of the general group, but in the end, the results were not included in the data analysis.

5.4 Comparison With Other Studies

Similarities did exist between this study and two major studies of recent years (Shaw et al, 1985 and Newman et al, 1987). The neuropsychological assessment of patients did include similar tests to identify cognitive impairment after cardiac surgery. The principal aim of the assessments in the three studies was to determine a change in performance as a result of the surgery. The data were examined prospectively in all three investigations.

However, some differences were also apparent. Two computer applications of the tests were used in the study described in this thesis; a more modern, objective approach to cognitive assessment. Both Shaw et al (1985) and Newman et al (1987) compared patients undergoing major vascular surgery with those undergoing coronary artery bypass surgery. The investigation described here, compares the results of patients undergoing general surgery with those of patients undergoing elective cardiac surgery as a study control.

Differences relating to the method of defining cognitive impairment were also evident. The three studies used group comparison methods of analysis. Shaw et al (1985) and

Newman et al (1987) calculated a standard deviation from all the preoperative scores. Any patient who showed a postoperative reduction of one standard deviation or more from his/her preoperative score was considered to have a deficit in that test. Although a group comparison method of defining cognitive impairment was used in the study described in this thesis, it was derived using a statistical calculation of impairment. This method was described in detail in chapter four.

Newman (1995) suggested an alternative method of defining cognitive impairment where changes in individual test performance over time was examined. This allowed the design of studies to use each patient as his or her own control. Cognitive impairment was defined when a reduction of more than 20% was seen on individual test performance.

The method of defining cognitive impairment used by the investigators of this study were compared with the methods used by Shaw et al (1985) and Newman et al (1987, 1995). Although some overlap of methods exist, no agreement of results was noted.

Another difference is subtle but statistically powerful. In the other studies, the patients in whom data were incomplete, were ignored. This biases the data to the more able patients. In this study, the statisticians estimated missing values using Maximum Likelihood Estimation.

CHAPTER SIX

CONCLUSION AND RECOMMENDATIONS

Conclusion

Despite rigorous analyses of the study data the original hypothesis was not supported, therefore, the null hypothesis was more probable.

According to the results of the neuropsychological assessment, patients developed cerebral impairment as a result of cardiac surgery. Thirty nine per cent of the cardiac patients were impaired at the six day postoperative assessment; only 12% showed impairment six months after surgery.

The technology (CCOUM), used in the study to determine intraoperative cerebral function during cardiac surgery, did not provide measurements that enabled prediction of impairment. No separation could be seen between impaired and unimpaired cardiac patients using this monitor, therefore, the study hypothesis was disproved.

Recommendations

Since the Critikon Cerebral Oxygen Utilisation Monitor was devised, research has revealed that that a larger proportion of the optical pathlength passes through extra-cerebral tissue. Cerebrospinal fluid (CSF) acts as a short cut route for light passing from the emitter to the detector of the sensor. Therefore, as a consequence of these findings, concentration changes occurring in the cerebral tissue may be underestimated by the monitor. Programmes are required to investigate and compensate for the effect of CSF

and other extracerebral tissues. Further development of this technology is necessary before it could be used as a clinical monitoring tool.

Following the completion of the thesis, correspondence was received from Johnson and Johnson Medical, parent company of Critikon who made the CCOUM. The company informed the research team, that as a result of the latest published information about NIRS technology and their own internal development, significant technical hurdles would require to be addressed before it could be used as a clinically validated monitoring technique. Reappraisal of business priorities had resulted in the company decision to discontinue the advancement of NIRS technology - they stopped marketing NIRS technology.

Because of the traumatic nature of cardiac surgery, and each individual's response to it, the author proposes that future research into the problem of cerebral impairment as a result of cardiac surgery should include a method of measuring the patients' physical state. No measurement of physical condition was used in this study.

It is important that research of this subject continues until the problem can be defined. Future meetings, such as the Lauderdale Conference in 1995, will be important to bring together researchers with an interest of this subject. Consolidation of knowledge and exchange of ideas would help to elucidate this complex problem.

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APPENDIX 1

World Health Organisation Mortality Rates for Coronary Artery Disease

1. 1977
2. 1994

1 - World Health Organisation Coronary Artery Disease Mortality Rates for Males and Females in Different Countries - 1977

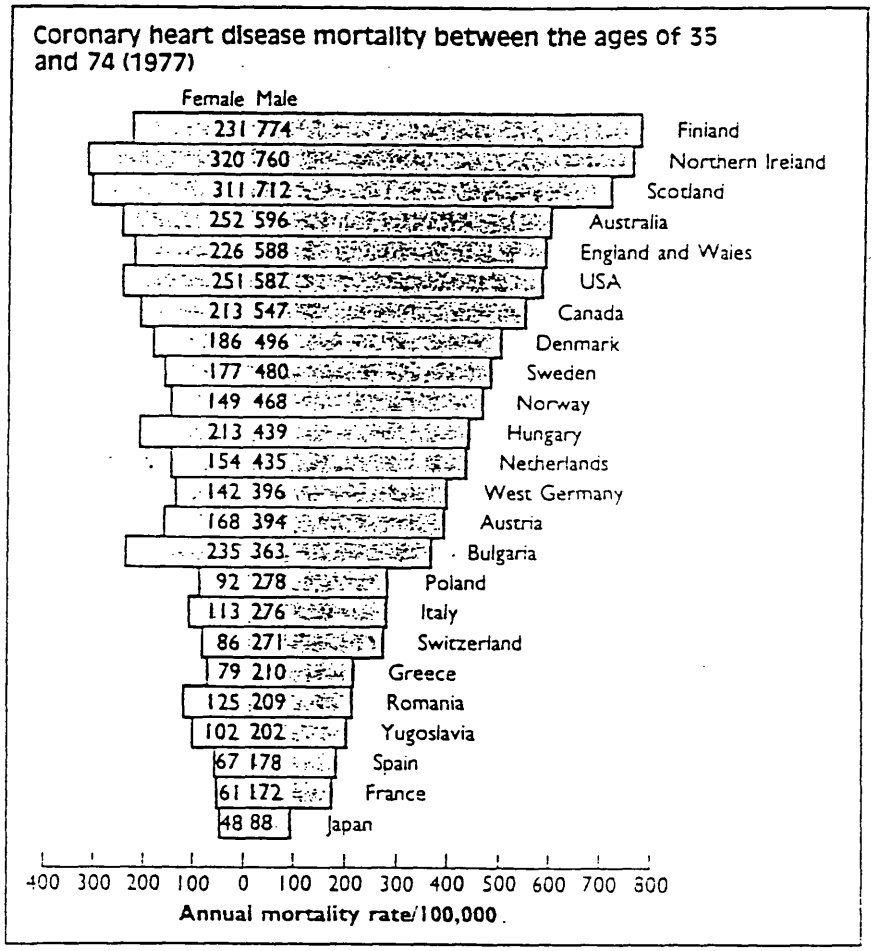

Diagram From - International Medicine, UK Edition,

Vol 1 No 20, August 1982

2 - World Health Organisation Coronary Artery Disease Mortality Rates for Males and Females in Different Countries - 1994

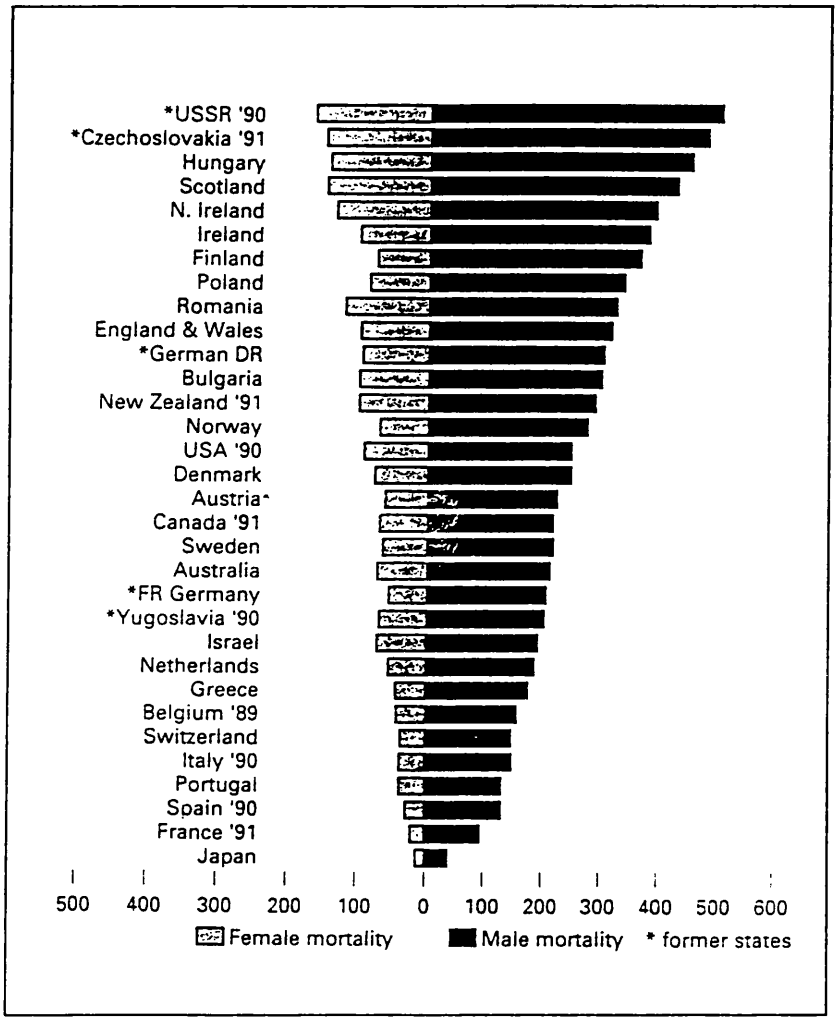

Diagram From - Coronary Heart Disease Prevention (1997) G Lindsay A Gaw with permission from Churchill Livingstone Edinburgh.

Original Source - Professor H Tunstall-Pedoe, Cardiovascular Epidemiological Unit, Dundee

APPENDIX 2

Research Team

RESEARCH TEAM

Study Investigators

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APPENDIX 3

Copy of Research Consent Form

Copy of Operation History Chart

Case Record File

GREATER GLASGOW HEALTH BOARD

THE WEST ETHICAL COMMITTEE

FORM OF CONSENT FOR PATIENTS/VOLUNTEERS IN CLINICAL RESEARCH PROJECT

Brief Title of Project

The relationship between intraoperative cerebral oxygen utilisation and postoperative cognitive defects in patients undergoing cardiac surgery.

Patient's Summary [Purpose of study, nature of procedure, discomfort and possible risks in terms which the patient or volunteer can understand.]

The purpose of this study is to evaluate a new method of monitoring the oxygen supply to a patient's brain during operations. This new brain monitor is completely non-invasive, and you will not be aware of its use. Our interest is to find out whether this monitor could give us warning that a patient's brain is short of oxygen during an operation, warning in time to take preventative action. A patient whose brain has insufficient oxygen during the operation, might for example have memory problems after the operation.

You are shortly scheduled to have surgery, and we invite you to participate in this study. On the day before the operation a research worker will visit you, ask some questions and invite you to undertake some psychological tests on a computer. These tests are rather like computer games. You will then have your operation exactly as normal, with the exception that during the operation a small rubber sensor pad will be placed on your forehead.

The psychological tests will be repeated on the sixth day after surgery. We will then visit you at home six months later, and will invite you to do the tests again.

There are no known risks associated with the brain monitoring technique or the psychological tests.

The information we collect will be securely stored and only available to the investgators. Your participation in this trial may not be of direct benefit to you, but may help future patients. You may withdraw from this trial at any time without affecting your treatment. If you agree to participate, your GP will be informed of the management that you receive.

Consent

I, ---------- of ----------

give my consent to the research procedures described above, the nature, purpose and possible consequences of which have been described to me by:-

---

Signed ---------- **Date ----------**

Witness ----------

OPERATION DETAILS

Event	Time	Sys	Dia	MAP	HR	SpO2				Intervention/Event

Recorded by :	**Date :**
File name :	**Sheet of**
	Study No.

LJW/SF205A

CASE RECORD FILE

Project Title

Is there a relationship between intraoperative brain oxygenation and oxygen utilisation measurements and neuropsychological damage after cardiac surgery.

Study Investigators

Dr A J Asbury

Professor K Millar

Dr G Murray

Co-workers

Marie Pollock

Michele Robertson

Patient Details

Hospital	Study no.	Page no.
Hospital no.	Ward	Consultant
Surname	Other Names	
Address		
Post code	Tel. home	Tel.daytime
DotB	Age	
Occupation	Keyboard user	
Next of kin	Name	
Address		
Post code	Tel. home	Tel. daytime
General practitioner	Name	
Address		
Post code	Tel. no.	

Date		Initials		Study no.	

Clinical Information [cardiac]

Cardiac diagnosis			
Cardiac operation			
Other diagnosis [non-cardiac]			
Cardiac failure	Y/N	History of cardiac failure with/without treatment	Y/N
History of CVA	Y/N	History of TIA	Y/N
Periph. vascular disease: [1]Carotid and cerebrovasculature [2]Aortic aneurysm [3]Abnorm. lower vascular tree	 ☐ ☐ ☐	Carotid / subclavian bruit [1]Carotid [2]Subclavian	C'S/N
Pacing	Y/N	Severity of illness score	
Drugs: [1]Antiarrhythmics ☐ [2]Nitrates / Vasodilators ☐ [3]Ace Inhibitors ☐ [4]Other			

General Information

Date of admission	
Date of informed consent	
Date of operation	
Change of operation plans	
Date of transfer to other hospital/discharge	

Assessment Dates

Pre-operative assessment date	

Date		Initials		Study no.	

Intraoperative data - cardiac surgery

Preoperative Details

Preoperative medication :
[1] Tranquillizers / Sedatives ☐
[2] Analgesics ☐
[3] Vasodilators ☐
[4] Other

Anaesthetic Room

Time of induction of anaesthesia	
Anaesthetic agents for induction and maintenance : [1] IV Anaesthetic agent ☐ [2] Inhalational anaesthesia ☐ [3] Muscle relaxants ☐ [4] Inotropes ☐ [5] Vasoconstrictors ☐ [6] Nitrates ☐	
Other drugs:	
Arterial oxygen saturation - pre-induction	
Arterial oxygen saturation - post-induction [10 min]	

Date		Initials		Study no.	

Intraoperative data - cardiac surgery

Pre bypass

Mechanical ventilation			
Fio2		Tidal volume	
Peak pressure		Mechanical rate	
Arterial oxygen saturation - on incision			
Temperature			
Core temperature [on incision]		Peripheral temperature [on incision]	
Additional drugs : [1]Inhalational anaesthesia ☐ [2]Analgesia ☐ [3]Other			
ABG'S			Time
PaO2		H+	
PaCO2		Hb	
K+			
Heparin administration			
ACT-[pre-heparinisation] control		ACT- [post-heparinisation]	
Time heparin administered			
Heparin [iu]			
Cannulation			
Arterial cannulation [event no.]			Time
Problems on arterial cannulation			
Venous cannulation [event no.]			Time
Problems on venous cannulation			
Sao2 - pre-bypass			

Date		Initials		Study no.	

Intraoperative data - cardiac surgery

On by-pass

Time on bypass [event no.]			
Priming solution			
Full CPB achieved	hrs	Mechanical ventilation suspended	hrs
Sao2 - on full by-pass			
Cardiopulmonary by-pass circuit			
Fio2 - pump		Flow rate [l/min]	
MAP - planned			
Action required to increase/decrease steady arterial pressure			
Heparin-bonded CPB circuit [Y/N]			
Cooling procedure commenced - [event no.]			hrs
Clamping of aorta			hrs
Myocardial protection [method eg. cardioplegia.cold or fibrillation]			
Start of surgery on or in the heart			
Activated clotting time - post heart stop			
Temperature [when heart surgery commences]			
Core temp.		Peripheral temp.	
ABG's			
Pa02		H+	
PaCO2		K+	
Hb		PCV [%]	

Date		Initials		study no.	

On by-pass [cont]

End of actual surgery on the heart			
Activated clotting time at end of surgery			
Temperature - lowest during CPB			
Core temp.		Peripheral temp.	
Time of lowest core temp.		Time of lowest peripheral temp.	
Other drugs required: [1]Anaesthetic agents ☐ [2]Inhalational anaesthesia ☐ [3]Analgesia ☐ [4]Tranqiilizers / Sedatives ☐ [5]Other			

Date	Initials	Study no.

Intraoperative data - cardiac surgery

Coming off by-pass

Start time of rewarming of blood [event no.]	
Temperature [time]	
Core temperature	Peripheral temperature
Aortic cross clamp removed [hrs]	
Problems during declamping	
Recommencement of mechanical ventilation [hrs]	
Additional drugs given during CPB: [1] IV anaesthetic agent ☐ [2]Inhalational anaesthesia ☐ [3]Analgesia ☐ [4]Other	

Mechanical ventilation			
Fio2		Tidal volume	
Peak pressure		Mechanical rate	
Sao2			

Protamine sulphate administration			
ACT - pre-administration		ACT - post administration	
Time protamine sulphate administered			
Protamine sulphate [dose]			

Date		Initials		Study no.	

Intraoperative data - cardiac surgery

Termination of bypass

Discontinuation of cardiopulmonary bypass [hrs]			
Removal of venous cannula [event no.]			Time
Problems in decannulation			
Removal of arterial cannula [event no.]			Time
Problems in decannulation			
Arterial oxygen saturation - peripheral			
Replacement blood volume [mls]			
Haemodynamic parameters			
Systolic BP		Heart rate	
Diastolic BP		CVP	
MAP			
ABG's			
FiO2		PaO2	
H+		PaCO2	
Hb			
Temperature			
Core temperature		Peripheral temperature	
Additional drugs: [1] Analgesia ☐ [2] Other			
Time off operating table [event no.]			
Operation			

Date		Initials		Study no.	

Postoperative Data - cardiac surgery

6 Day Assessment

Postoperative date	
Time of extubation	
Intra-aortic balloon pump	Y/N
Use of pressor agents	Y/N
Postoperative hypertension	Y/N
Postoperative new arrhythmias	Y/N
Length of stay in CICU	
Drugs: [1] Analgesics ☐ [2] Sedation ☐ [3] Anticoagulants ☐ [4] Other ☐	

Survival status		
Patient alive on day of assessment		Y/N
patient died	Date	Time
Post mortem	Yes/No	

Date	Initials	Study no.

Preoperative Neuropsychological Assessment

Psychological Test	Date	Score
National Adult Reading Test		
Personality Inventory - EPI [1] E [2] N [3] L		
Beck's Depression Inventory		
STAI State Anxiety Inventory Trait Anxiety Inventory		
PsychE Tests		
Dual Tracking and Reaction Time Reacts Mean react False Misses On target		
Vigilance No. of hits No. of misses No. of false alarms		

Wechsler Tests		
Digit Span Digits forward Digits backward Maximum Total		
Verbal Paired Associates Maximum easy Maximum hard Maximum total		
Delayed Verbal Paired Associates Maximum easy Maximum hard Maximum total		
Visual Paired Associates Sets I - III Set IV Set V Set VI		
Delayed Visual Paired Associates		
Figural Memory - to be replaced with		
Benton Visual Retention Test Test form C Test form D Test form E		

Digit Symbol Substitution Task Total no. of symbols copied Total correct copied Total correct / total copied [illegible]		
Stroop Test Colour task Correct Incorrect Corrected [illegible] Colour-word task Correct Incorrect Corrected [illegible]		

Date	Initials	Study no.

Postoperative Neuropsychological Assessment

Psychological Test	Date	Score
National Adult Reading Test		
Personality Inventory - EPI [1] E [2]N [3]L		
Beck's Depression Inventory		
STAI State Anxiety Inventory Trait Anxiety Inventory		
PsychE Tests		
Dual Tracking and Reaction Time Reacts Mean react False Misses On target		
Vigilance No. of hits No. of misses No. of false alarms		

Wechsler Tests		
Digit Span Digits forward Digits backward Maximum [illegible]		
Verbal Paired Associates Maximum easy Maximum hard Maximum total		
Delayed Verbal Paired Associates Maximum easy Maximum hard Maximum total		
Visual Paired Associates Sets I - III Set IV Set V Set VI		
Delayed Visual Paired Associates		
Figural Memory - to be replaced with		
Benton Visual Retention Test Test form C Test form D Test form E		

Digit Symbol Substitution Task Total no. of symbols copied Total correct copied Total correct / total copied [illegible]		
Stroop Test Colour task Correct Incorrect Corrected [illegible] Colour-word task Correct Incorrect Corrected [illegible]		

Date		Initials		Study no.	

6 Month Neuropsychological Assessment

Psychological Test	Date	Score
National Adult Reading Test		
Personality Inventory - EPI [1] E [2]N [3]L		
Beck's Depression Inventory		
STAI State Anxiety Inventory Trait Anxiety Inventory		
PsychE Tests		
Dual Tracking and Rraction Time Reacts Mean react False Misses On target		
Vigilance No. of hits No. of misses No. of false alarms		

Wechsler Tests		
Digit Span Digits forward Digits backward Maximum [illegible]		
Verbal Paired Associates Maximum easy Maximum hard Maximum total		
Delayed Verbal Paired Associates Maximum easy Maximum hard Maximum total		
Visual Paired Associates Sets I - III Set IV Set V Set VI		
Delayed Visual Paired Associates		
Figural Memory - to be replaced with		
Benton Visual Retention Test Test form C Test form D Test form E		

Digit Symbol Substitution Task Total no. of symbols copied Total correct copied Total correct / total copied [illegible]		
Stroop Test Colour task Correct Incorrect Corrected [illegible] Colour-word task Correct Incorrect Corrected [illegible]		

APPENDIX 4

Neuropsychological Tests

NEUROPSYCHOLOGICAL TESTS

Questionnaires

1 - Eysenck Personality Inventory (EPI)

Various approaches have been used by psychologists to define personality types. One such approach, called factor analysis, was used by British psychologist Hans Eysenck (Eysenck, 1981). Factor analysis is a mathematical method that identifies groups of traits which correlate with each other but are uncorrelated with other groups. Each group of traits is given a name that describes the underlying personality dimension.

Hans Eysenck recognised two clearly defined dimensions; these have been called Extroversion - Introversion and Emotionality - Stability (also called neuroticism).

Extroversion - Introversion: -

Extroverts are outgoing and sociable, enjoy parties and social activities, need people to talk to and have many friends. Introverts tend to be quiet, thoughtful and reserved, enjoy solitary pursuits and avoid social activities.

Emotionality - Stability (neurotocism):-

At one extreme are traits such as moodiness, worry, anxiety, restlessness and other negative emotions. People at the other end of this dimension are calm, relaxed, even-tempered and emotionally stable.

Lie-scale

An 18 item Lie-scale has been included in the EPI. This is designed to measure a tendency to put oneself in an unrealistically positive light. (Sample copy in Appendix 5)

Administration of EPI

Patients are presented with a record form containing questions about the way they behave, feel and act. After each question is a space for answering 'YES' or 'NO'. The patients are then asked to decide whether 'YES' or 'NO' represents their usual way of acting or feeling. They are then asked to put a cross in the appropriate circle under the heading 'YES' or 'NO'. The patients are asked to give their first reaction and not to deliberate over any question.

Scoring

The EPI is scored using a Scoring Key and the total scores are calculated for each category i.e., extroversion, neuroticism and lie detection.

Normal Scores

Extroversion	9.5 (SD 4.0)
Neuroticism	9.1 (SD 4.8)
Lie	3.6 (SD 2.5)

2 - Beck's Depression Inventory

The original Beck's Depression Inventory (BDI) was developed in 1961 (Beck, Ward , Mendelson, Mock and Erbaugh, 1961). This was based on clinical symptoms frequently

given by depressed psychiatric patients as contrasted with those infrequently given by non-depressed psychiatric patients. The clinical observations and the patient descriptions were systematically grouped into 21 symptoms and attitudes which could be rated in a four-point scale from 0-3 in terms of severity.

The revised version of the Beck's Depression Inventory was used in this study. The test, was revised by Beck, Rush, Shaw and Emery in 1979 at the Centre for Cognitive Therapy (CCT) of the University of Pennsylvania Medical School. It is a 21-item instrument test used by psychologists and psychiatrists as a measurement of severity of depression in psychiatric as well as normal patients.

Administration of BDI

The revised BDI is self-administered and requires approximately five to ten minutes to complete. Patients are requested to encircle the score (0-3) according to the statement of choice in each group. Instructions given by the test administrator must carefully indicate that the chosen statement should describe how the patient has been feeling in the past week including the day of assessment. The patient may choose more than one statement in each group.

Scoring

The score is the sum of the ratings given by the patient for each of the 21 groups. The maximum total score is 63. If the patient scores more than one item in each group, the highest rating is chosen to calculate the score.

Normal Scores

0-4 none or minimal

5-7 mild

8-15 moderate

16+ severe

3 - State-Trait Anxiety Inventory (STAI)

The concepts of state and trait anxiety were developed by psychologist Charles Spielberger in 1966. They have been reviewed several times leading to the present measuring instrument, the State-Trait Anxiety Inventory (Spielberger, Gorsuch, Lushene, Vagg, Jacobs, 1983). Spielberger and colleagues believe that an emotional state exists at a given moment in time and at a particular level of intensity. Anxiety states are characterised by subjective feelings of tension, apprehension, nervousness and worry and by activation or arousal of the autonomic nervous system. Trait anxiety refers to an individuals proneness to anxiety in stressful situations and State anxiety reflects the level of intensity of an individual's response to this situation.

Administration of STAI

The State-Anxiety scale consists of twenty statements that evaluate how the patient feels *'right now at this moment'*. The patient chooses the appropriate statement according to the self-report scales. The Trait-Anxiety scale consists of twenty statements that assess how the patient '*generally*' feels and again the patient chooses the appropriate statement from the self-report scales.

The State-Anxiety and Trait-Anxiety are printed on opposite sides of a single-page test form (Sample copy in Appendix 5).

Scoring

Each STAI item is given a weighted score of one to four.. To obtain scores for the State-Anxiety and Trait-Anxiety, the weighted scores are totalled, using a Scoring Key, for the twenty items that make up each scale.

Maximum Score = 80

Minimum Score = 20

4 - Subjective Assessment Scale

This is a self-assessment of memory. Nine questions are asked and the patient responds by choosing the most appropriate answer from multiple-choice statements. The patient is asked to make a subjective assessment of memory, ability to concentrate, attention span, concentration and quick response to situations. A comparison of the patient's perception of his/her cognitive state will be compared with the results of the neuropsychological tests at the end of the study analysis.

Psychomotor Evaluation

PsychE is the name of the computer program used for conducting psychomotor assessment. The program includes an integrated database for storage and manipulation of patient details. The length and speed of the test can be defined (Hope, Woolman, Gray, Asbury, Millar, 1998).

1 - Numeric Vigilance

The test is based on those described by Smith, Kendrick and Maben (1992) and Wesnes (Wesnes, Simpson and Christmas, 1989). Three-digit numbers are presented on the computer screen at the rate of 100 per minute. Each number differs randomly from the previous number by one digit. Eight percent of these numbers are duplicates of the previous number. The patient is required to identify these duplicates and press the spacebar as they occur. Correct responses, missed duplicates and superfluous responses are recorded. The test duration is four minutes.

Scoring

The Numeric Vigilance Test measures:-

Number of Hits

Number of Misses

Number of False Alarms

2 - Dual Task : Tracking (primary) and Visual Reaction Time

It is well established that the requirement to divide attention between two tasks is sensitive to impairment (Kaneman, 1973). While the patient concentrates upon a demanding primary task he/she simultaneously performs an easier secondary task.

The primary task requires the patient to use the computer mouse to control the screen cursor which must follow a smoothly but randomly moving target on the computer screen. The percentage of time on target is recorded. At random intervals the secondary

task stimulus (a small 'sun' icon) is presented and the total reaction time taken for the patient to press the spacebar is measured. Means and standard deviations of the times are calculated. The test lasts for three minutes.

Scoring

Dual Task measures:-

Number of Reactions

Mean Reaction Time in milliseconds (Standard Deviation)

False Reactions

Misses

Tracking component Percentage Time On Target

Assessment of Intelligence

National Adult Reading Test (NART)

The National Adult Reading Test (McKenna,1975) was constructed by psychologist Hazel McKenna, who recognised that word-reading ability was associated with intelligence. The test comprises of a list of 50 words which are read aloud by the patient. The words are relatively short and are printed in order of increasing difficulty. This test is frequently used by clinical psychologists, particularly when assessing patients with senile dementia. Although commonly used in the field of psychiatry, it is also recognised as a valid method of measuring general intelligence in the normal adult population.

Scoring

The tester should be familiar with the correct pronunciation of the list of words before administering the test. As the patient reads aloud, the tester should note the number of errors. An attempt should be made to complete all the words in the list.

Maximum Score = Zero errors

Minimum Score = 50 errors

Wechsler Memory Scale - Revised (WMS-R)

Charles Wechsler developed the original Wechsler Memory Scale in 1945 and completed the major changes to the Wechsler Memory Scale - Revised version prior to his death in 1981 (Wechsler Memory Scale - Revised, 1987). It is an individually administered clinical instrument for assessing the major dimensions of memory function. The functions assessed for this project are verbal and visual stimuli; delayed as well as immediate recall.

Subtests of WMS-R used in this study

Immediate Recall

1 - Digit Span

2 - Visual Paired Associates

3 - Verbal Paired Associates

Delayed Recall

1 - Visual Paired Associates

2 - Verbal Paired Associates

1 - Digit Span

Administration

There are two parts to the Digit Span subtest, Digits forward and Digits Backward. These two tests are administered separately. For Digits Forward, the patient is read number sequences of increasing length. After each sequence, the patient is then asked to repeat it from memory. On Digits Backward, the patients are read similar number sequences and the patient is then asked to repeat it backwards. Each subtest consists of six items (Item 1 consists of three digits, Item 2 consists of four digits etc.). Two trials are allowed for each Item (Trials 1 and 11). The patient would discontinue the test after failure of both tests of any item (see sample copy in Appendix 5).

Scoring

Each item is scored two, one, or zero, as follows:-

Two points if the patient passes both trials

One point if patient passes only one trial

Zero points if the patient fails both trials

Maximum score for Digit Span Subtest = 24

2 - Visual Paired Associates 1 (Immediate Recall)

Administration

The patient is shown six abstract line drawings, each paired with a different colour, then after a pause of 10 seconds, the patient is asked to indicate the appropriate colour associated with each figure. There are six sets of tests for presentation and each set contains six drawings associated with an individual colour.

The first three sets are administered to all patients. If the patient answers all six items on the third set, the subtest should be discontinued. If all items are not answered correctly on the third set, the fourth set should be presented and the fifth and sixth if necessary. When the subtest is discontinued, the patient should be reminded that the test will be repeated after an interval of approximately 30 minutes.

Scoring

One point is awarded for each correct response. The total score is based on the first three sets only.

Maximum Score = 18

Visual Paired Associates 11 (Delayed Recall)

Administration

This is a delayed recall trial of Visual Paired Associates 1. A single delayed-recall version of this test should be administered after an interval of approximately 30 minutes. This indicates how much learned material has been retained after this time delay.

Scoring

Score one point for each correct response.

Maximum score = 6

3 - Verbal Paired Associates 1 (Immediate Recall)

Administration

The patient is read a group of eight word pairs, then is read the first word of each pair, and is asked to supply the second word from memory. Each subtest contains six sets of word pairs and each set consists of eight pairs of words. The first three sets are administered to all patients. If the patient answers all eight items correctly on the third recall, the subtest should be discontinued. If all eight items on the third list are not correct, then the fourth list should be presented and if necessary, the fifth and sixth. The patient should then be reminded that the test will be repeated at a later stage.

Scoring

The patient's response is scored as follows:-

One point for correct association.

Zero points for incorrect association.

Maximum score = 12 easy, 12 hard, 24 total

Verbal paired Associates 11 (Delayed Recall)

Administration

This is a delayed recall trial of Verbal Paired Associates 1. A single delayed recall version of this test should be administered after a delay of approximately 30 minutes. This should indicate how much learned material has been retained within this time period.

Scoring

The patient's response is scored as follows:-

Score one point for a correct association.

Score zero points for an incorrect association.

Enter a dash (-) for no response.

Maximum Score = Four easy, Four hard, Eight total

Visual Memory

Benton Visual Retention Test (BVRT)

The Benton Visual Retention Test was developed by Arthur L Benton and the first version was published in 1946. Continuous revision of the test to improve its design and its use as a research instrument has led to the most recent version in 1992. Figure - drawing tasks are used frequently in neuropsychological testing assessing both visual perception and memory.

There are three forms (a,b,c) of the BVRT (Sivan,1992). Any of the three forms may be administered by any of the four methods (A,B,C,D) of administration. In this study,

method A was used consistently. The form presented to the patient was changed at each assessment stage of the study.

Administration of the BVRT

A stimulus booklet booklet containing 10 designs is placed between the examiner and the patient. The patient views each design for 10 seconds and immediately reproduces the design from memory; a response booklet, containing 10 blank pages is provided for this purpose.

Scoring

The graphical data is then analysed and scrutinised for errors such as omissions, distortions, rotations, misplacements and size errors. Two scores for describing the patient's performance are then possible. One score is based on the number of correct reproductions which is a measure of the patient's overall level of performance. The other score records the number of errors.

Tests of Mental Flexibility

1 - Digit Symbol Substitution Test (DSST)

The Digit Symbol test (WAIS-R) is a subtest of the Wechsler Adult Intelligence Scale - Revised requiring efficient performance in visual-motor speed and scanning. These areas of functioning are particularly susceptible to disruption by central nervous system insults.

Administration of DSST

The patient is asked to refer to a table of numbers one to nine; each number has an associated symbol. Below the table, are four rows of digits and underneath each digit, an empty box (see sample copy in Appendix 5). The patient is then asked to view the digits, scan the table, and insert the associated symbol under each digit. The patient is asked to enter the symbols in sequence. Speed of performance is an important aspect of this test and the patient is asked to complete as many symbols as quickly as possible in 90 seconds. If the patient has not completed three rows within this time, they are then asked to continue until the third row is completed and the total time is recorded.

Scoring

The examiner must ensure that all symbols have been entered correctly then the following data is recorded:-

Total number of symbols copied in 90 seconds

Total number of correct symbols copied in 90 seconds

Total correct copied/total copied (%)

Total time taken to complete three rows

Total number of symbols copied

Total number of correct symbols copied

2 - Stroop Test

The Stroop Test (Trenberry, Crosson, DeBoe, Leber, 1989) has existed since 1935. It has been revised many times since then but its endurance proves its usefulness as a neuropsychological measurement of cerebral damage; particularly frontal lobe damage.

Administration of the Stroop Test

The materials required for the Stroop Test consist of Form C Stimulus Sheets, Form C-W Stimulus Sheets and Stroop Record Forms (Sample copies in Appendix 5). The Form C Stimulus Sheets consist of 112 colour names (red, green, blue, tan) arranged in four columns of 28 names. The names are printed in one of four different colours of ink (red, green, blue, tan), but no name is printed in its matching colour. The Form C-W Stimulus Sheet is the same as the C Stimulus Sheet, except for the order of the colour names. Both forms are used in the administration of the Colour and Colour-Word Tasks, respectively.

The Record Form is used to record responses for the Colour and Colour-Word Tasks.

Two tasks are involved in the administration of the Stroop Test:-

Colour Task - Form C Stimulus Sheet

The patient is instructed to read the words aloud as quickly as possible. Starting at the first column, each column should be read from top to bottom. On completion of this column the patient is then instructed to move to the second column and to continue in this manner. The patient is allowed 120 seconds to respond to this task.

Colour-Word Task - Form C-W Stimulus Sheet

The patient is requested to name aloud the colour of ink (red, blue, green, tan) in which the word is printed. This should be completed as quickly as possible and again 120

seconds is allowed to respond. Administration of the test should be terminated if the patient is unable to identify the four colours.

Scoring

For both the Colour Task and the Colour-Word Tasks the following data is recorded:-

The number of responses completed

The number of correct responses

The number of incorrect responses

The number of corrected responses

APPENDIX 5

Copies of Neuropsychological Test Record Forms

National Adult Reading Test (NART)

SECOND EDITION

Answer/Record Sheet

Name:..... Date of test:.....

	Errors		Errors
CHORD		SUPERFLUOUS	
ACHE		SIMILE	
DEPOT		BANAL	
AISLE		QUADRUPED	
BOUQUET		CELLIST	
PSALM		FACADE	
CAPON		ZEALOT	
DENY		DRACHM	
NAUSEA		AEON	
DEBT		PLACEBO	
COURTEOUS		ABSTEMIOUS	
RAREFY		DETENTE	
EQUIVOCAL		IDYLL	
NAIVE		PUERPERAL	
CATACOMB		AVER	
GAOLED		GAUCHE	
THYME		TOPIARY	
HEIR		LEVIATHAN	
RADIX		BEATIFY	
ASSIGNATE		PRELATE	
HIATUS		SIDEREAL	
SUBTLE		DEMESNE	
PROCREATE		SYNCOPE	
GIST		LABILE	
GOUGE		CAMPANILE	

Pronunciation guide

CHORD	körd	SUPERFLUOUS	sōō-pûr'flŏŏ-əs, sū-pûr'flŏŏ-əs
ACHE	āk	SIMILE	sim'i-li
DEPOT	dep'ō	BANAL	bən-al'
AISLE	īl	QUADRUPED	kwod'rŏŏ-ped
BOUQUET	bōōk'a, bōōkā', bōkā'	CELLIST	chel'ist
PSALM	säm	FACADE	fa-säd'
CAPON	kā'pn	ZEALOT	zel'ət
DENY	di-nī	DRACHM	dram
NAUSEA	nö'si-ə,nö'zhə	AEON	ē'on
DEBT	det	PLACEBO	plə-sē'bō
COURTEOUS	kûrt'yəs	ABSTEMIOUS	ab-stē'mi'əs
RAREFY	rār'-i-fī	DETENTE	dā-tāt (Fr.)
EQUIVOCAL	ı-kwiv'ə-kl	IDYLL	id'il, id'əl
NAIVE	nä-ēv	PUERPERAL	pū-ûr'pər-əl
CATACOMB	kat'ə-kōōm	AVER	ə-vûr'
GAOLED	jāld	GAUCHE	gō sh
THYME	tīm	TOPIARY	tō'pi-ə-ri
HEIR	ār	LEVIATHAN	le-vī'ə-thən
RADIX	rā'diks	BEATIFY	bi-at'i-fi
ASSIGNATE	as'-ig-nāt	PRELATE	prel'it
HIATUS	hī-ā'təs	SIDEREAL	sī-dē'ri-əl
SUBTLE	sut'l	DEMESNE	di-mān', di-men'
PROCREATE	prō'kri-āt	SYNCOPE	sing'kə-pē
GIST	jist	LABILE	lā'bīl
GOUGE	gowj	CAMPANILE	kam-pan-ē'lā, kam-pan-ē'lē

STROOP
Neuropsychological Screening Test
RECORD FORM

Max R. Trenerry, Ph.D.
Bruce Crosson, Ph.D.
James DeBoe, Ph.D.
William R. Leber, Ph.D.

Name _____

Sex _____ Age _____ Date _____

Reason for Referral _____

Diagnosis/Notes _____

_____

_____

SCORES

	Color Task	Color-Word Task
Number of Responses	_____	_____
Incorrect Responses	_____	_____
Score	_____	_____
Percentile		_____
Pr (Brain Damage)		_____

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9876

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Form C Stimulus Sheet

BLUE	RED	TAN	RED
GREEN	GREEN	RED	TAN
TAN	TAN	TAN	RED
RED	BLUE	BLUE	TAN
GREEN	GREEN	TAN	BLUE
BLUE	BLUE	RED	GREEN
GREEN	TAN	GREEN	RED
BLUE	GREEN	RED	BLUE
RED	TAN	BLUE	RED
BLUE	BLUE	TAN	TAN
TAN	GREEN	RED	GREEN
RED	BLUE	GREEN	TAN
TAN	GREEN	RED	BLUE
GREEN	RED	TAN	RED
BLUE	BLUE	BLUE	BLUE
TAN	GREEN	TAN	RED
GREEN	TAN	GREEN	GREEN
RED	RED	TAN	RED
TAN	TAN	BLUE	BLUE
RED	GREEN	TAN	TAN
TAN	TAN	BLUE	BLUE
RED	RED	GREEN	GREEN
GREEN	BLUE	RED	BLUE
RED	RED	GREEN	RED
TAN	GREEN	TAN	BLUE
BLUE	RED	RED	TAN
GREEN	TAN	GREEN	BLUE
TAN	BLUE	BLUE	GREEN

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Form C-W Stimulus Sheet

BLUE	GREEN	RED	GREEN
GREEN	BLUE	GREEN	TAN
RED	RED	BLUE	RED
TAN	BLUE	TAN	TAN
GREEN	TAN	RED	BLUE
BLUE	RED	TAN	TAN
RED	GREEN	BLUE	GREEN
TAN	TAN	TAN	RED
RED	GREEN	RED	GREEN
BLUE	BLUE	BLUE	RED
RED	RED	RED	BLUE
TAN	TAN	TAN	GREEN
BLUE	GREEN	BLUE	TAN
TAN	RED	GREEN	BLUE
RED	BLUE	TAN	GREEN
BLUE	GREEN	BLUE	RED
GREEN	RED	TAN	GREEN
TAN	GREEN	BLUE	TAN
GREEN	BLUE	RED	GREEN
TAN	TAN	GREEN	BLUE
RED	GREEN	BLUE	TAN
BLUE	RED	GREEN	BLUE
RED	TAN	BLUE	GREEN
TAN	BLUE	GREEN	RED
RED	TAN	RED	BLUE
TAN	RED	GREEN	GREEN
GREEN	TAN	TAN	RED
TAN	GREEN	RED	BLUE

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Form: **C D E**
Administration: **A B C D**

ENTON SUAL TENTION TEST® RECORD FORM

e _____ Testing Date _____

ress _____ Testing Site _____

_____ Examiner _____

_____ Gender _____

Design	Score (0 or 1)	Types of Errors*	Number of Errors
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
Number Correct Score			Number Error Score

*Use symbols listed in Chapter 3 of Manual.

Number of Errors According to Error Category

	Left	Right	Total
Omissions			
Distortions			
Perseverations			
Rotations			
Misplacements			
Size Errors			
	Total Left	Total Right	Total

vioral Observations: _____

9 10 11 12 A B C D E

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WMS-R
Wechsler Memory Scale-Revised

RECORD FORM

ıme _____

x _____ Education _____

ıce of Testing _____

aminer _____

ason for Referral _____

_____

_____

	Year	Month	Day
Date of Testing			
Date of Birth			
Age			

SUBTEST RAW SCORES AND INDEXES

Subtest	Raw Score	Weight	Verbal Memory	Visual Memory	General Memory	Attention/ Concentration	Delayed Recall
Information and Orientation[1]							
Mental Control		x 1					
Figural Memory		x 1					
Logical Memory I		x 2					
Visual Paired Associates I		x 1					
Verbal Paired Associates I		x 1					
Visual Reproduction I		x 1					
Digit Span		x 2					
Visual Memory Span		x2					
Logical Memory II		x 1					
Visual Paired Associates II		x 2					
Verbal Paired Associates II		x 2					
Visual Reproduction II		x 1					
Weighted Raw Score Sums				+	=		
Indexes							

This subtest is not used in the calculation of any of the Indexes.

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9-987371

DIGIT SPAN Discontinue after failure on both trials of any item.
Administer both trials of each item, even if the first trial is passed.

DIGITS FORWARD

Item	Trial I	Pass-Fail	Trial II	Pass-Fail	Score 2, 1, or 0
1.	6-2-9		3-7-5		
2.	5-4-1-7		8-3-9-6		
3.	3-6-9-2-5		6-9-4-7-1		
4.	9-1-8-4-2-7		6-3-5-4-8-2		
5.	1-2-8-5-3-4-6		2-8-1-4-9-7-5		
6.	3-8-2-9-5-1-7-4		5-9-1-8-2-6-4-7		
				Max. = 12 Total Forward	

DIGITS BACKWARD Administer Digits Backward even if examinee scores 0 on Digits Forward.

Item	Trial I	Pass-Fail	Trial II	Pass-Fail	Score 2, 1, or 0
1.	5-1		3-8		
2.	4-9-3		5-2-6		
3.	3-8-1-4		1-7-9-5		
4.	6-2-9-7-2		4-8-5-2-7		
5.	7-1-5-2-8-6		8-3-1-9-6-4		
6.	4-7-3-9-1-2-8		8-1-2-9-3-6-5		
				Max. = 12 Total Backward	Max. Total = 24

VISUAL MEMORY SPAN Discontinue after failure on both trials of any item.
Administer both trials of each item, even if the first trial is passed.

TAPPING FORWARD

Item	Trial I	Pass-Fail	Trial II	Pass-Fail	Score 2, 1, or 0
1.	2-6		8-4		
2.	2-7-5		8-1-6		
3.	3-2-8-4		2-6-1-5		
4.	5-3-4-6-1		3-5-1-7-2		
5.	1-7-2-8-5-4		7-3-6-1-4-8		
6.	8-2-5-3-4-1-6		4-2-6-8-3-7-5		
7.	7-5-6-3-8-7-4-2		1-6-7-4-2-8-5-3		
				Max. = 14 Total Forward	

TAPPING BACKWARD Administer Tapping Backward even if examinee scores 0 on Tapping Forward.

Item	Trial I	Pass-Fail	Trial II	Pass-Fail	Score 2, 1, or 0
1.	3-6		7-4		
2.	6-8-5		3-1-8		
3.	8-4-1-6		5-2-4-1		
4.	4-6-8-5-2		8-1-6-3-7		
5.	7-1-8-3-6-2		3-8-1-7-5-4		
6.	1-5-2-7-4-3-8		6-7-4-3-1-5-2		
				Max. = 12 Total Backward	Max. Total = 26

RBAL PAIRED ASSOCIATES I If the examinee answers all eight items correctly on the third set, discontinue the subtest. Otherwise, present Sets IV, V, and VI until all eight items are correct.

T I	Recall	Easy	Hard	SET IV	Recall	Easy	Hard
tal—Iron	Fruit	_____		Crush—Dark	School		_____
by—Cries	Obey		_____	Cabbage—Pen	Metal	_____	
ush—Dark	Rose	_____		Fruit—Apple	Obey		_____
hool—Grocery	Baby	_____		Obey—Inch	Crush		_____
se—Flower	Cabbage		_____	Baby—Cries	Fruit	_____	
ey—Inch	Metal	_____		Rose—Flower	Baby	_____	
it—Apple	School		_____	Metal—Iron	Cabbage		_____
bbage—Pen	Crush		_____	School—Grocery	Rose	_____	
	Total	_____	_____		**Total**	_____	_____
T II	Recall	Easy	Hard	**SET V**	Recall	Easy	Hard
se—Flower	Cabbage		_____	Fruit—Apple	Rose	_____	
bbage—Pen	Baby	_____		School—Grocery	Crush		_____
ey—Inch	Metal	_____		Rose—Flower	Baby	_____	
it—Apple	School		_____	Cabbage—Pen	Metal	_____	
hool—Grocery	Rose	_____		Metal—Iron	Obey		_____
tal—Iron	Crush		_____	Crush—Dark	Cabbage		_____
ush—Dark	Fruit	_____		Baby—Cries	School		_____
by—Cries	Obey		_____	Obey—Inch	Fruit	_____	
	Total	_____	_____		**Total**	_____	_____
T III	Recall	Easy	Hard	**SET VI**	Recall	Easy	Hard
by—Cries	Obey		_____	Metal—Iron	Baby	_____	
ush—Dark	Fruit	_____		Rose—Flower	Fruit	_____	
hool—Grocery	Baby	_____		Crush—Dark	Cabbage		_____
se—Flower	Metal	_____		Baby—Cries	Rose	_____	
bbage—Pen	Crush		_____	Obey—Inch	School		_____
it—Apple	School		_____	Fruit—Apple	Obey		_____
ey—Inch	Rose	_____		Cabbage—Pen	Crush		_____
tal—Iron	Cabbage		_____	School—Grocery	Metal	_____	
	Total	_____	_____		**Total**	_____	_____

Total Sets I-III	Max. Easy = 12	Max. Hard = 12	Max. Total = 24	

SUAL REPRODUCTION I Use VRI Copying Sheet.

nd used: _____ Right _____ Left

em	Score (see Visual Reproduction Scoring Summary)	
1		Observations:
2		
3		
4		
. = 41 Total		

;UAL PAIRED ASSOCIATES I

If the examinee answers all six items correctly on Set III, discontinue the subtest. Otherwise, present Sets IV, V, and VI until all six items are correct.

SET I				SET II				SET III			
	Key	Response	Score 1 or 0	Item	Key	Response	Score 1 or 0	Item	Key	Response	Score 1 or 0
	G			1	Y			1	B		
	Pu			2	R			2	G		
	R			3	B			3	Pu		
	Y			4	Pu			4	Pk		
	Pk			5	G			5	Y		
	B			6	Pk			6	R		
		Set I Total				Set II Total				Set III Total	
										Max. = 18 Total Sets I-III	

SET IV				SET V				SET VI			
	Key	Response	Score 1 or 0	Item	Key	Response	Score 1 or 0	Item	Key	Response	Score 1 or 0
	G			1	Pu			1	G		
	Pu			2	B			2	Y		
	R			3	Y			3	B		
	Y			4	Pk			4	R		
	Pk			5	R			5	Pu		
	B			6	G			6	Pk		
		Set IV Total				Set V Total				Set VI Total	

SUAL PAIRED ASSOCIATES II			
m	Key	Response	Score 1 or 0
	Pk		
	R		
	G		
	B		
	Y		
	Pu		
		Max. = 6 Total	

RBAL PAIRED ASSOCIATES II			
mulus Word (and correct response)	Response		
	Easy	Hard	
SE — (Flower)	_____		
TAL — (Iron)	_____		
HOOL — (Grocery)		_____	
BBAGE — (Pen)		_____	
BY — (Cries)	_____		
USH — (Dark)		_____	
EY — (Inch)		_____	
UIT — (Apple)	_____		
Total	Max. = 4	Max. = 4	Max. Total = 8

SUAL REPRODUCTION II Use VRII Copying Sheet.		
nd used: _____ Right _____ Left		
em	Score (see Visual Reproduction Scoring Summary)	
1		Observations:
2		
3		
4		
= 41 Total		

. Digit Symbol

1	2	3	4	5	6	7	8	9
—	⊥	⊐	L	∪	○	∧	×	=

PLES

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

5	4	2	7	6	3	5	7	2	8	5	4	6	3	7	2	8	1	9	5	8	4	7	3

2	5	1	9	2	8	3	7	4	6	5	9	4	8	3	7	2	6	1	5	4	6	3	7

2	8	1	7	9	4	6	8	5	9	7	1	8	5	2	9	4	8	6	3	7	9	8	6

Raw Score

30"

30"

30"

MAX=93

Total Score

90"

Total Time for 3 rows in seconds

git Symbol A

2	8	1	7	9	4	6	8	5	9	7	1	8	5	2	9	4	8	6	3	7	9	8	6

Number of Correct Symbols Recalled

MAX=9

Number of Incorrect Symbols

e Recall

MAX=9

ber of Correct Symbols

ber of Incorrect Symbols

First published 1963
Impression number 31 30 29 28 27 26 25 24 23
Year 1998 1997 1996 1995 1994

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E.P.I.

FORM A

NAME..... AGE.....

OCCUPATION..... SEX.....

N= ☐ E= ☐ L= ☐

Instructions

Here are some questions regarding the way you behave, feel and act. After each question is a space for answering "YES" or "NO".

Try to decide whether "YES" or "NO" represents your usual way of acting or feeling. Then put a cross in the circle under the column headed "YES" or "NO". Work quickly, and don't spend too much time over any question; we want your first reaction, not a long-drawn out thought process. The whole questionnaire shouldn't take more than a few minutes. Be sure not to omit any questions.

Now turn the page over and go ahead. Work quickly, and remember to answer every question. There are no right or wrong answers, and this isn't a test of intelligence or ability, but simply a measure of the way you behave.

N L

FORM A

	YES	NO
Do you often long for excitement?	○	○
Do you often need understanding friends to cheer you up?	○	○
Are you usually carefree?	○	○
Do you find it very hard to take no for an answer?	○	○
Do you stop and think things over before doing anything?	○	○
If you say you will do something do you always keep your promise, no matter how inconvenient it might be to do so?	○	○
Does your mood often go up and down?	○	○
Do you generally do and say things quickly without stopping to think?	○	○
Do you ever feel "just miserable" for no good reason?	○	○
Would you do almost anything for a dare?	○	○
Do you suddenly feel shy when you want to talk to an attractive stranger?	○	○
Once in a while do you lose your temper and get angry?	○	○
Do you often do things on the spur of the moment?	○	○
Do you often worry about things you should not have done or said?	○	○
Generally, do you prefer reading to meeting people?	○	○
Are your feelings rather easily hurt?	○	○
Do you like going out a lot?	○	○
Do you occasionally have thoughts and ideas that you would not like other people to know about?	○	○
Are you sometimes bubbling over with energy and sometimes very sluggish?	○	○
Do you prefer to have few but special friends?	○	○
Do you daydream a lot?	○	○
When people shout at you, do you shout back?	○	○
Are you often troubled about feelings of guilt?	○	○
Are *all* your habits good and desirable ones?	○	○
Can you usually let yourself go and enjoy yourself a lot at a lively party?	○	○
Would you call yourself tense or "highly-strung"?	○	○
28. After you have done something important, do you often come away feeling you could have done better?	○	○
29. Are you mostly quiet when you are with other people?	○	○
30. Do you sometimes gossip?	○	○
31. Do ideas run through your head so that you cannot sleep?	○	○
32. If there is something you want to know about, would you rather look it up in a book than talk to someone about it?	○	○
33. Do you get palpitations or thumping in your heart?	○	○
34. Do you like the kind of work that you need to pay close attention to?	○	○
35. Do you get attacks of shaking or trembling?	○	○
36. Would you always declare *everything* at the customs, even if you knew that you could never be found out?	○	○
37. Do you hate being with a crowd who play jokes on one another?	○	○
38. Are you an irritable person?	○	○
39. Do you like doing things in which you have to act quickly?	○	○
40. Do you worry about awful things that might happen?	○	○
41. Are you slow and unhurried in the way you move?	○	○
42. Have you ever been late for an appointment or work?	○	○
43. Do you have many nightmares?	○	○
44. Do you like talking to people so much that you never miss a chance of talking to a stranger?	○	○
45. Are you troubled by aches and pains?	○	○
46. Would you be very unhappy if you could not see lots of people most of the time?	○	○
47. Would you call yourself a nervous person?	○	○
48. Of all the people you know, are there some whom you definitely do not like?	○	○
49. Would you say that you were fairly self-confident?	○	○
50. Are you easily hurt when people find fault with you or your work?	○	○
51. Do you find it hard to really enjoy yourself at a lively party?	○	○
52. Are you troubled with feelings of inferiority?	○	○
53. Can you easily get some life into a rather dull party?	○	○
54. Do you sometimes talk about things you know nothing about?	○	○
55. Do you worry about your health?	○	○
56. Do you like playing pranks on others?	○	○
57. Do you suffer from sleeplessness?	○	○

SELF-EVALUATION QUESTIONNAIRE

Developed by Charles D. Spielberger
in collaboration with
R.L. Gorsuch, R. Lushene, P.R. Vagg, and G.A. Jacobs

STAI Form Y-1

Name: _____ Date: _____ S _____

Age: _____ Sex: M _____ F _____ T _____

DIRECTIONS: A number of statements which people have used to describe themselves are given below. Read each statement and then blacken in the appropriate circle to the right of the statement to indicate how you feel *right* now, that is, *at this moment*. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

		NOT AT ALL	SOMEWHAT	MODERATELY SO	VERY MUCH SO
1.	I feel calm	①	②	③	④
2.	I feel secure	①	②	③	④
3.	I am tense	①	②	③	④
4.	I feel strained	①	②	③	④
5.	I feel at ease	①	②	③	④
6.	I feel upset	①	②	③	④
7.	I am presently worrying over possible misfortunes	①	②	③	④
8.	I feel satisfied	①	②	③	④
9.	I feel frightened	①	②	③	④
10.	I feel comfortable	①	②	③	④
11.	I feel self-confident	①	②	③	④
12.	I feel nervous	①	②	③	④
13.	I am jittery	①	②	③	④
14.	I feel indecisive	①	②	③	④
15.	I am relaxed	①	②	③	④
16.	I feel content	①	②	③	④
17.	I am worried	①	②	③	④
18.	I feel confused	①	②	③	④
19.	I feel steady	①	②	③	④
20.	I feel pleasant	①	②	③	④

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SELF-EVALUATION QUESTIONNAIRE

STAI Form Y-2

Name: _____ Date: _____

DIRECTIONS: A number of statements which people have used to describe themselves are given below. Read each statement and then blacken in the appropriate circle to the right of the statement to indicate how you *generally* feel. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe how you generally feel.

		ALMOST NEVER	SOMETIMES	OFTEN	ALMOST ALWAYS
21.	I feel pleasant	①	②	③	④
22.	I feel nervous and restless	①	②	③	④
23.	I feel satisfied with myself	①	②	③	④
24.	I wish I could be as happy as others seem to be	①	②	③	④
25.	I feel like a failure	①	②	③	④
26.	I feel rested	①	②	③	④
27.	I am "calm, cool, and collected"	①	②	③	④
28.	I feel that difficulties are piling up so that I cannot overcome them	①	②	③	④
29.	I worry too much over something that really doesn't matter	①	②	③	④
30.	I am happy	①	②	③	④
31.	I have disturbing thoughts	①	②	③	④
32.	I lack self-confidence	①	②	③	④
33.	I feel secure	①	②	③	④
34.	I make decisions easily	①	②	③	④
35.	I feel inadequate	①	②	③	④
36.	I am content	①	②	③	④
37.	Some unimportant thought runs through my mind and bothers me	①	②	③	④
38.	I take disappointments so keenly that I can't put them out of my mind	①	②	③	④
39.	I am a steady person	①	②	③	④
40.	I get in a state of tension or turmoil as I think over my recent concerns and interests	①	②	③	④

BDI®

Date: _____

e: _____ Marital Status: _____ Age: _____ Sex: _____

pation: _____ Education: _____

questionnaire consists of 21 groups of statements. After reading each group of statements carefully, e the number (0, 1, 2 or 3) next to the one statement in each group which **best** describes the way you been feeling the **past week, including today.** If several statements within a group seem to apply equally circle each one. **Be sure to read all the statements in each group before making your choice.**

0 I do not feel sad.
1 I feel sad.
2 I am sad all the time and I can't snap out of it.
3 I am so sad or unhappy that I can't stand it.

0 I am not particularly discouraged about the future.
1 I feel discouraged about the future.
2 I feel I have nothing to look forward to.
3 I feel that the future is hopeless and that things cannot improve.

0 I do not feel like a failure.
1 I feel I have failed more than the average person.
2 As I look back on my life, all I can see is a lot of failures.
3 I feel I am a complete failure as a person.

0 I get as much satisfaction out of things as I used to.
1 I don't enjoy things the way I used to.
2 I don't get real satisfaction out of anything anymore.
3 I am dissatisfied or bored with everything.

0 I don't feel particularly guilty.
1 I feel guilty a good part of the time.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

0 I don't feel disappointed in myself.
1 I am disappointed in myself.
2 I am disgusted with myself.
3 I hate myself.

8
0 I don't feel I am any worse than anybody else.
1 I am critical of myself for my weaknesses or mistakes.
2 I blame myself all the time for my faults.
3 I blame myself for everything bad that happens.

9
0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10
0 I don't cry any more than usual.
1 I cry more now than I used to.
2 I cry all the time now.
3 I used to be able to cry, but now I can't cry even though I want to.

11
0 I am no more irritated now than I ever am.
1 I get annoyed or irritated more easily than I used to.
2 I feel irritated all the time now.
3 I don't get irritated at all by the things that used to irritate me.

12
0 I have not lost interest in other people.
1 I am less interested in other people than I used to be.
2 I have lost most of my interest in other people.
3 I have lost all of my interest in other people.

13
0 I make decisions about as well as I ever could.
1 I put off making decisions more than I used to.
2 I have greater difficulty in making decisions than before.
3 I can't make decisions at all anymore.

_____ Subtotal Page 1

CONTINUED ON BACK

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0 I don't feel I look any worse than I used to.
1 I am worried that I am looking old or unattractive.
2 I feel that there are permanent changes in my appearance that make me look unattractive.
3 I believe that I look ugly.

0 I can work about as well as before.
1 It takes an extra effort to get started at doing something.
2 I have to push myself very hard to do anything.
3 I can't do any work at all.

0 I can sleep as well as usual.
1 I don't sleep as well as I used to.
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3 I wake up several hours earlier than I used to and cannot get back to sleep.

0 I don't get more tired than usual.
1 I get tired more easily than I used to.
2 I get tired from doing almost anything.
3 I am too tired to do anything.

0 My appetite is no worse than usual.
1 My appetite is not as good as it used to be.
2 My appetite is much worse now.
3 I have no appetite at all anymore.

19
0 I haven't lost much weight, if any, lately.
1 I have lost more than 5 pounds.
2 I have lost more than 10 pounds.
3 I have lost more than 15 pounds.

I am purposely trying to lose weight by eating less. Yes _____ No _____

20
0 I am no more worried about my health than usual.
1 I am worried about physical problems such as aches and pains; or upset stomach; or constipation.
2 I am very worried about physical problems and it's hard to think of much else.
3 I am so worried about my physical problems that I cannot think about anything else.

21
0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

_____ Subtotal Page 2

_____ Subtotal Page 1

_____ Total Score

Subjective Assessment Scale

For each question, simply tick the box next to the statement that you think is the most appropriate answer.

Which of the following statements best describes your memory?

1. My memory is as good now as it ever was ☐
2. My memory is better now than ever ☐
3. My memory is less good now than it was ☐

Which of the following statements best describes your ability to solve problems or puzzles?

1. I can solve problems and puzzles now as easily as before ☐
2. I find it more difficult now to solve problems and puzzles ☐
3. I find it easier now to solve problems and puzzles than before ☐

Which of the following statements best describes how clearly you think?

1. I think less clearly nowadays ☐
2. I think more clearly nowadays ☐
3. I think as clearly as I have always done ☐

Which of the following statements best describes your concentration?

1. I concentrate as well now as I have always done ☐
2. I concentrate better now than before ☐
3. I concentrate less well now than before ☐

Which of the following statements best describes your tendency to make mistakes?

1. I make more mistakes now than I used to ☐
2. I make fewer mistakes now than I used to ☐
3. I make the same sort of mistakes now as I ever did ☐

Which of the following statements best describes your ability to pay attention?

1. I pay attention to things now as well as I ever did ☐
2. I find it more difficult now to pay attention to things ☐
3. I find it easier now to pay attention to things ☐

Which/

Which of the following statements best describes your clumsiness?

1. I am less clumsy now than I used to be ☐
2. I am no more or less clumsy now than I used to be ☐
3. I am more clumsy now than I used to be ☐

Which of the following statements best describes how you make decisions?

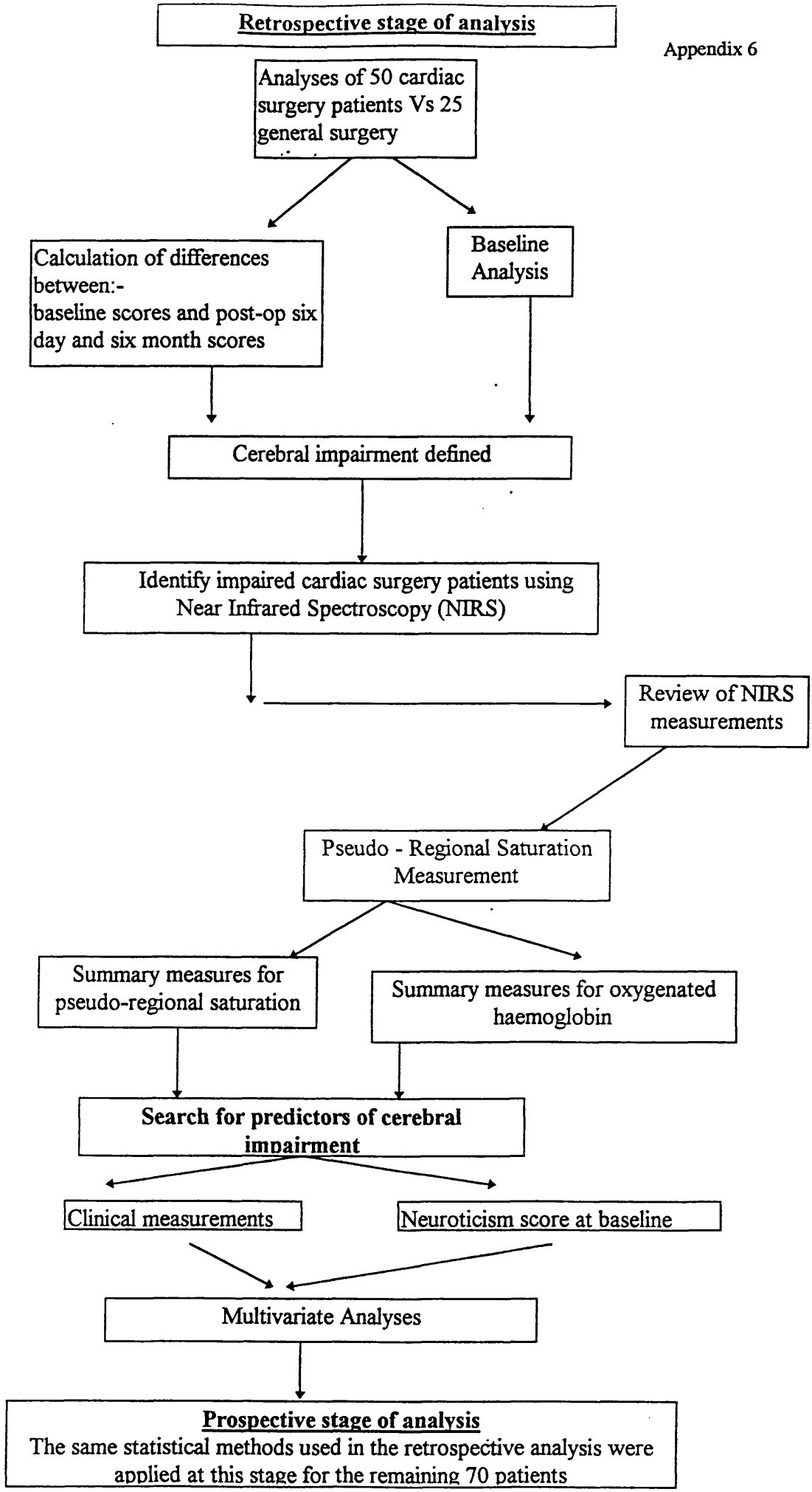
1. I find it more difficult now to make decisions than before ☐
2. I find it easier now to make decisions than before ☐
3. I find it just as easy to make decisions now as before ☐

Which of the following statements best describes how quickly you can respond or react?

1. I do not respond or react now as quickly as I used to do ☐
2. I respond or react now just as quickly as I ever did ☐
3. I respond or react now more quickly than I used to do ☐

Appendix 6

Flowchart - Stages of Data Analyses

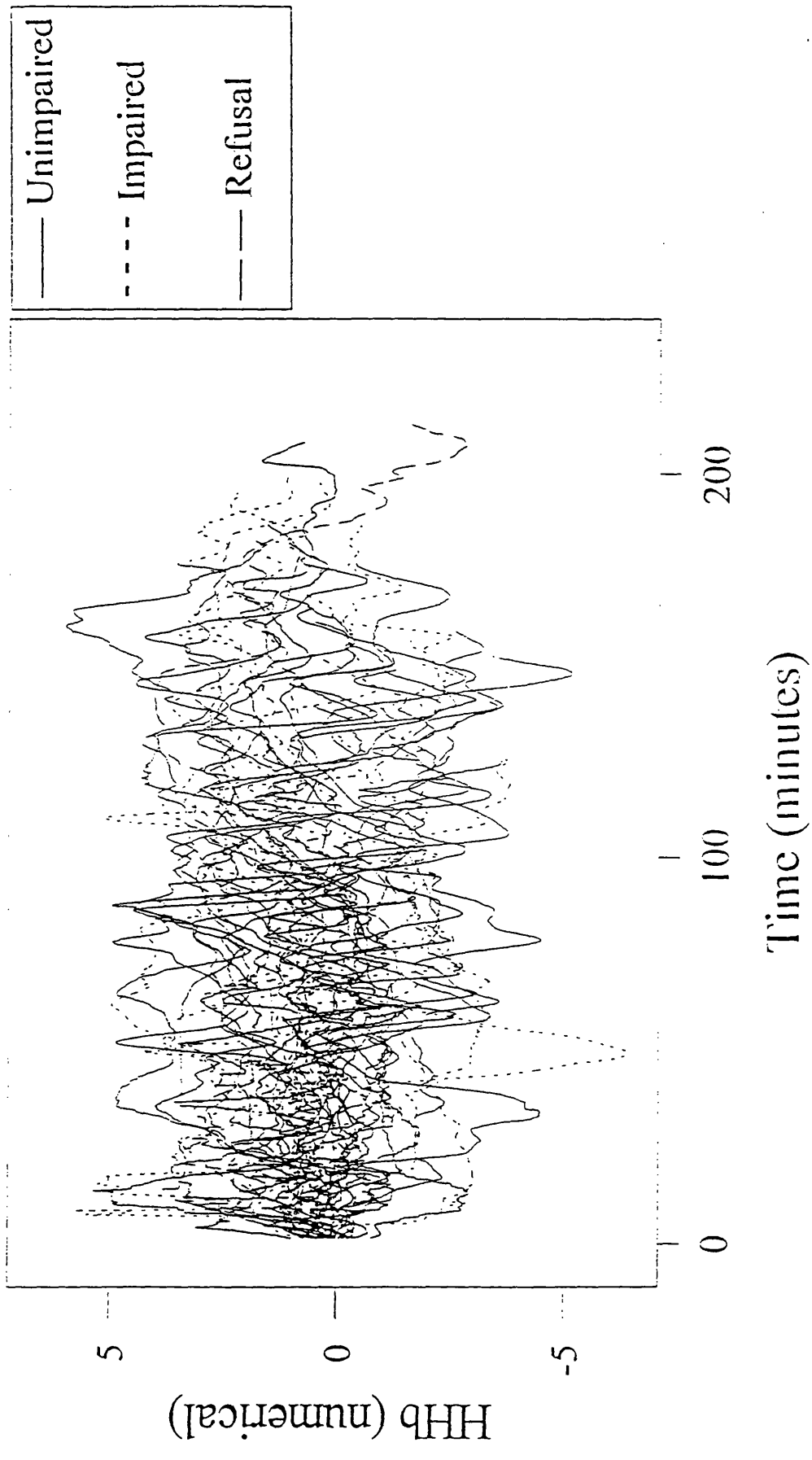

Retrospective stage of analysis
Analyses of 50 cardiac surgery patients Vs 25 general surgery
Calculation of differences between:-
baseline scores and post-op six day and six month scores
Baseline Analysis
Cerebral impairment defined
Identify impaired cardiac surgery patients using Near Infrared Spectroscopy (NIRS)
Review of NIRS measurements
Pseudo - Regional Saturation Measurement
Summary measures for pseudo-regional saturation
Summary measures for oxygenated haemoglobin
Search for predictors of cerebral impairment
Clinical measurements
Neuroticism score at baseline
Multivariate Analyses
Prospective stage of analysis
The same statistical methods used in the retrospective analysis were applied at this stage for the remaining 70 patients

APPENDIX 7

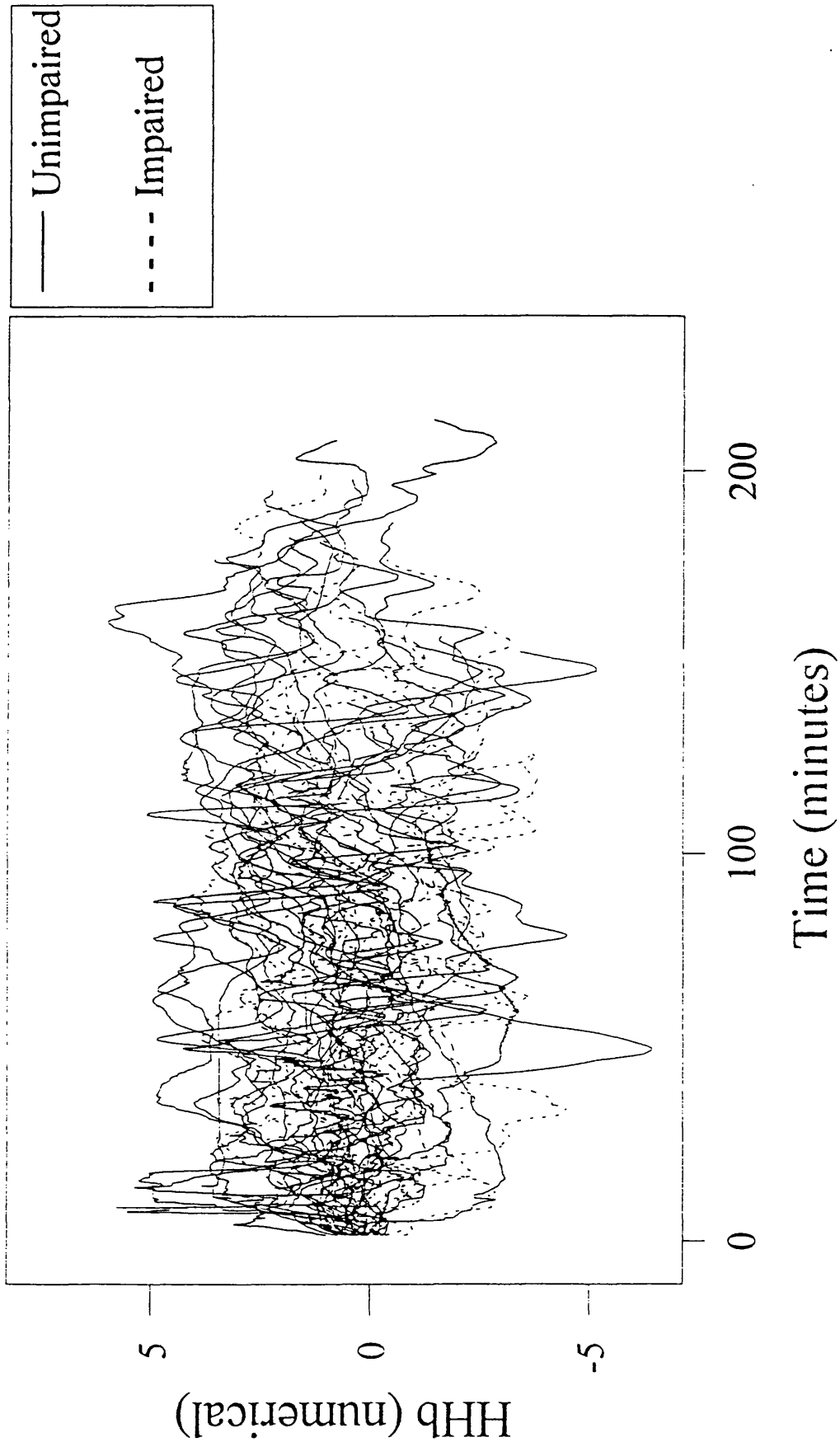
Graphs

Recordings from Critikon Cerebral Oxygen Utilisation Monitor

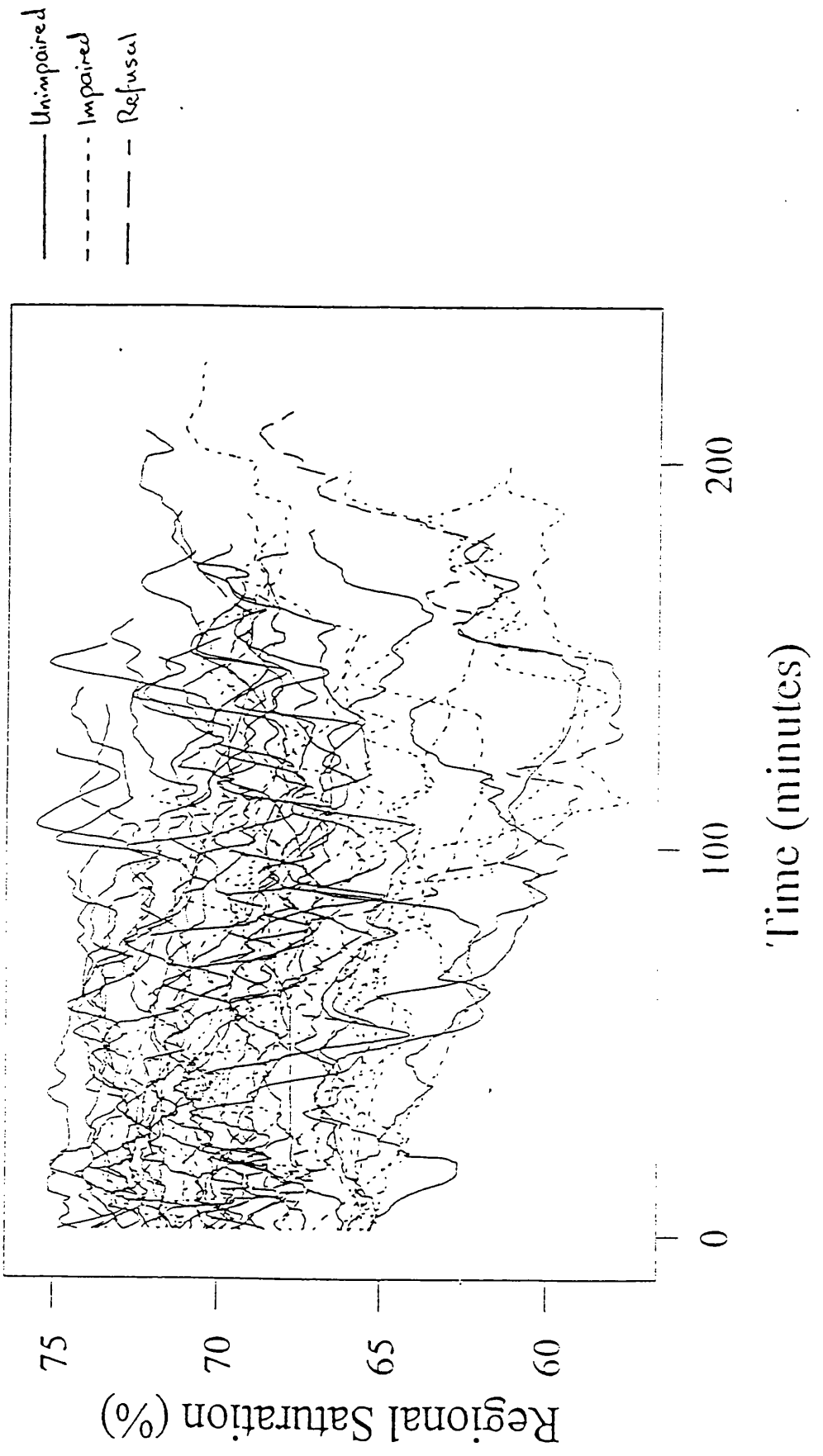
Whole Operation For All Cardiac Patients (Smoothed) - Impairment at Six Days



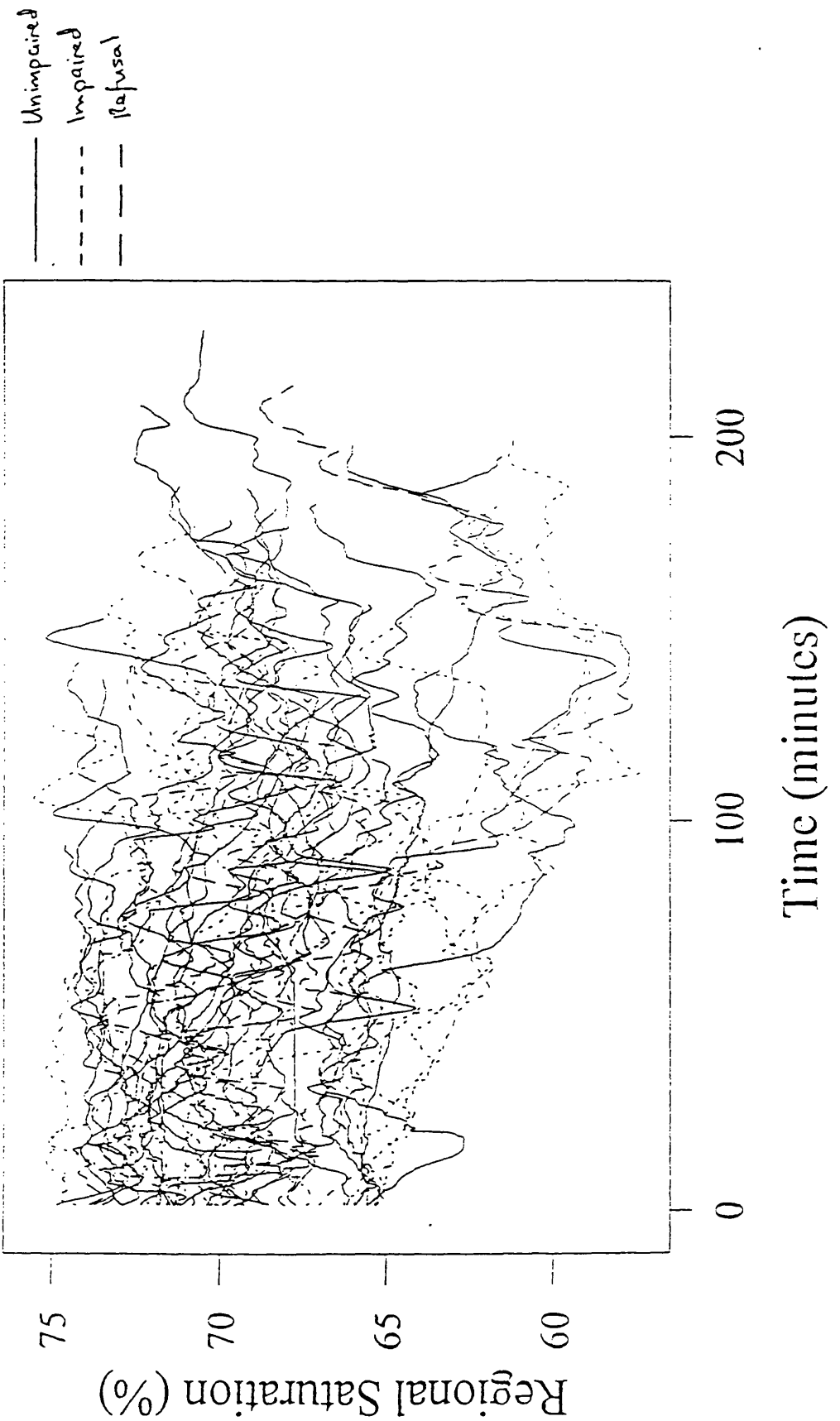
Whole Operation for All Cardiac Patients (Smoothed) - Impairment at Six Months



Pseudo - Regional Saturation (%) - Impairment at Six Days - Whole Operation (Smoothed)



Pseudo - Regional Saturation (%) - Impairment at Six Months - Whole Operation (Smoothed)



APPENDIX 8

Detailed Data Analyses Results

Retrospective Stage - Operation Details

There was interest in the following measurements of the cardiac operation:-

- Core temperature at rewarming
- Core temperature at off bypass
- Lowest mean arterial pressure during bypass
- Lowest core temperature during bypass
- Total time on bypass

Temperature and Pseudo-Regional Saturation

Pseudo-regional saturation summaries were calculated previously at rewarming and off bypass (mean and gradient). Rank correlations were calculated (due to the skewness of some of the data) as follows:-

	Correlation	Probability
Core Temperature Rewarm vs pseudo-Regional Saturation Average Rewarm	0.17	0.31
Core Temperature Rewarm vs pseudo-Regional Saturation Gradient Rewarm	0.12	0.47
Core Temperature Off Bypass vs pseudo-Regional Saturation Average Off Bypass	0.06	0.72
Core Temperature Off Bypass vs pseudo-Regional Saturation Gradient Off Bypass	0.03	0.86

No significant correlation was found between pseudo-regional saturation and core temperature.

Analyses of Temperatures, Time and Arterial Pressure

Impaired/Unimpaired Patients (impaired if patient's impairment score was less than zero)

Measure	Period	Probability	Confidence Interval
Core Temperature at Rewarming	Six days	0.96	(-0.60, 1.70)
	Six Months	0.50	(-0.60, 2.20)
Core Temperature at Off Bypass	Six days	0.56	(-0.50, 0.20)
	Six months	0.08	(-0.00, 0.80)
Lowest Mean Arterial Pressure	Six days	0.12	(-1.00, 12.00)
	Six months	0.12	(-2.00, 11.00)
Lowest Core Temperature	Six days	0.38	(-0.40, 2.70)
	Six months	0.93	(-1.40, 0.90)
Total Time On Bypass	Six days	0.60	(-19.01, 8.99)
	Six months	0.16	(-5.00, 23.00)

No significant difference was found between the impaired and unimpaired patients for any temperature, time or pressure. The closest to significance was the Core Temperature at Off Bypass at six months with a probability of 0.80.

Continuous Definition of Impairment

	Six Days		Six Months	
	Correlation	**Probability**	**Correlation**	**Probability**
Core Temperature at rewarming	-0.110	0.529	-0.090	0.635
Core Temperature at Off Bypass	-0.192	0.270	0.103	0.587
Lowest Mean Arterial Pressure	0.230	0.184	0.262	0.162
Lowest Core Temperature	0.057	0.744	-0.122	0.521
Total Time On Bypass	0.055	0.753	0.346	**0.061**

No significant correlation could be found between the temperatures, pressure or time and the actual level of impairment. The closest to significance was the Total Time on Bypass at six months with a probability of 0.061.

Retrospective Stage - Analysis of Neuroticism Score at Baseline

Impaired/Unimpaired Patients (impaired if patient's impairment score was less than zero)

Measure	Period	Probability	Confidence Interval
Neuroticism at Baseline	Six days	**0.08**	(-5.12, 0.30)
	Six months	0.37	(-4.35, 1.70)

Although no statistically significant difference could be found the values at six days had a probability of 0.08. The impaired group had a higher neuroticism score than the unimpaired group.

Actual Level of Impairment

	Six Days		Six Months	
Measure	**Correlation**	**Probability**	**Correlation**	**Probability**
Neuroticism at Baseline	-0.464	**0.005**	-0.232	0.218

The neuroticism at baseline was highly negatively correlated with the actual level of impairment at six days with a probability 0.005. As before the higher the neuroticism score the more impaired the patient was.

Retrospective Stage - Multivariate Analyses

Univariate Tests

There was interest in finding useful predictors of impairment at six days and six months. Before performing the multivariate analysis, univariate tests were carried out on the State and Trait Anxiety, Sex and Age to determine if any differences were noted between the impaired and unimpaired patients. The results were as follows:-

State and Trait Anxiety at Baseline

Impaired/Unimpaired Patients (Impaired if patient's impairment score was below zero)

Measure	Period	Probability	Confidence Interval
State Anxiety at Baseline	Six days	0.41	(-4.4, 10.6)
	Six months	0.97	(-8.4, 8.1)
Trait Anxiety at Baseline	Six days	0.95	(-6.9, 6.4)
	Six months	**0.07**	(-12.9, 0.6)

No differences were significant at the 5% level, although the comparison of Trait Anxiety at Baseline between the impaired and unimpaired patients at six months was close to the borderline (probability of 0.07). The impaired group had higher trait anxiety scores than the unimpaired group.

Continuous Level of Impairment

	Correlation	Probability	Correlation	Probability
State Anxiety at Baseline	0.094	0.596	0.085	0.660
Trait Anxiety at Baseline	-0.130	0.465	-0.228	0.233

For the continuous definition of impairment neither the state or trait anxiety scores was correlated with impairment, at six days or six months.

Age and Sex

For the impaired and unimpaired patients two sample t-tests were carried out for age. The results were as follows:-

Age

Impaired/Unimpaired (Impaired if patient's impairment score is below zero)

Measure	Period	Probability	Confidence Interval
Age	Six days	**0.02**	(-14.0. -1.1)
	Six months	0.35	(-10.3, 3.8)

There was a statistically significant difference in ages at six days, with the impaired patients being older than average.

Sex

Chi-squared analyses were carried out to test for any differences between the unimpaired and impaired patients for the males and females. The results were as follows:-

Impaired/Unimpaired (Impaired if patient's impairment score is below zero)

Measure	Period	Probability
Sex	Six days	**0.09**
	Six months	0.60

There was no statistically significant difference in impaired patients between the males and females, although at six days a higher proportion of females than males were impaired, with a probability of 0.09.

Age and Sex

The actual level of impairment was then used to test for any relationship with the age and sex.

Age

Correlations were calculated as follows:-

Continuous Level of Impairment

	Six Days		Six Months	
Measure	**Correlation**	**Probability**	**Correlation**	**Probability**
Age	-0.443	**0.008**	-0.235	0.212

As for the binary definition of impairment, a significant correlation exists between impairment at six days and age. The higher levels of impairment are for older patients on average.

Sex

For the male and female patients two sample t-tests were carried out, for impairment at six days and six months. The results are as follows:-

Continuous Level of Impairment

Measure	Period	Probability	Confidence Interval
Sex`	Six days	0.26	(-2.3, 8.3)
	Six months	0.13	(-1.2, 8.7)

No statistically significant difference was found between males and females at either six days or six months.

Prospective Stage - Analysis of Summary Measures For Pseudo-Regional Saturation

Individual Neuropsychological Tests

As the overall level of impairment was not found to correlate with the summary measures, the individual test results were used instead. The differences from pre- to six day postoperative result or from pre- to six month postoperative result were used. In all cases the data were converted so that a positive value indicated an improvement.

The correlation between individual tests and the summary measures were calculated. As the data from the tests are not all normally distributed Spearman's correlation coefficient was used.

Significant correlations were found in the following cases:-

Measurement	Period	Correlation	Probability
Average Off Bypass and Vigilance False	Six days	0.287	**0.048**
Gradient Rewarming and Digit Symbol Substitution Task - Proportion Correct	Six days	-0.296	**0.033**
Gradient Rewarming and Digit Symbol Substitution Task - Total Copied Correct In Time	Six days	-0.349	**0.012**
Gradient Rewarming and Visual Paired Associates 1 - 3	Six months	0.288	**0.047**
Gradient Off Bypass and Verbal Paired Associates - Maximum Hard.	Six days	0.279	**0.047**
Average Off Bypass-Average Rewarming and Beck's Depression Inventory	Six days	0.290	**0.043**
Average Off Bypass-Average Rewarming and Digits Total	Six days	0.271	**0.048**
Average Off Bypass-Average Rewarming and Psyche Test - On Target	Six months	0.367	**0.013**
Average Off Bypass-Average Rewarming and Digit Symbol Substitution Task - Total Time To Copy Three Rows	Six months	0.315	**0.026**

Although significant correlations exist for the above variables, the relationships are weak.

Prospective Stage - Analysis of Summary Measures For Oxygenated Haemoglobin

As the overall level of impairment was not found to correlate with the summary measures, the individual test results were analysed. The differences from the pre- to six day postoperative results or from the pre- to six month postoperative results were used. In all cases the data were converted so that a positive value indicated an improvement.

The correlation between individual tests and the summary measures were calculated. In this instance as the data from the tests are not all normally distributed Spearman's correlation coefficient was used.

Significant correlations were found in the following cases:-

Measurements	Period	Correlation	Probability
Mean Rewarming time and State Anxiety	Six days	-0.292	**0.039**
Mean Rewarming time and Vigilance False	Six days	-0.326	**0.024**
Mean Rewarming time and Digits Total	Six days	-0.294	**0.031**
Mean Rewarming and Verbal Paired Associates - Maximum Easy	Six months	0.296	**0.035**
Mean Off Bypass time and Vigilance False	Six days	-0.304	**0.035**
Mean Off Bypass time and Mean Reaction Time	Six months	0.424	**0.0004**
Gradient Rewarming and Digit Symbol Substitution Task - Proportion Correct	Six days	-0.278	**0.046**
Gradient Rewarming And Visual Paired Associates 1 - 3	Six months	0.297	**0.040**
Gradient Off Bypass and State Anxiety	Six days	0.340	**0.016**

In some of the above the significant correlation is due to a test having only one or two values, i.e. Mean Rewarming time and Vigilance False at Six days. In the other tests

although a trend can be observed, either negative or positive, no variable seems to be a suitable predictor of the summary value of oxygenated haemoglobin.

Prospective Stage - Operation Details

Analyses of Temperature, Time and Arterial Pressure

Impaired and Unimpaired Patients (Impaired if patient's impairment score is below zero)

The results are as follows:-

Measure	Period	Probability	Confidence Interval
Core Temperature	Six days	0.44	(-0.30, 1.40)
at Rewarming	Six months	0.06	(-0.00, 1.80)
Core Temperature	Six days	0.07	(-0.70, 0.00)
at Off Bypass	Six months	0.50	(-0.30, 0.40)
Lowest Mean	Six days	0.17	(-6.00, 1.00)
Arterial Pressure	Six months	0.87	(-3.00, 4.00)
Lowest Core	Six days	**0.02**	(0.10, 1.10)
Temperature	Six months	0.13	(-0.10. 1.10)
Total Time	Six days	**0.01**	(-26.00, -4.01)
On Bypass	Six months	0.11	(-22.00, 3.00)

Significant differences were found between the impaired and unimpaired patients for Lowest Core Temperature, at six days, and Total Time On Bypass, at six days. The impaired patients, at six days, have a lower core temperature, and have a longer time on bypass. This difference is not apparent between the impaired and unimpaired patients at six months.

Prospective Stage - Operation Details (Continued)

Continuous Definition of Impairment

Rank correlations were calculated as follows:-

	Six Days		Six Months	
	Correlation	**Probability**	**Correlation**	**Probability**
Core Temperature at Rewarming	0.129	0.352	0.225	0.112
Core Temperature at Off Bypass	-0.081	0.562	0.006	0.968
Lowest Mean Arterial Pressure	-0.135	0.331	0.002	0.987
Lowest Core Temperature	0.245	0.075	0.155	0.277
Total Time On Bypass	-0.326	**0.016**	-0.156	0.275

A significant correlation was found between the Total Time On Bypass and the level of impairment at six days. As with the previous definition of impairment, the higher the level of impairment the longer the bypass time. Although the same trend is noted with the impairment scores at six months, it is no longer statistically significant.

Prospective Stage - Multivariate Analyses

Age

Impaired and Unimpaired Patients (Impaired if patient's impairment score is below zero)

The results are as follows:-

Measure	Period	Probability	Confidence Interval
Age	Six days	**0.02**	(-10.3, -0.8)
	Six months	0.20	(-1.8, 8.4)

Ther was a statistically significant difference in ages at six days, with the impaired patients being older on average.