A STUDY OF SHORT TERM COGNITIVE OUTCOME IN POST CABG PATIENT

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By

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ABBREVIATIONS

ACS	Acute coronary syndrome
ACT	Activated clotting time
AV	Atrio-ventricular
AVN	Atrioventricular node
AVR	Aortic valve replacement
BLC	Big little circle
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CANTAB®	Cambridge Neuropsychological Test Automated Battery®
CHD	Coronary heart disease
CICU	Cardio-thoracic Intensive Care Unit
CNS	Central nervous system
COAD	Chronic obstructive airway disease
CPB	Cardio-pulmonary bypass
CPS	Cardiopulmonary support
CRF	Chronic renal failure
CT	Computed tomography
DIVC	Disseminated intravascular coagulopathy
ECG	Electrocardiography
ECMO	Extracorporeal membrane oxygenation
GCS	Glascow coma scale

ICD	International coding of disease
IED	Intra/Extra dimensional
IHD	Ischemic heart disease
LAD	Left anterior descending a.k.a Left circumflex (LCx)
LCA	Left coronary artery
LCx	Left circumflex branch
LHB	Left heart bypass
LMS	Left main stem
MCS	Middle cerebral artery
MI	Myocardial infarction
MMSE	Mini mental state examination
NCVD-ACS	National Cardiovascular Disease-Acute Coronary Syndrome
OPCAB	Off-pump coronary artery bypass
PAL	Paired Associate Learning
PCI	Percutaneous coronary intervention
POCD	Post-operative cognitive decline
PTCA	Percutaneous coronary angiography
PVC	Polyvinyl chloride
RA	Right atrium
RCA	Right coronary artery
SAN	Sinoatrial node
SD	Standard deviation
SST	Stop Signal Task
TIA	Transient ischemic attack

TOE	Trans-oesophageal echocardiography
VD	Vessel disease
2VD	2-vessels disease
3VD	3-vessel disease

ABSTRAK

KAJIAN MENGENAI KESAN JANGKA PENDEK FUNGSI KOGNITIF BAGI PESAKIT SELEPAS PEMBEDAHAN PINTASAN KORONARI

Objektif: Mengkaji kesan fungsi kognitif jangka pendek bagi pesakit selepas pembedahan pintasan jantung koronari, dan mengenalpasti faktor-faktor yang terlibat.

Metodologi: Ini adalah kajian kohort. Empat puluh tiga pesakit yang terlibat adalah pesakit yang menjalani pembedahan pintasan jantung koronari sepanjang bulan Mac 2011 sehingga Julai 2012. Tahap fungsi kognitif mereka dikaji dan direkod sebelum dan satu minggu selepas pembedahan menggunakan CANTAB®. Data sosio-demografik, keadaan kesihatan dan karekter prosedur direkodkan.

Keputusan: Sejumlah 40 pesakit dikaji tahap fungsi kognitif mereka sebelum pembedahan dan seminggu selepas pembedahan pintasan jantung koronari. Terdapat kemerosotan (>20% daripada nilai dasar) di dalam ketiga-tiga sub-ujikaji CANTAB®, dengan nilai Intra/Extradimensional (IED) 35% (n=14), Paired Associate Learning (PAL) 35% (n=14) dan Stop Signal Task (SST) 27.5% (n=11) secara keseluruhannya. Tiada hubungan yang signifikan ($p>0.05$) bagi perubahan kognitif ini dengan umur pesakit, tahap pendidikan, jenis prosedur, jangka masa anesthesia, pembedahan, CPB dan 'rewarming', serta kadar 'rewarming'.

Kesimpulan: Terdapat kemerosotan fungsi kognitif pada interval satu minggu selepas pembedahan di kalangan pesakit yang menjalani pembedahan pintasan koronari, dengan

domain utama yang terlibat adalah fungsi eksekutif dan memori visual. Oleh itu, penerangan lanjut mengenai kemerosotan neurokognitif ini perlu diberikan kepada pesakit sebelum pembedahan. Di dalam kajian ini, ia tidak dapat mengenalpasti faktor-faktor yang berkaitan dengan kemerosotan fungsi kognitif.

KATA KUNCI: Pindahan pintasan jantung, fungsi kognitif

ABSTRACTS

A STUDY OF SHORT TERM COGNITIVE OUTCOME IN POST CABG PATIENT

Objectives: To evaluate the outcomes on short-term cognitive function in post CABG patients and to identify its risk factors.

Method: This is a prospective cohort study. Forty three patients subjected for CABG between March 2011 to July 2012 were enrolled in this study. Their cognitive function preoperative and 1 week postoperatively were documented with CANTAB®. The sociodemographic, medical and procedure characteristics were recorded in the data form.

Result: The total of 40 patients' cognitive function were assessed and recorded before operation and at 1 week interval after CABG. There were impairment noted (>20% from baseline value) in three subtest of CANTAB® during post-operative period, with Intra/Extradimensional (IED) test 35% (n=14), Paired Associate Learning (PAL) test 35% (n=14) and Stop Signal Task (SST) test 27.5% (n=11) of the total subject. There were no significant correlation of these cognitive changes (P>0.05) with few variables such as age, education level, type of procedure, duration of anesthesia, surgery, CPB and rewarming, and also rate of rewarming.

Conclusion: A presence of cognitive decline at 1 week interval post-operatively was observed among patient subjected for CABG. The main domains involved were executive function and visual memory. Thus pre-procedural details should be address to the patients in

term of this neurocognitive impairment. In this study, there was no confounding factor noted related to cognitive changes.

KEYWORDS: CABG; Cognitive Function

CHAPTER ONE

INTRODUCTION

Recently, increasing number of patients has been diagnosed to have coronary arterial disease. And some of them have been reported to have severe coronary arterial diseases such as involvement of the left main-stem of coronary artery, which then been subjected for surgical intervention for the correction of coronary artery obstruction in order to improve circulation to the heart. One of the method that been well established currently were coronary artery bypass grafting (CABG), and this procedure involving major operation which might cause significant complications. Cardiovascular and respiratory complications were main concern in this case. Cerebral complications of it were taken lightly by most of the patients and clinicians, as it considered giving minor impact on patients' life. However, there is a high incidence of post-operative cerebral complications in patients undergoing CABG with a wide spectrum of the dysfunction that include post-operative decline of cognitive function. Apart from its effect on quality of life, this postoperative cognitive decline is associated with high morbidity and mortality and the percentage of it had been reported is 10% (Newman *et al.*, 2002). This problem should be investigated further, and interventions for prevention should be taken into account.

Cognitive impairments are one of the adverse effects of anesthesia. But this problem is not highlighted by our community as the effect of it been taken lightly by most of the patients and physicians (Selnes *et al.*, 1999). Postoperative cognitive decline have more significant

association with cardiac surgery. The incidence of neuropsychological dysfunction after CABG is as high as 50% (Newman *et al.*, 2002) in early post-operative period. These incidences are associated with multiple factors. Few factors that been postulate for this adverse events are its association with cardio-pulmonary bypass supported cardiac surgery. In the past, few studies had been conducted to elicit the incidence and factors related to postoperative cognitive decline in patients undergoing CABG with on-pump technique (usage of cardiopulmonary-bypass (CPB) machine) (Newman *et al.*, 2002). However, the assessments of this neuropsychological testing initially were limited to assessment by using conventional method, predominantly by application of Mini-mental State Examination (MMSE). Even though this assessment provide excellent sensitivity towards screening of dementia, but it is less sensitive to identify subtle cognitive changes. Roebuck et al found that computerized testing batteries are one of good tools to assess changes in cognition as they allow for randomization of the stimuli, creating near limitless alternate forms and reducing practice effect (Roebuck-Spencer *et al.*, 2007). Fritzsche *et al* had recommend the practice of fully automated system for assessment of cognitive function for reliable diagnostic information, and also easier to validate without having to deal with biased human input (Fritzsche *et al.*, 2008). Aharonson *et al* also suggested that computer method for assessment of cognitive function is faster, cheaper, and more applicable to wide use (Aharonson *et al.*, 2007).

CANTAB® (Cambridge Neuropsychological Test Automated Battery) is one of automated computerized cognitive testing batteries provided by Cambridge Cognition that developed to assess main cognitive domains (Cambridge, 2006). This study was conducted to identify the cognitive changes in patients undergoing CABG surgery supported by CPB with CANTAB®

as the assessment tool used, and also to identify factors that are associated with cognitive dysfunction.

CHAPTER TWO

LITERATURE REVIEW

2.1 Cognition

Cognitive function is important process that involved in gaining knowledge and comprehension. It is an interaction between knowledge driven process and sensory process, and between controlled process and automatic processes (McGraw, 2002). It also refers to the mental process of comprehension. This function is used to describe a person' state of consciousness (alertness and orientation), memory, attention span, and insight. Apart of that it also used to describe individual's knowledge processes including sensation, perception, memory, language, thinking and reasoning.

Cognition involves various different kinds of information processing which occur at different stages. The initial stage for cognition is *perception*; in which analysis of input content occur. Process of perception often lead to making record of input received, and this involve *learning* and *memory storage*. Once the memory had been created, it can be retained for later uses that require *retrieval* of the information. Retrieval is often used to assist the thought process for further mental activities such as thinking. Sometimes this involved rearrangement and manipulation of stored information (Groome *et al.*, 2006).

Figure 2.1: The Main Stages Of Cognitive Processing

Reference: (Groome *et al.* 2006)

The internal structures of cognitive functions are components of higher mental functions of the brain and this network consist of large connections of cortical cells with the neural switchboard that give rise to conscious thinking (Kirschner, 2012). The origin of this network for cognition and action are theoretically from the frontal lobes which act as executive centre of the brain that determine attention act and motor planning. As described by *Cumming,* there are five frontal networks for consciousness and behaviour, and this frontal cortex projects to the basal ganglia, then to thalamic nuclei, and back to the cortex.

The frontal lobes of the brain include the motor region of the cortex, which control movement. It also consist Broca's area which control the production of speech. Other part of frontal lobes seems to be involved in central executive systems which control conscious mental process and production of conscious decisions (Groome *et al.*, 2006). Visual input process take place in occipital lobes of the brain, while the parietal lobes concern with

perception, and also involved in some aspects of short-term memory. Temporal lobes involved with memory of language and understanding of speech.

Attention is defined as holding of something before the mind to the exclusion of all else, in which it helps guide processing to important objects. The disorder of perception and attention can be debilitating and distressing condition which severely disables the individual who suffer it (Groome *et al.*, 2006).

Memory is the process of storing information and experiences for possible retrieval at some point in the future, and it is essential to function as human beings (Groome *et al.*, 2006). Memory itself can be further categorized into episodic memory and semantic memory. Episodic memory is the most memory retrieval in everyday life, which is involved memory for events and episodes in our own lives (Tulving and Donaldson, 1972). Semantic memory is a more structured record of facts, meanings, concepts and knowledge about external that had been acquired. It is abstract and relational, and associated with verbal symbols (Memory).

Executive cognitive function is an integrative ability that is broadly referred to mental agility, abstract reasoning, and problem solving. it represents processes that support mental flexibility, adaptability, focus, and tenacity, and it is also closely related to control of personal actions and regulation of interpersonal relationships, and it denotes how a person behaves, particularly towards other people (Cecil, 2011). One of the aspect assessing the central

executive function of the brain is assessment of the working memory also known as short-term memory, and it is function as an active mental workspace in which variety of processing operations are carried out. Impairment of the central executive is known as dysexecutive syndrome, and been found to be associated with frontal lobe lesion. It is considered to play a part in certain clinical disorders such as Alzheimers disease, autism and schizophrenia (Groome *et al.*, 2006).

2.2 Cognitive Impairment

Personnel with cognitive impairment often presented with vague and subjective symptoms of declining cognitive performance. This will be notice by family members and closed friends as the person was not like his or herself. An epidemiological research showed that the prevalence of mild cognitive impairment in general elderly population was 3-19%, with the incidence of it was 8-57 per 1000 per year (Ritchie and Ritchie, 2004). Decline in the cognitive function might involve few aspects of cognition itself. Poor performance in delayed recall and executive function test via standard neuropsychological assessment has been indicated as a high risk progression to dementia (Flicker *et al.*, 1991). Some individual with mild cognitive impairment appear to be stable and return to normal over time, but unfortunately more than half had progress to dementia within 5 years. Therefore this mild cognitive impairment can be regarded as a state at risk of dementia, subsequently the identification of this condition could lead to prevention of dementia (Gauthier *et al.*, 2002). This impairment can be due to virtually any disorder that causes brain dysfunction.

There are few common causes that might contribute to cognitive decline for example Alzheimer's disease, cerebrovascular disease, Parkinson's disease and metabolic and endocrine disease including cobalamin deficiencies. Few infections also may cause cognitive changes such as HIV infection and cerebral infection. The changes might also arise secondary to traumatic brain injury and adverse central nervous system effects of drugs and toxicants. Cognitive impairment may also occur due to depression, cognitive adverse effect of sleep disorders and chronic psychological stress. Few epidemiological studies done found that there are many factors affecting cognitive performance apart from neurodegenerative disorders such as level of education (Ganguli *et al.*, 2004; Ritchie and Ritchie, 2004).

This mild cognitive impairment associated with subcortical cerebrovascular disease (Galluzzi *et al.*, 2005). Pathological findings noted in patient with mild cognitive impairment were presence of neurofibrillary tangles in the mesial temporal structures (Morris *et al.*, 2001). From the population based study in 2004 found that causal factors of cognitive impairment are interacting combination of causes including white-matter lesions, cerebral infarctions, extracellular amyloid deposition, and intracellular neurofibrillary tangle formation. These may subsequently increase the risk of progression of this impairment into full blown Alzheimers disease (Ritchie and Ritchie, 2004).

Even though that there is no specific disease modifying treatment yet been shown to be effective for this problem, the control of the risk factors might contribute to reduction in the incidence and severity of it (Gauthier *et al.*, 2002).

2.2.1 Postoperative Cognitive Decline

In patients with decline in cognitive functions after surgery and anesthesia is called post-operative cognitive dysfunction (POCD). It has been previously observed that surgery and even anesthesia itself are associated with changes in cognition, but those are varies in term of severity and its duration (Bedford, 1955). Cognitive changes after administration of anesthesia are known before, but it is ethically unacceptable to perform surgery without anesthesia.

Postoperative cognitive decline traditionally can be divided into early and late types, in which the early cognitive dysfunction noted in the first few days or weeks after the surgery, and the reported incidence of it ranging from 33% (Savageau *et al.*, 1982) to 83% (Surgery *et al.*, 1987).

Largest study conducted investigating POCD in major non-cardiac surgery found that the incidence was 26% after 1 week of surgery (Moller *et al.*, 1998). The dysfunction of cognition postoperatively is a major clinical problem of uncertain pathogenesis. It is common especially in elderly during the first week of post-operation. This POCD may temporarily or permanently affect patients' ability to cope with everyday's chores, and associated with increased mortality (Grape *et al.*, 2012). This complication may implicate significant functional decline for weeks to months after discharge from hospital (Funder and Steinmetz, 2012). Furthermore this cognitive dysfunction is correlated with patient's quality of life.

(Newman *et al.*, 2001) Study by Steinmetz *et al* infers that daily function was decreased in patients who had displayed short term POCD (Steinmetz *et al.*, 2009).

The presentation of this condition is usually subtle, and may occur even after in uncomplicated minor surgery and anesthesia. It may influence isolated domain of cognition in verbal memory, visual memory, language comprehension, visuospatial abstraction, attention or concentration. In contrast to delirium postoperatively with fluctuating mental status, in this postoperative cognitive decline the consciousness is normal. More subtle changes of cognition are found such as impairment in memory, concentration, language comprehension, abstract thinking and social integration. It is characterized by subtle impairment of memory, concentration and information processing. It is not categorized as formal psychiatric disorder, and distinct from delirium and dementia (Funder and Steinmetz, 2012). As the nature of this POCD is discrete, the dysfunctions is only notice by the patients and / or relatives when resuming to daily activities. POCD can be diagnosed by neuropsychological tests that been conducted before and after anesthesia and surgery (Grape *et al.*, 2012). As this deficit are not pronounced, it has not been possible to detect the changes with low sensitivity neuropsychological tests (Rasmussen, 2006).

The mechanisms that related to POCD are still not yet fully discovered, but there are few potential risk factors contribute to it. It been agreed that POCD are multifactorial, and involves a complex relationship between many precipitating factors in the peri-operative period. Rasmussen et al concluded in their systemic review, that the risk of POCD increases with age and type of surgery as there is less incidence of postoperative cognitive decline

associated with minor surgery (Rasmussen, 2006). Moller *et al* in their observational study relates POCD with duration of anesthesia in non-cardiac surgery population. (Moller *et al.*, 1998).

2.3 Coronary Arterial Disease

Myocardial ischemia commonly occurs as a result of obstructive coronary artery disease. The principle cause of coronary arterial disease is coronary arterial atherosclerosis. There will be formation of atherosclerotic changes in the wall of coronary arteries, and this is a progressive condition in which the presentation will be later. Atherosclerotic formation in the wall of arteries characterized by presence of endothelial dysfunction, vascular inflammation and build up of lipid, cholesterol, calcium and cellular debris within the intima of the vessel wall. This changes of atherosclerosis may result in formation of atherosclerotic plaque, vascular remodeling, acute and chronic luminal obstruction, abnormal blood flow and also diminished perfusion to the heart, and further lead to myocardial ischemia (F Brian Boudi *et al.*, 2012).

Coronary atherosclerosis begins during early adulthood and slowly results in stenosis of the lumen of coronary arteries. Sudden occlusion of a major artery by an embolus may lead to the region of myocardium supplied by the occluded vessels become infarcted, known as myocardial infarction. As the coronary athersoclerosis progress, there is development of collateral vessels that permit adequate perfusion to the heart continues. Despite this compensatory mechanism, the heart may not have adequate perfusion to the myocardium in

situations that require high oxygen demand from the heart as example in strenuous exercise. This may lead to myocardial ischemia (Moore and Dalley, 1999).

Arterial supply to the epicardium and myocardium to the heart arises from coronary arteries which is the first branch of aorta. There are right and left coronary arteries which arise from corresponding aortic sinus at the proximal part of ascending aorta. The right coronary artery (RCA) arise from right aortic sinus of ascending aorta, and further giving branches into right marginal branch and posterior interventricular branch, then anastomoses with the circumflex and anterior interventricular branches of the left coronary artery at the apex. RCA supplies right atrium, most of the right ventricle and part of left ventricle and part of conducting system which are Sinoatrial node (SA Node) and atrioventricular node (AV Node). The left coronary artery (LCA) arises from the left aortic sinus of ascending aorta. The LCA then divides into two branches; anterior interventricular branch, also known as Left anterior descending artery (LAD), and a circumflex branch (LCx). The anterior interventricular branch runs to the apex of the heart, then turn around the inferior border and anastomoses with posterior interventricular branch of RCA. The circumflex branch of LCA gives branch as diagnol branch (lateral branch) and terminates on posterior aspect of the heart and often anastomoses with posterior interventricular branch of the RCA. Two of these arteries arise from a common stem called Left Main Stem (LMS). These arteries supplies typically the left atrium, most of the left ventricle, part of the right ventricle, most of the interventricular septum including the AV bundle of conducting tissue, and SA node in 40% of people (Moore and Dalley, 1999).

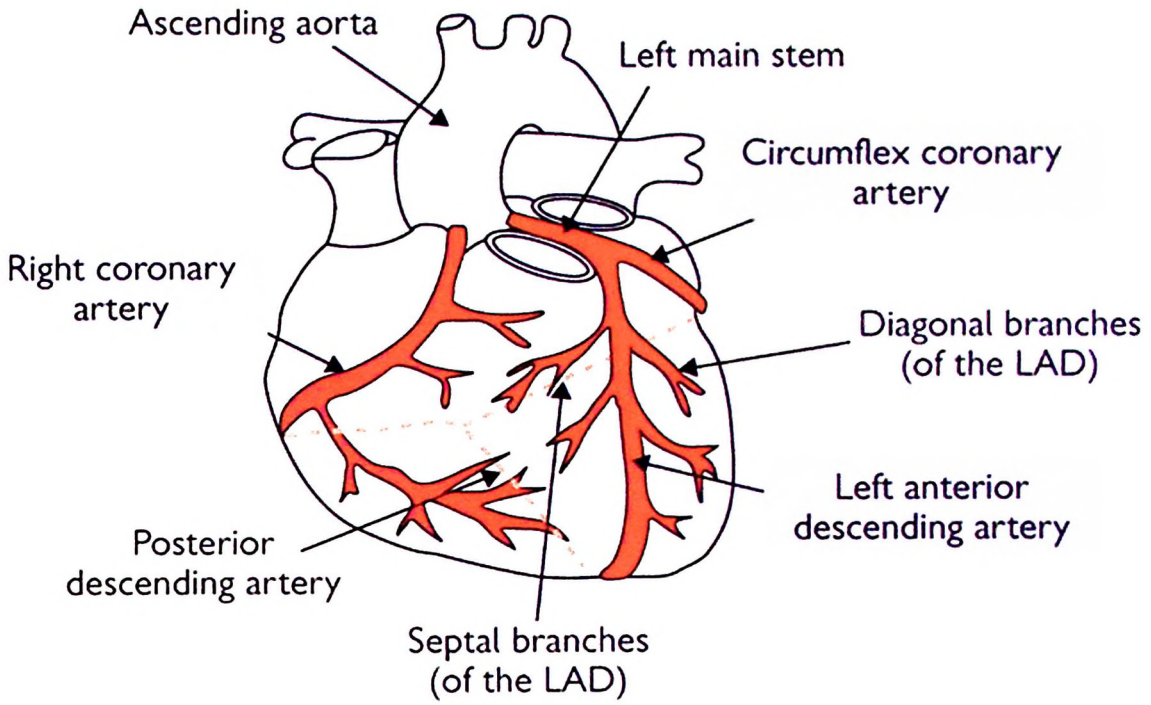

Figure 2.2: Anatomy Of Coronary Artery

Reference: (drchander.com)

Major vessels important to supply the heart muscle are the RCA, the LAD and LCx artery. Severity of the coronary artery disease increase with involvement of the LMS as it supply majority portion of the heart. Any obstruction to any of these major vessels may cause symptoms such as angina, and also may lead to myocardial infarction. Severity of coronary artery disease can also be grading base on number of major vessels involved, which are single vessel disease, double vessel disease or triple vessel disease, together with LMS obstruction involvement. (cybermedicine).

In Malaysia, cardiovascular disease remains an important cause of death that contributes to 20-25% of all death in government hospital from 2000 to 2005. It accounted for about a fifth of the total number of admission in year 2000; with the cardiovascular burden was 32% (Health, 2009). The mortality rate documented secondary to myocardial infarction was 20%, but in developed country the mortality rate reduce to less than 9% in early 2000's (Hasai *et al.*, 2002). There has been reduction in mortality secondary to coronary arterial disease that had been contributed by the presence of CABG, thrombolytic therapy, percutaneous coronary intervention and emphasis on lifestyle modification (Health, 2009).

All patients with stable coronary artery disease will be treated with non-pharmacological treatment, pharmacological treatment and interventional treatment depends on the severity of the illness and the degree of myocardial ischaemia. The objectives of the treatment are to minimize or relieve the symptoms, to slow down the progression of the disease and also to improve the prognosis by preventing myocardial infarction and death. Treatment strategies to achieve these aims includes medical therapy, Percutaneous Coronary Intervention (PCI) and Coronary Artery Bypass Surgery (CABG) (Katritsis and Meier, 2008). Interventional technique aims for revascularization of the coronary arteries in patients with significant angina especially with recent history of Myocardial Infarction (MI) within 3 months (Katritsis and Meier, 2008), patients with large area of ischemia on non-invasive testing and those whose symptoms were initially well controlled but with recurrence of symptoms with evidence of worsening ischaemia on non-invasive testing (Boden *et al.*, 2007; Patel *et al.*, 2012). Revascularization is also indicated with evidence from angiographic features that is suggestive of subtotal occlusion supplying non-infarcted myocardium, stenosis greater than

90%, significant complex lesion that are prone to develop total occlusions and with reduce fractional flow reserve (Katritsis and Meier, 2008).

2.4 Coronary Artery Bypass Grafting (CABG)

In high risk individuals with complex coronary anatomy such as left main stem and triple vessel disease, CABG has been shown to have a survival benefit. (Taggart, 2006; Patel *et al.*, 2012). CABG has been shown to lower 5 years risk of death in patients with diabetes and multi-vessels disease with impaired left ventricular systolic function (Serruys *et al.*, 2001; Hoffman *et al.*, 2003; Serruys *et al.*, 2009)

There are two principal indications for coronary CABG which are for symptoms control and to improve survival. Surgery will provide dramatic relief from angina in 90% of cases in those patients who remain symptomatic despite on optimal medical therapy and whose disease is not suitable for PTCA (Camm, 2002). There are evidences showed that CABG had improved in survival in patients with severe three vessel disease, with significant proximal stenosis in all three main coronary arteries, particularly those with impaired left ventricular function and in those with left main stem disease. These patients obtain prognostic benefit from CABG, irrespective of symptoms (Camm, 2002).

CABG is indicated in patients with coronary arterial disease who had failure of medical treatment to adequately control the symptoms. Study conducted for patients with evidence of ischaemic disease, carried out in North America and Europe, found that there was survival advantage in those groups who were treated surgically (Malaysia Academy of Medicine, 2007). The benefits were marked particularly in patients with Left main stem coronary artery stenosis (>50%), followed by those patients with proximal stenosis of three major coronary arteries (Triple vessels disease), then followed by those with two major coronary arteries stenosis (Malaysia Academy of Medicine, 2007). Surgical intervention also been suggested to improve in survival in those patient with left ventricular dysfunction. Therefore, in order to make decision-making for prognostic implication of ischemic heart disease (IHD), coronary angiography is essential (Malaysia Academy of Medicine, 2007).

Conduct of CABG surgery started with induction of anaesthesia. This is proceed with skin preparation and draping. Median sternotomy is performed by cardiothoracic surgeon, with the lung deflated simultaneously. Conduits for coronary bypass are harvested from the leg, arm or chest. After full heparinization, aorta and right atrium (RA) cannulated, then later to be connected to heart-lung machine. Patient was put on bypass with unclamping of the venous cannula. The blood from RA will flow into oxygenator of cardiopulmonary bypass (CPB) machine and the blood will be oxygenated. The oxygenated blood will pump into aorta. The surgery conducted to the heart starts with cross-clamping of the aorta, and this considered as starting of ischemic time for the heart, and appropriate myocardial protection will be administered. After the main cardiac surgery completed and adequate de-airing achieved, the heart is ready to coming-off bypass. Few criteria is required before coming–off bypass. The aortic cross clamp will be removed, that will allow perfusion to the coronary arteries, and the

heart will come to life. With satisfactory condition to coming off bypass, the heart lung machine will then stopped, and the caval cannula will be removed. Finally, heparin will be reversed with the antidote, protamine. After all haemostasis have been secured, then the chest is closed with appropriates drains and epicardial pacing wires. Patients then will be transferred to critical care area for further monitoring and management. (Nashef, 2004).

Recent advances in order to reduce the side effect of CPB, off-pump surgery can be conducted. In this condition, there is absent of aortic cannulation, extracorporeal circulation or cross clamping of the aorta. However, this technique is not feasible for all cases of cardiac surgery.

2.4.1 Cardiopulmonary Bypass (CPB)

The development on cardiopulmonary bypass pump initiated due to realization that during the cardiac surgery, support of artificial heart and artificial lung is required during the procedure. While cooling during the period of cardiac surgery will allow longer period of cardiac standstill. The early heart-lung machine was complicated, but newer modes of cardiopulmonary bypass machine is safer and more user-friendly. (Nashef, 2004). CPB is a form of extracorporeal circulation in which the patients' blood is rerouted outside the vascular system, and the function of the heart and lungs are temporarily taken over by the CPB assumed by surrogate technology. The goal of this CPB is to provide motionless and

bloodless field for the surgeon to operate on the heart. In CPB the entire cardiac output will be rerouted from the patients' heart and lungs. Other techniques that provide extracorporeal circulation include left heart bypass (LHB), cardiopulmonary support (CPS), and extracorporeal membrane oxygenation (ECMO) (Nussmeler *et al.*, 2010).

During CPB, the heart is empty but the coronary arteries are still perfuse from the aorta by the heart lung machine. Bloodless field of the surgery is achieved by clamping of the aorta at the site of aortic cannula insertion and origin of coronary arteries, but there is risk of global ischemic of the heart. Therefore steps taken to protect the heart from global ischemia during clamping known as cardioprotection (Nashef, 2004).

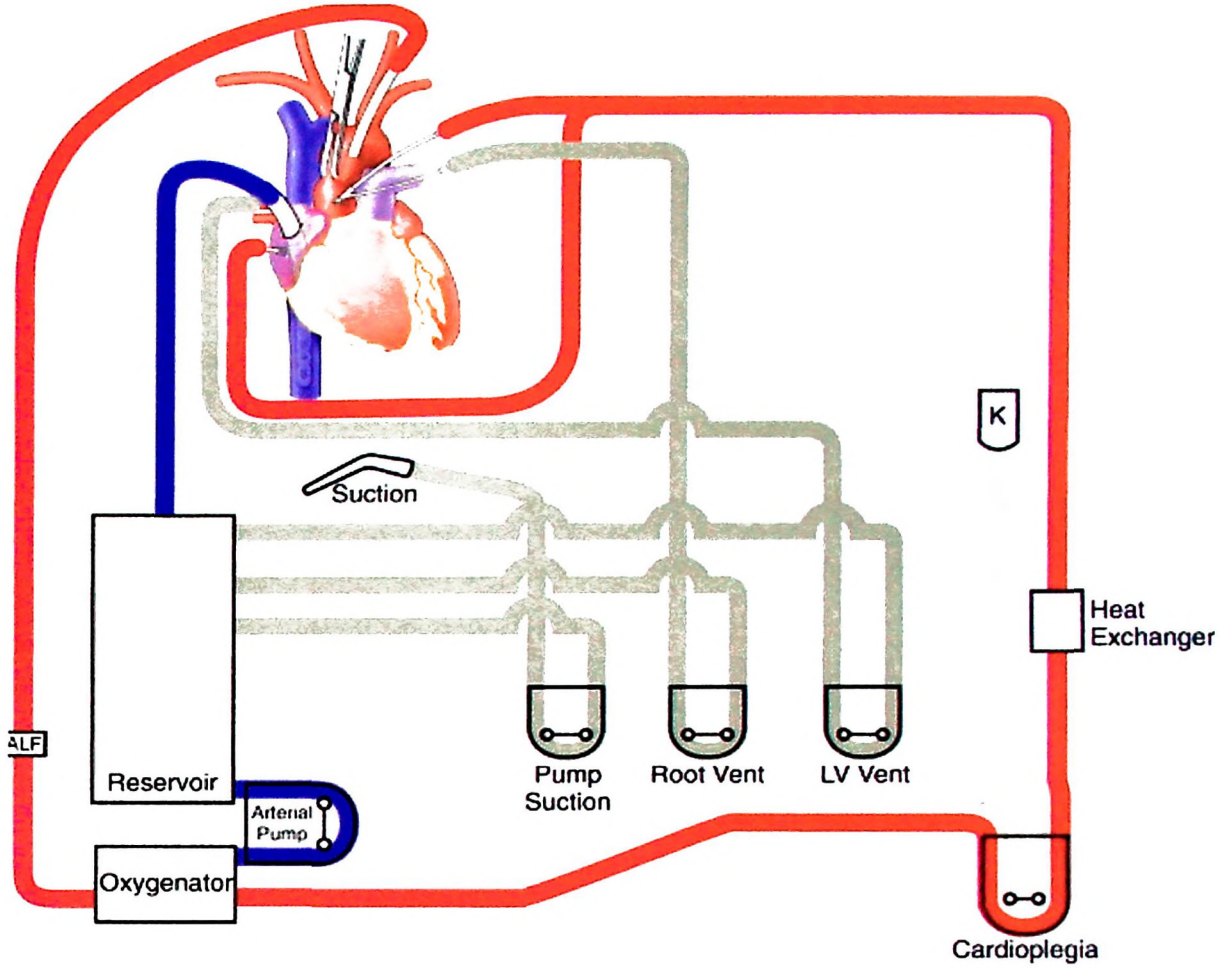

Figure 2.3: Schematic Diagram Of Cardiopulmonary Bypass (CPB) Machine

Reference: (Nussmeler *et al.*, 2010)

The venous blood is intercepted when it returns to RA, diverted through the venous line of the CPB to a venous reservoir. The arterial pump withdraw blood from the reservoir and act as artificial heart as it propel the blood through a heat exchanger, an artificial lung (the oxygenator) and an arterial line filter before returns to the patients arterial system. In order to

assist the operation, additional pump and components situated in the CPB includes the pump suckers which act to manage the shed blood, vent to decompress the heart, and components to deliver cardioplegia solution (Nussmeler *et al.*, 2010).

The blood tubing used to connect the various components in CPB system is medical grade polyvinyl chloride (PVC). Previously, the tubing used was untreated PVC. However, the new generation of the tubing has its surface coatings and other modifications that significantly alter the bioactivity of the surface. It has been shown with the introduction of this new medical grade PVC for CPB system tubing, it reduce markers of subclinical coagulation and also attenuate the elevation of cytokines and other inflammatory markers (Schreurs *et al.*, 1998; somer *et al.*, 2000; Nutter *et al.*, 2004; Ask *et al.*, 2006).

Venous reservoir is situated between the venous line and the arterial pump. It facilitate the displacement of a large volume of blood out of the circulation at strategic times during the operation, therefore , it play an important function in the conduct of CPB (Nussmeler *et al.*, 2010).

As a replacement of the function of the heart, a pumping device is used in CPB. Generally, there are two types of technologies applied in this pumping device, a roller pump or a centrifugal pump. Both pump technologies are traumatic to the blood elements, however the centrifugal pumps are thought to be less traumatic than roller pumps (Nishinaka *et al.*, 1996; Linneweber *et al.*, 2002).

Heat exchangers are important to CPB as it facilitate management of patient's blood temperature. During the period of CPB, about 20-35% of patient's blood volume circulates outside the body and exposed to the ambient temperature of the operating theatre, which can cause hypothermia. Therefore, the blood should be rewarmed before termination of the CPB. Apart from that, some amount of hypothermia in many surgical procedures is desirable to reduce the patients' metabolic rate (Nussmeler *et al.*, 2010). The degree of hypothermia can be mild, with patients' temperature around 35 °C. The temperature reduction in the conduct of CPB can be profound until around 18 °C. The heat exchangers may be used to reduce the temperature during the initiation of CPB and to warm the blood before the termination of it. (Nussmeler *et al.*, 2010).

The oxygenator substitutes patient's native lung, in which it provide essential function for gas exchange. It has separate gas inlet and outlet ports and can refresh the gas inside its gas space with a continuous flow of gas through the oxygenator. Venous blood entering the oxygenator directed across the fibers of the oxygenator, while gas is concurrently circulated through the inside of the fibers. Oxygen driven across the membrane due to pressure gradient across it, and into the blood, whereas carbon dioxide is driven out of the blood. There is a risk of formation of gaseous emboli in the blood whenever the pressure in the gas space not exceeding the pressure in the blood space, therefore extreme caution should be taken to prevent it. In addition, most oxygenators are design with multiple gas outlet ports in order to eliminate this risk. (Nussmeler *et al.*, 2010).

Arterial line filters located at the arterial line, which blood pasess through it before returns to the patient. The small pore sizes of the arterial line filters increase patient safety by removing particulate and gaseous microemboli (Nussmeler *et al.*, 2010).

2.4.1(a) Conduct Of Cardiopulmonary Bypass

Before the patient is anesthetized, the CPB system is assembled, primed and tested, and the supplied CPB set are 'closed' in which the arterial line and the venous line are in continuity to preserve the sterility and to allow circulation of priming before connection to the patient. During this priming period, the prime solution will be filtered to remove bubbles and particulate matters, and it is warmed to 37 °C. Typically, an adult CPB system requires 1400-200mL of priming solution, consisting crystalloid, colloid and/or blood. Heparin, calcium and mannitol will be added to the priming solution, and some circumstances require further addition to the priming solution depends on the patient condition and also institution. Conduct of CPB system is carried out by perfusionist, who then will calculate the pump flow based on body surface area of the patients and also calculate the potential requirement for packed red cells based on the predicted initial haematocrit on CPB. Clear communication between perfusionist, anaesthetist and surgeon is essential in order for the safe conduct of CPB (Gray and Gifford, 2004).

One of requirement in CPB is adequate systemic anticoagulation, usually with unfractionated heparin. There are varies within practices of precise timing of anticogulation, but usually

heparin is administered preceding, or simultaneously with cannulation of the patient. Adequacy of anticoagulation should be achieved before initiating CPB with ACT monitoring. In our centre, there is routine practice for usage of lysine analogue, which is tranexemix acid in order to reduce perioperative blood loss and transfusion requirement. (Gray and Gifford, 2004)

Ascending aorta or occasionally the femoral artery will be cannulated first, and during this procedure, anaesthetist will avoid excessive hypertension to reduce risk of localized arterial dissection. The connection of CPB system between arterial and venous lines is then cut for it to be attached to the arterial cannula. This step is taken to prevent air trapping. Following arterial cannulation is venous cannulation. This is because RA cannulation may be accompanied by haemodynamic instability secondary to atrial dysrythmia, impeded venous return or haemorrhage. Therefore, arterial cannulation allow fluid administration with the occurrence of hemodynamic instability (Gray and Gifford, 2004).

The CPB initiated with gradually releasing the venous line clamp, which then diverting the venous blood into the venous reservoir. The speed of the pump will be later increased. After establishment of the full flow of the CPB pump, the anaesthetist will off the ventilation of the lungs. During CPB, frequent ABG sampling is monitored for adequacy of CPB, and maintenance of anaesthesia continues with inhalational agent through the CPB machine (Gray and Gifford, 2004).

Cardioplegia will be given intraoperatively to provide myocardial protection throughout the procedure. There are crystalloid type cardioplegia and blood cardioplegia that can be administered to the heart. In our institution, crystalloid cardioplegia is the standard type of cardioplegia that will be given during cardiac surgery. It is important to assure that the cardioplegia solution is free of air or particulate matter (Gray and Gifford, 2004). To provide motionless field for the surgeon, the heart is arrested in diastole by administration of a potassium-enriched cardioplegia solution to the heart. Heart metabolism reduced by interrupting the myocardial electromechanical activity. Potassium will induced arrest in which it cause marked reduction of cardiac metabolism by 90%. Hypothermia further augments this reduction of metabolism. The combined influence of potassium arrest and myocardial temperature lower than 22°C will reduce myocardial oxygen consumption by 97%, therefore, allow myocardium to withstand interruption of blood flow for periods of up to 20 to 40 minutes while the surgeon operating on the heart. Reperfusing the heart with warm normokalemic blood will reverse the heart function. Cardioplegia solution administered intermittently at volume dosing regimen and the intraoperative evaluation of the adequacy of myocardial protection is empirical and is based on the quiescence of the ECG, the time since the last dose was administered, and the temperature of the heart (Nussmeler *et al.*, 2010).

One of reliable method of neuroprotection is deliberate hypothermia and is often use during routine CPB. Even mild hypothermia as little as 1-2 °C minimizes the severity of cerebral ischemia in animal models (Wass *et al.*, 1995). In contrast, hyperthermia is known deleterious effects on cerebral. Elevation of body temperature as little as 2 °C will lead to intolerant of cerebral towards ischemia (Nussmeler *et al.*, 2010).

This test consists of two parts, which initially the subject is introduced to the press pad, and told to press the left hand button when a left-pointing arrow appears on the screen. When the right-pointing arrow appears, the patients need to press the right hand button on the press pad. There is one block of 16 trials for the patient to practice on it. In the second part, the subject is told to continue pressing the buttons on the press pad when the arrows appear, but, if they hear an auditory signal, which is a beep sound, they should withhold the response and not to press the button.

The table below summarized the tests used for this study and its domain.

Table 2.1: Cognitive Test Summary

	Estimated conduct duration	Domain	Area of brain involved
BLC	3 minutes	Induction Comprehension Learning and reversal	-
IED	9 minutes	Executive function Working memory planning Rule of acquisition and reversal Visual discrimination Attentional set formation Maintenance, shifting and flexibility of attention	Frontal lobe
PAL	10 minutes	Visual memory New learning Simple visual pattern and visuospatial associate learning Delayed response procedure Conditional learning task	Medial temporal lobe
SST	Depends on subject performance	Reaction time Decision making and response control	Frontal lobe: - Medial frontal - Inferior gyrus - Orbitofrontal - Anterior cingulated - Dorsolateral Temporal lobe Parietal lobe Cerebellum Basal ganglia

Reference: (Elliot *et al.*, 1995; Jakala *et al.*, 1999; McGinty *et al.*, 2012)

CHAPTER THREE

METHODOLOGY

3.1 Objective Of Study

The objectives of this study were divided into general and specific objectives.

3.1.1 General Objective

The general objective of this study was to determine the outcomes on short-term cognitive function in post CABG patients.

3.1.2 Specific Objectives

a. to evaluate degree of short term cognitive changes post-CABG

b. to identify domain of cognitive function involved post CABG

c. to determine factors governing cognitive decline post CABG

3.2 Study Design

This study was a prospective cohort study. A sample size of 43 patients was planned. Calculation of sample size is based on one-mean sample size calculation showed that at least 39 subjects were needed to provide an 80% power of study. This was based on previous study by Ahlgren E *et al* in their Neurocognitive Impairment And Driving Performance After Coronary Bypass Surgery, that published in European Journal of Cardiothoracic Surgery in 2003, with the parameter use for the sample size calculation were based on reaction time domain.

Calculation with one-mean for sample size calculation:

$\sigma = 7.8$ $\Delta = 5$ $Z_\alpha = 1.96$ (for $\alpha = 0.05$) $Z_\beta = 0.84$ (for power 80%)

$$\text{Sample size (n)} = \frac{2\,(7.8)^2}{5^2}\,[\,0.84 + 1.96^2\,]$$

$= 38$ (+10% drop-out)

$= 43$

3.3 Inclusion Criteria

Participants involved and selected for this study should fulfil few criteria before included into this study. The criteria were patients for elective CABG and age between 18 to 75 years old.

3.4 Exclusion Criteria

There were few exclusion criteria for this study in which patients with this characteristic will be excluded from this study. The exclusion criteria were patients for emergency CABG, patients with previous history of CABG, patients with symptoms of visual impairment, patients with previous stroke with residual deficit, patients with significant psychiatric disorder and patients who's in unstable general condition

The study had been approved by the Ethical Committee, Hospital Universiti Sains Malaysia, Kubang Kerian, Kelantan. (Approval reference number: USMKK/PPP/JEPeM [238.3.(03)]). This study was carried out over the period of 17 months from March 2011 to July 2012.

3.5 Details Of Methodology

Patients who fulfilled the criteria were invited to participate in the study during the premedication round one to two days prior to surgery. Written consents were taken from the patients after proper explanation including on the CANTAB® use. Demographic data were collected during the initial assessment before the operation together with patient medical status and preoperative routine blood investigation results. During the preoperative visit, patients' baseline cognitive functions were assessed via CANTAB® program, with all four test administered (BLC, IED, PAL and SST). The baseline cognitive assessment conducted at bedside or at the ward counter. During the assessment, the surrounding condition was assured that it is conducive for the test and devoid of external stimuli that might impair the patients result. Subjects were seated at a comfortable height and at the eye level with the monitor. Patients were instructed to carry out the tasks by touching the screen. After an initial explanation and successfully completing the screening test, which was BLC; subjects were instructed to continue with another three tests which were IED, PAL and SST. Throughout the test period, patients were allowed to take a break and free to terminate the test if patient unable to continue with the test at any point.

On the day of operation, patient undergone standardised technique of anaesthesia, surgery and CPB. Intraoperatively, data collected includes duration of anaesthesia, surgery, CPB and rewarming. Degree of temperature reduction during rewarming period is also recorded.

After completion of the surgery, patients were transferred to the critical care unit; standard monitoring and care instituted to the patients during the stay in CICU. Overall management were taken care by the primary team. Decision of extubation post-operatively was made by the managing physician. Day of extubation was recorded, and any significant post-operative complication identified and recorded.

Second cognitive assessments were administered to patients after about 6 to 7 days post-operation, in which patients usually was ready to be discharged home. Patients' hemodynamic stability and condition were taken into account before conducting the second cognitive testing to avoid patients' fatigue. During this period, similar sets of cognitive assessment were conducted.

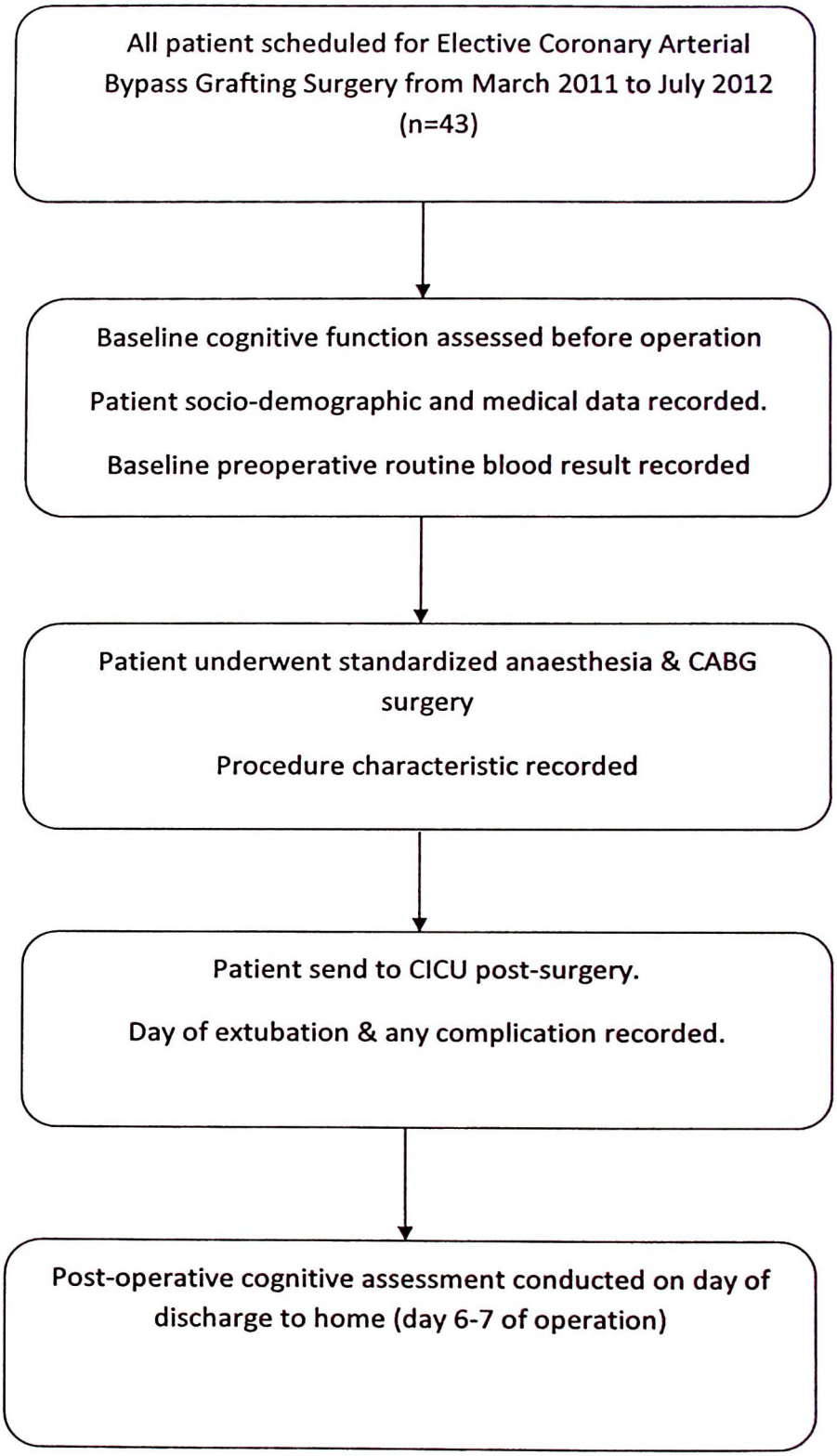

Figure 3.1: Flow Chart Of The Study

3.6 Statistical Analysis

All of the data involved in this study were parametric data. The collected data were entered and analyzed using Statistical Program for Social Sciences (SPSS) version 20.0. Data checking and cleaning were performed before analysis.

Objective 1 was to determine the outcomes on short-term cognitive function in post CABG patients. Descriptive analysis was done to look into this objective.

Objective 2 was to identify domain of cognitive function involved post CABG. The result obtained was based on the descriptive analysis done.

Objective 3 was to determine factors governing cognitive decline post CABG. The dependent variables were cognitive decline in IED test, PAL test and SST test. The independent variables were age, education level, type of procedure either CABG with valve repair or CABG alone, anaesthesia duration, surgery duration, CPB duration, rewarming period duration, and rate of temperature increment during rewarming phase.

The analyses for these objectives comprised of descriptive analyses and analysis with multiple linear regression.

The distribution and frequencies were examined via descriptive analyses. All continuous variables were expressed as mean and standard deviations. Frequency and percentage for categorical variables were calculated. Meaningful combination of categories was done when indicated.

Multiple Linear Regression was used to determine the associated factors for cognitive changes while controlling other confounders in the model.

Simple Linear Regression was used as a screening in selection of variables for further analysis. All variables with P value less than 0.05 for variables selection and clinically significant variables were included in Multiple Linear Regression. The variables were age, education level, type of procedure, duration of anaesthesia, duration of surgery, duration of CPB, duration of rewarming and rate of rewarming. This process of deleting, refitting and verifying continued until it appeared that all important variables were included in the model. At this step, the preliminary main effect model was obtained.

CHAPTER FOUR

RESULTS

A total of 43 patients were included in this study and had performed the pre-operative cognitive testing via CANTABeclipse® and successfully underwent CABG. However, postoperatively, only 40 patients able to proceed with post-operative assessment of cognitive function with 3 of the patients not capable to proceed with it due to complications post surgery. 2 of the patients had postoperative cerebrovascular accident with one subject had hemiparesis, and another subject had reduce in conscious level (impaired GCS). One patient had developed arrhythmia and later had severe stroke eventually requiring tracheostomy postoperatively. This patient succumbed to death at home secondary to chronic bed bound complications.

4.1 Socio-Demographic Characteristic:

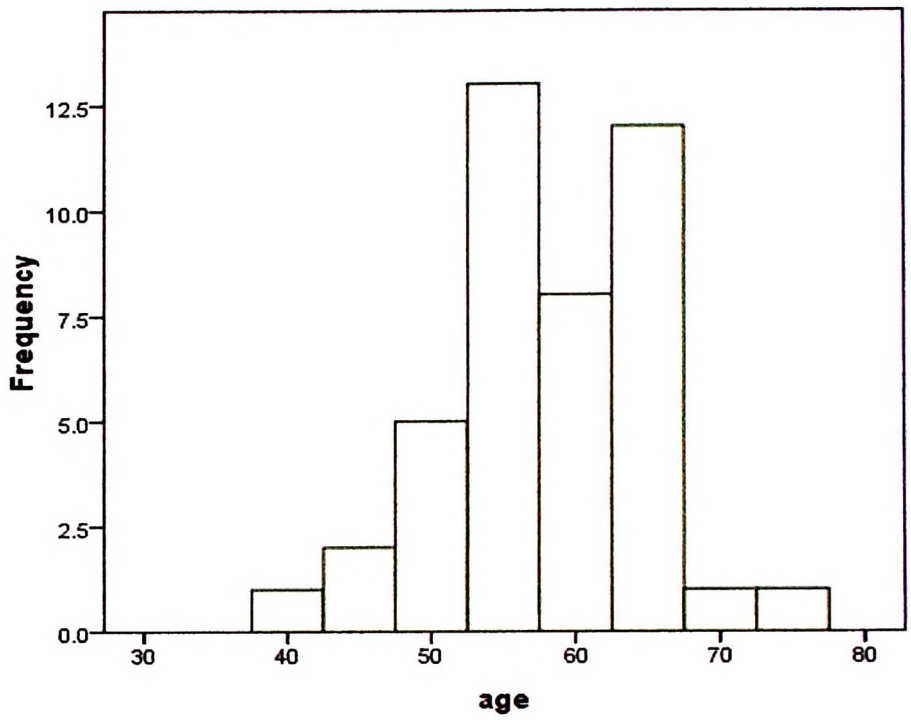

Figure 4.1: Distribution Of Patient According To Age

Mean age of subjects in this study was 58 years old with the minimum age and maximum age of the patients involved in this study were 40 and 75 years old respectively.

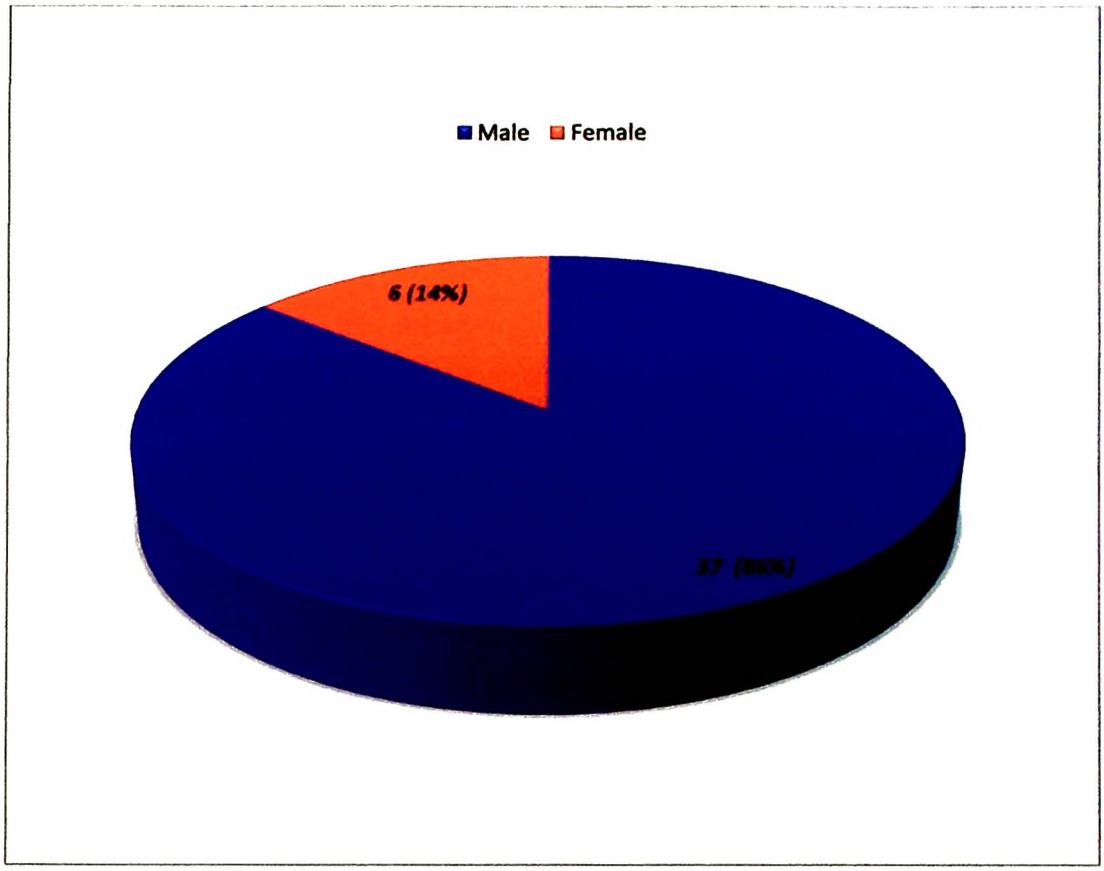

Figure 4.2: Frequency Of Patient According To Gender

Majority of patients involved in this study came from male gender with 86% of them (n= 37), while six female patients were included in this study (14%).

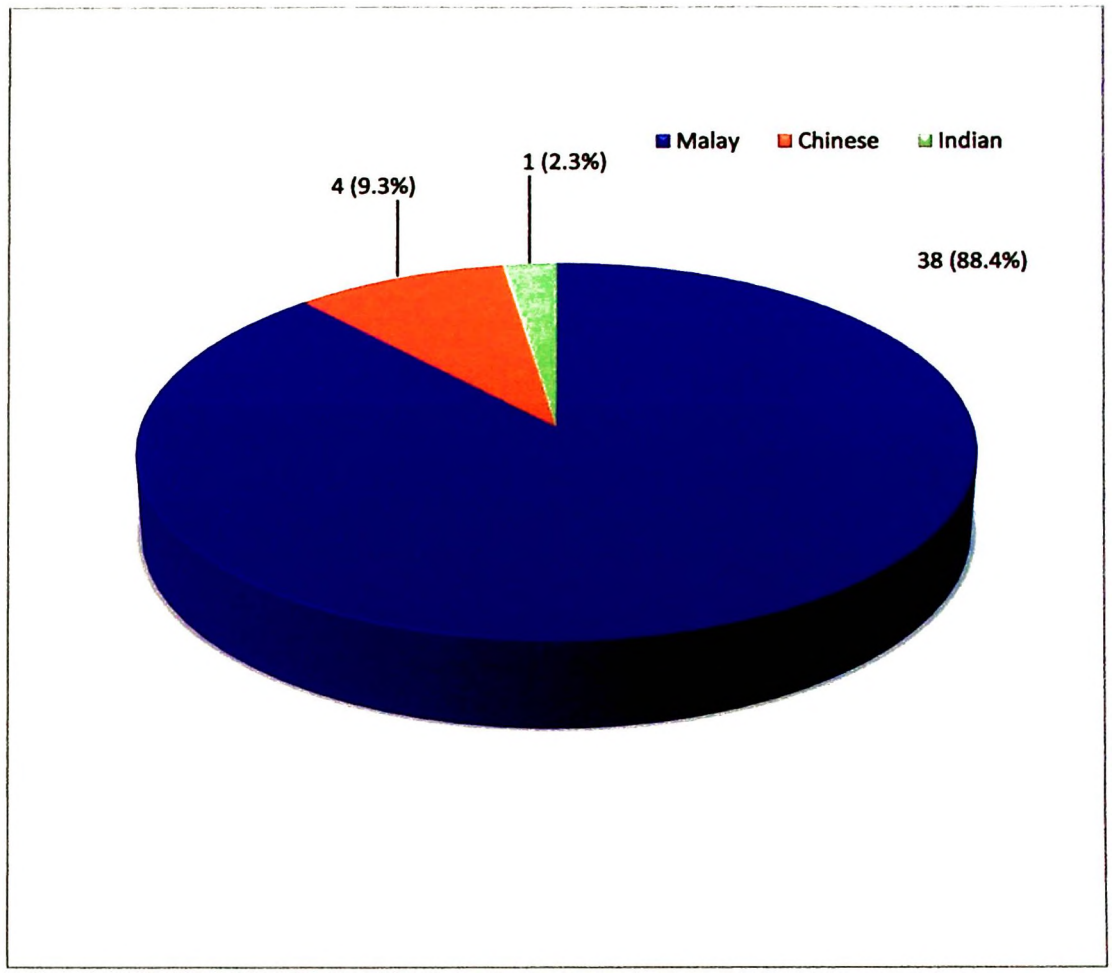

Figure 4.3: Frequency Of Patient According To Race

Races of patients involved in this study were Malay, Chinese and Indian. Majority of the patients were Malays with percentage of 88.4% (n=38). It followed by Chinese with 9.3% (n=4) and only single patient was an Indian (2.3%).

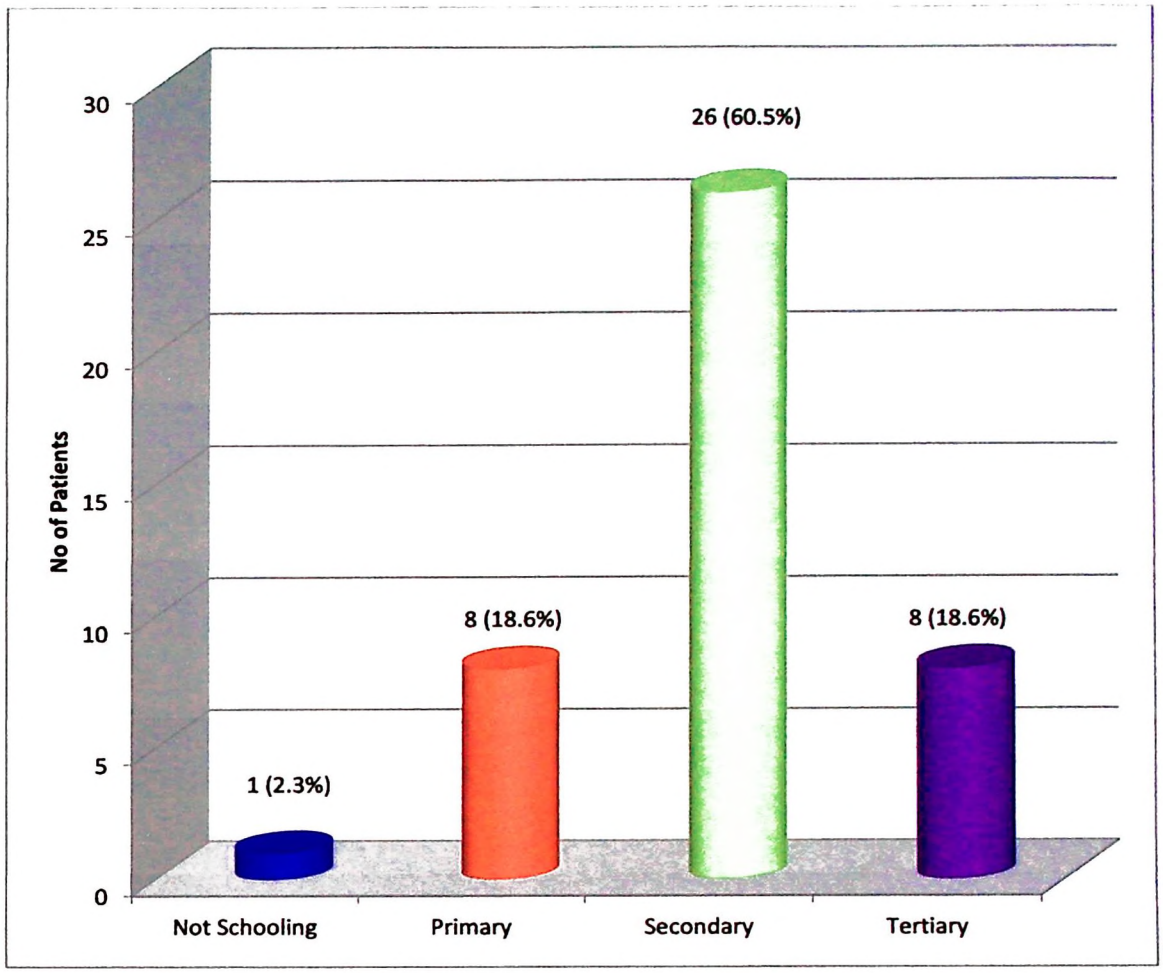

Figure 4.4: Frequency Of Patient According To Education Level

Education level for the majority of patients involved in this study were secondary school with 26 of subjects attained secondary level of education (60.5%). Followed by primary schooling and degree holder with equivalence percentage of 18.6% (n=8) in both categories. One subject did not get any education with single subject and the percentage was 2.3%.

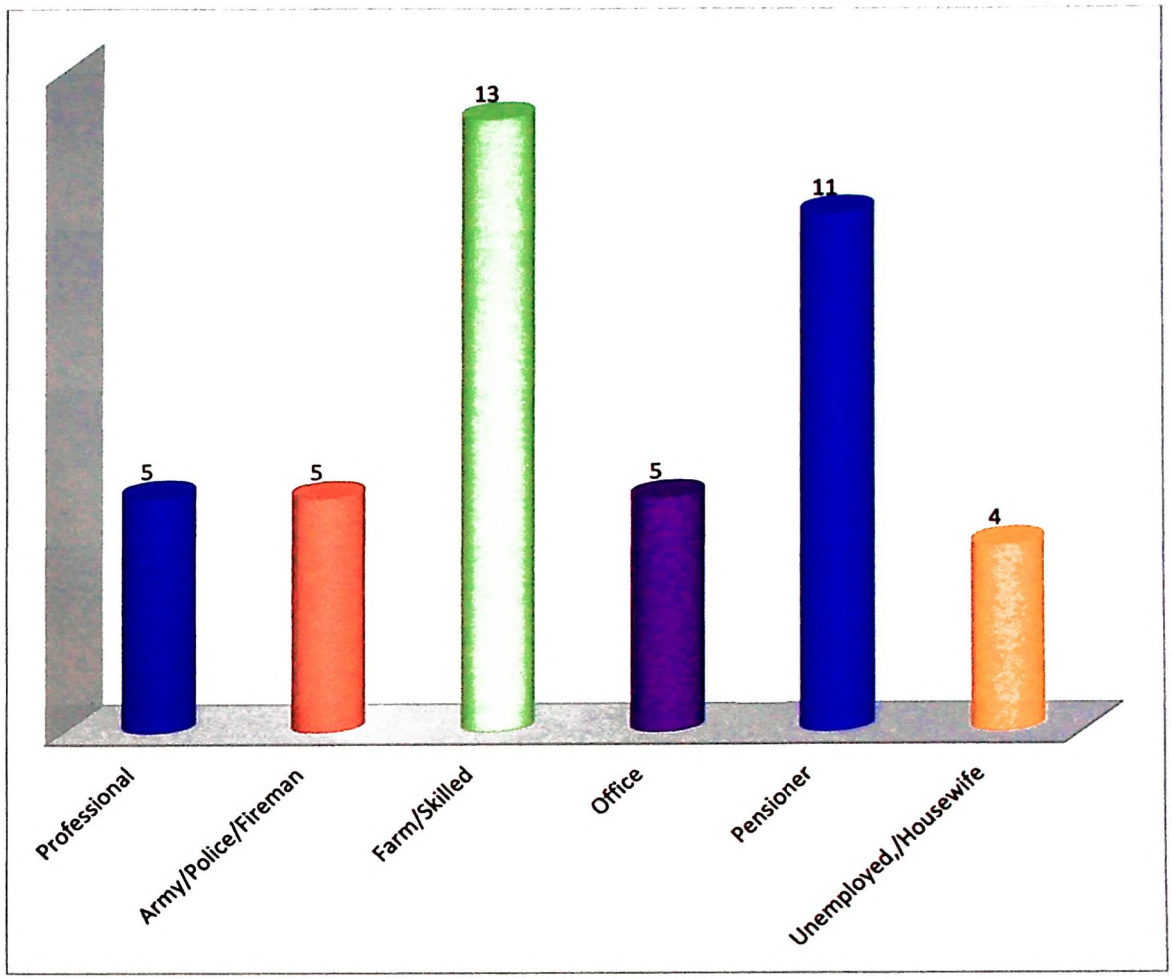

Figure 4.5: Frequency Of Patient According To Occupation

With a total of 43 participants in this study, 13 subjects (30.2%) work in a farm field or requiring skills, and there were 25.6% (11 subjects) were pensioner. Five subjects (11.6%) worked as professional, office worker or as army, police officer or fireman. 9.3% of participants were unemployed or working as a housewife (n=4).

4.2 Medical Characteristic:

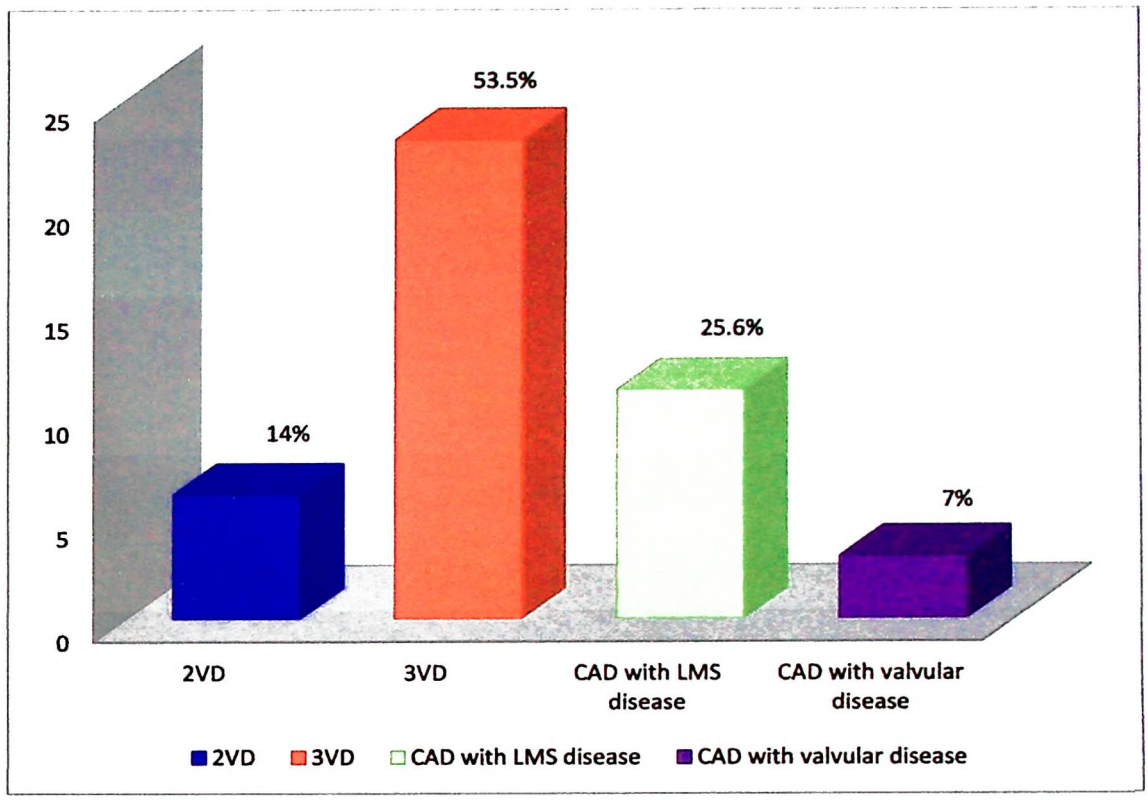

Figure 4.6: Frequency Of Patient According To Diagnosis For CABG

Majority of the patients were subjected for CABG in this study was diagnosed to have three-vessel disease (3VD) with 53.5% of them (n=23). 11 of subjects were diagnosed to have coronary artery disease (CAD) with left main stem disease (LMS) with the percentage of 25.6%. Followed by 6 patients (14%) diagnosed with two-vessel disease (2VD) and 3

patients (7%) diagnosed with CAD with valvular disease, which were severe aortic stenosis, severe mitral regurgitation and severe tricuspid valve regurgitation.

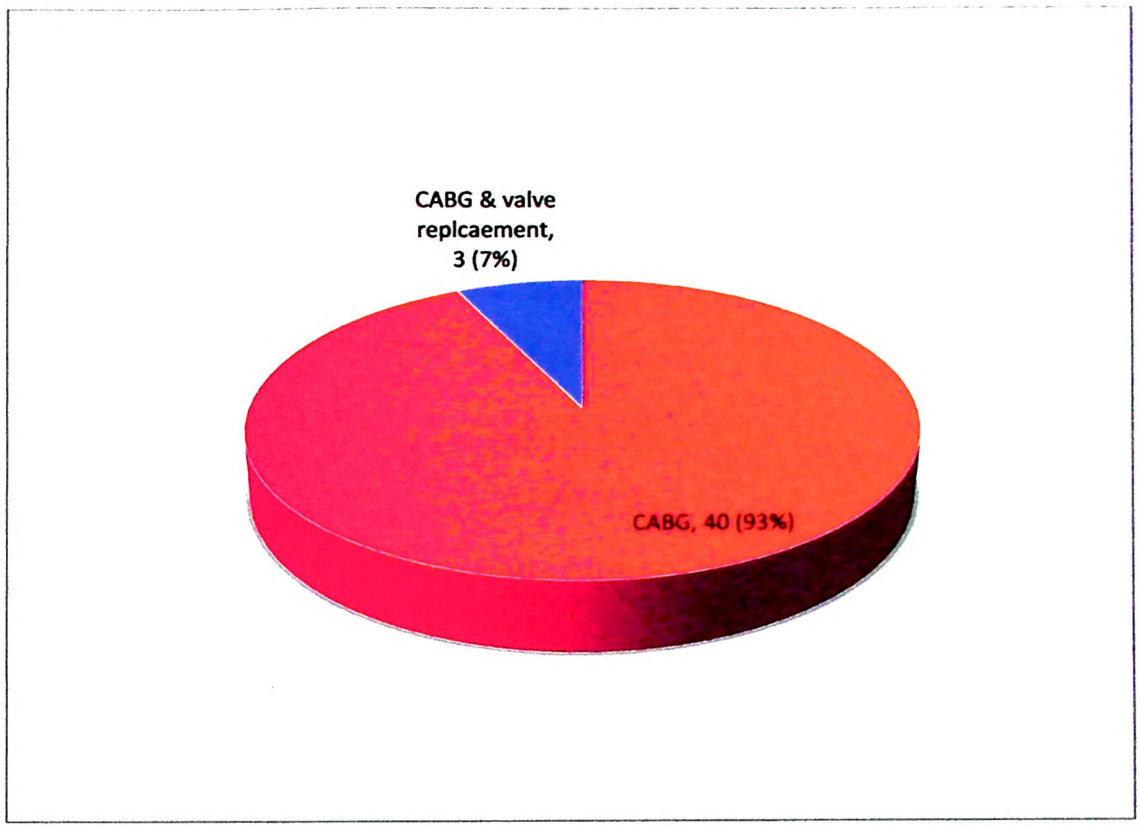

Figure 4.7: Frequency Of Patient According To Type Of Procedure

Most of the patients involved in this study had underwent CABG alone with total number of 40 patients (93%) while the other 7% had underwent CABG together with valve repair or replacement (n=3). Valvular surgery done in 3 of the subjects concurrently with CABG. The procedure were aortic valve replacement, mitral valve replacement and tricuspid valve annuloplasty.

Table 4.1: Concurrent Medical Illness Characteristic

Medical disease	Yes	No
	n (%)	n (%)
Ischemic heart disease	42 (97.7%)	1 (2.3%)
Diabetes mellitus	19 (44.2%)	24 (55.8%)
Hypertension	34 (79.1%)	9 (20.9%)
Hyperlipdemia	34 (79.1%)	12 (27.9%)
Renal dysfunction	7 (16.3%)	36 (83.7%)
Bronchial asthma/ COAD	2 (4.7%)	41 (95.3%)
Other illness	10 (23.3%)	33 (76.7%)

COAD – Chronic Obstructive Airway Disease

97.7% of patients were previously been diagnosed to have ischemic heart disease (IHD) and later been subjected for CABG for the correction of the coronary artery obstruction. There was one patient (2.3%) that previously not known to have ischemic heart disease before, but was noted to have accidental finding in ECG during preoperative assessment for elective traumatic fracture. This patient was further investigated with coronary angiogram and found to have coronary artery disease and later subjected for CABG.

About 79.1 percent of the subjects (34 patients) involved in this study had concomitant hypertension and also hyperlipidemia. While participants with diabetes mellitus were 44.2%

(n=19) of them that previously been diagnosed with this illness. 16.3% (n=7) of the patients had concomitant renal problem ranging from the varieties of renal impairment not requiring any renal replacement therapy to ESRF which on regular dialysis. 2 of the patients (4.7%) had underlying respiratory diseases which were COAD and bronchial asthma. 23.3% (n=10) of the patients were diagnosed to have other illness which were traditionally not known to be risk factors for CAD that include hepatitis B, hepatitis C, old pulmonary tuberculosis, mitral valve prolapsed with atrial fibrillation, hyperthyroidism, hypothyroidism, gouty arthritis and pseudothrombocytopenia.

4.3 Biochemistry Characteristic:

The mean value for preoperative hemoglobin (Hb) level for all participants involved in this study was 13.63 ± 1.55, with minimum value was 9.2 and maximum of 16 mmol/l, while the mean for hematocrit value (Hct) was 39.13 ± 6.96 with minimum and maximum level were 37 and 46.7 respectively. The minimum value in this study for Hb and Hct belongs to the subject with underlying ESRF who was on every alternate day hemodialysis. Mean value for Sodium (Na) and Potassium (K) level preoperatively prior to CABG were in normal range with 137.23 mEq/L for sodium and 4.133 mEq/L for potassium.

Table 4.2: Preoperative Routine Blood Investigation Result

Blood test	(Mean ±SD)	Minimum	Maximum
Hemoglobin (mmol/L)	13.63 ±1.55	9.2	16
Hematocrit (%)	39.13 ±6.96	3.7	46.7
Sodium (mEq/L)	137.23 ±2.78	132	143
Potassium (mEq/L)	4.13 ±0.51	3.2	5.7

4.4 Procedure Characteristic:

Mean duration for anesthesia conducted for all participants involved in this study was 330.33 ± 42.88 minutes. Minimum duration for anesthesia was 263 minutes with the maximum duration was 455 minutes.

Table 4.3: Intraoperative Procedure Characteristic

Variables	(Mean ±SD)	Minimum	Maximum
Anesthesia duration (min)	330.33 ±42.88	263	455
Surgery duration (min)	279.16 ±44.59	206	425
CPB duration (min)	123.52 ±30.08	73	192
Rewarming duration (min)	44.88 ±13.09	23	77
Temperature difference during Rewarming (°C)	4.16 ±1.14	1.50	6.00

Day of extubation	1.65 ±2.31	1	15

The mean duration for fonduct of surgery in this study was 279.19 ± 44.58 minutes with minimum and minimum duration was 206 and 425 minutes respectively.

Duration of CPB in this study were ranging from minimum duration of 73 minutes and maximum duration of 192 minutes, with mean duration of 123.51 ± 30.08 minutes.

Mean rewarming duration in this study was 44.88 ± 13.09 minutes with shortest duration was 23 minutes and longest duration was 77 minutes.

Mean degree of temperature increment during rewarming phase value 4.16 ± 1.14 °C with least changes of temperature with 1.5 °C increment and maximum increment of 6 °C difference.

Table 4.4 showed rewarming rate with time taken to increase every 1°C of temperature. The most rapid increment of temperature during rewarming period was 4.3 minutes, and the slowest time taken to increase the patient body temperature was 36.7 minutes in order to increase one degree of body temperature.

Table 4.4: Time Taken (minute) For Increment Of Every 1°C Body Temperature During Rewarming

Subject	Time taken to increase every 1°C	Subject	Time taken to increase every 1°C
1	10.6	23	30.0
2	10.5	24	11.6
3	14.0	25	8.4
4	8.7	26	6.6
5	21.4	27	11.7
6	13.8	28	4.3
7	8.3	29	10.3
8	20.0	30	36.7
9	6.9	31	10.3
10	17.4	32	7.6
11	7.2	33	14.0
12	11.5	34	10.4
13	8.4	35	9.0
14	17.3	36	14.5
15	7.2	37	5.8
16	18.9	38	6.0
17	15.4	39	8.8
18	29.3	40	11.6
19	15.3	41	5.7

20	7.8	42	11.0
21	8.6	43	6.8
22	7.7		

Most patients were wean off from ventilator and extubated in the early period of post-surgery in CICU with the mean day of stay was 1.65 ± 2.31. The earliest day of extubation was on day 1 of post-operation; and maximum day of extubation was on day 15 post-operation in which this patient noted to have poor conscious level secondary to acute stroke. Subsequently tracheostomy performed for this patient as an alternative airway for this patient due to prolonged mechanical ventilation.

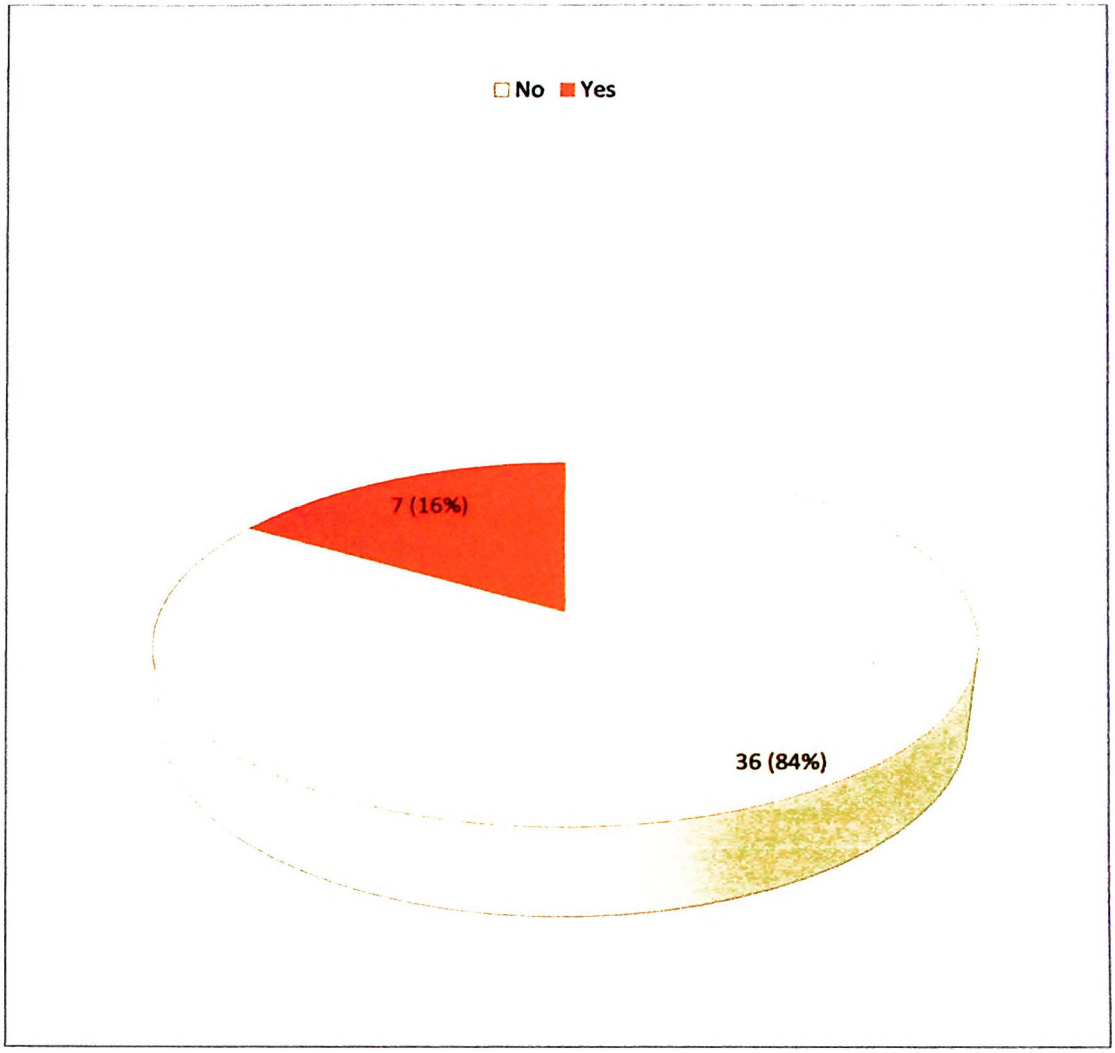

Figure 4.8: Frequency Of Postoperative Complication

Post-operatively, patients were send to CICU for further postoperative monitoring and management. In CICU, there were few major complications noted postoperatively with percentage of 16% (n=7) of participants had significant complications. There were complications related to surgery such as postoperative bleeding which required transfusion of

DIVC regime to the extent of reopen surgery due to cardiac temponade. There were also cardiac complications with unstable hemodynamic status and arrhythmia postoperatively. Apart from that, we also noted occurrences of major cerebral complication post operatively with one of the patient developed left hemiparesis and demonstrated in CT brain as right MCA distribution infarct. In this study, another subject had poor recovery of his conscious level after the CABG, and subsequent radiological investigation noted evidence of right ischemic stroke. This patient eventually had tracheostomy done on day 15 of operation as patient had prolonged ventilation with poor GCS recovery.

4.5 Cognitive Assessment Characteristic:

All participants in this study had their preoperative cognitive assessment as the baseline parameter of cognition. Mean time of baseline cognitive assessment was on day 1.37 ± 0.655 before the operation, with maximally patient been assessed 4 days prior to the operation day. Mean time for post-operative cognitive assessment was on day 7.35 ± 1.61, with minimum and maximum day of post-operative cognitive assessment was on day 5 and day 15 respectively.

Table 4.5: Cognitive Assessment Characteristic

Variables	(Mean ±SD)	Minimum	Maximum
Day baseline assessment	1.37 ±0.66	1	4
Day post-CABG assessment	7.35 ±1.61	5	15

4.6 Cognitive Function Characteristic

4.6.1 Big-Little Circle (BLC)

99.6 ± 0.9 % of the patient capable to pass the screening test which was BLC during the initial cognitive assessment; while postoperatively they had showed improvement with mean value for percentage of patient able to pass the screening test was 99.7 ± 0.8%.

4.6.2 Intra/Extra Dimensional (IED)

The parameter used for IED test was median from total adjusted error done by patient during conduct of the cognitive test. The median value were consider for the evaluation of this test as there were presence of 3 block of tests in the IED, and the median total adjusted error value was calculated via CANTAB® software.

Considering presence of cognitive impairment with the value of increment of total error in IED comparing to the baseline and postoperative period of 20%, 14 patients (35%) had impairment in IED test post CABG, with 11 patients (27.5%) had no changes in IED before and after operation, and 15 patients (37.5%) showed that the cognitive function were not impaired before and after CABG.

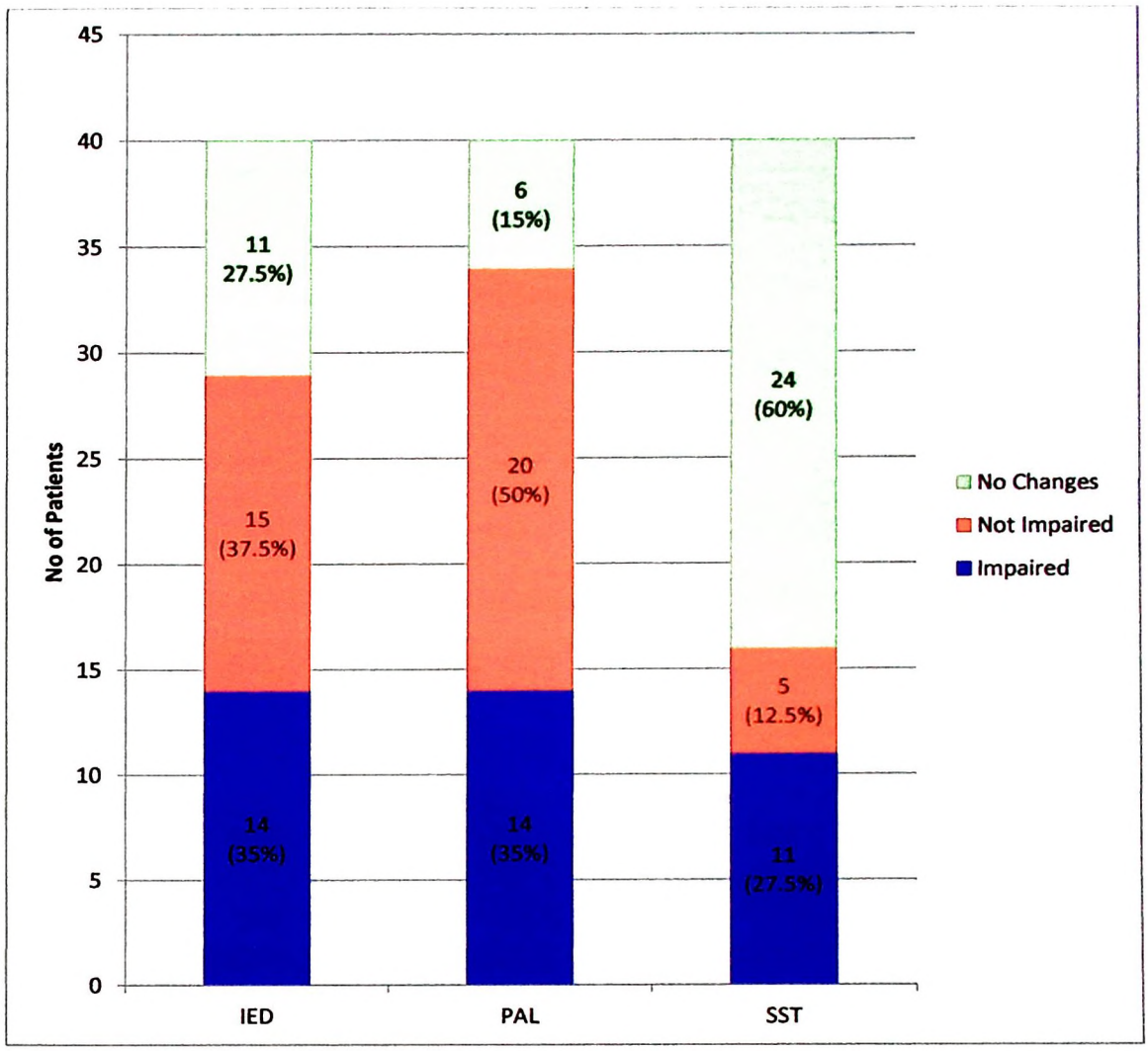

Figure 4.9: Proportion Of Significant Cognitive Changes According To Subtest

4.6.3 Paired Associate Learning (PAL)

The value for assessing PAL was total adjusted errors. In this test, the median value was analyzed in this study as there were present of multiple block of test in PAL, depending on subjects' capability to complete the test.

Considering impairment in PAL test with increment of 20% of total errors done post-operatively compared to baseline test done prior to the operation, 35% of patients showed impairement in this PAL test (n=14). However, majority of the patients with percentage of 50% (n=20) showed no impirment in their PAL test. The remaining 15% (n=6) had no changes of the PAL test preoperatively and postoperatively.

4.6.4 Stop Signal Task (SST)

The outcome of SST test for this study was the SST RT on GO trials. It describes the median reaction time for the GO trials in the test in milliseconds (ms) with the total of 40 patients capable to complete both preoperative and postoperative tests for SST

With definition of impairment in SST taken as 20% increment of duration taken to complete the test before and after the operation, 11 subjects had impaired in the SST test (27.5%) and 12.5% (n=5) showed no impairment in SST test with the remaining 60% (n=24) had no changes.

Overall, comparing significant impairment of 3 cognitive tests in CANTAB®, the most impaired test post CABG in this study was PAL and IED with 35% of the patients showed increment of total adjusted errors in both test.

4.6 Factors Related To Cognitive Changes

All parameters including age, education level, type of procedure, anesthesia duration, surgery duration, CPB duration, rewarming duration and rate of temperature increment during rewarming period of impaired cognitive function subjects, were analyzed with simple linear regression to determine any correlation of cognitive impairment with these factors before proceed to analysis with multiple linear regression test. Factors with significant *p*-value of less than 0.05 were accepted to be analyzed with multiple linear regressions. Analysis with multiple linear regression proceeds to evaluate any correlation related to cognitive impairment that might be risk factors for cognitive dysfunction post CABG with significant *p*-value accepted of less than 0.05.

Table 4.6: Associated Factors Related To IED Test Impairment – Simple Linear Regression

Model	Coefficient	*p-value
Age	3.102	0.369
Education	3.871	0.911
Procedure	-2.322	0.977
Anesthesia duration	-0.169	0.793
Surgery duration	-0.419	0.627
CPB duration	0.865	0.307
Rewarm Duration	2.445	0.056
Rate of rewarm	2.780	0.322

* using simple linear regression test, t-test

For IED, with simple linear regression, the result of it were analyze in correlation to few parameters which were age of the patients, education level, type of procedure done either CABG alone or CABG with valvular repair or replacement, anesthesia duration, duration of surgery, duration of CPB, rewarming phase duration and also rate of temperature increment during rewarming period. All of the variables were not significantly correlated with impaired IED with the p-value of more than 0.05.

Multiple linear regression proceed and showed that there were no significant correlation between IED cognitive test impairment with all of this parameter with *p*-value were greater than 0.05.

Table 4.7: Associated Factors Related To IED Test Impairment – Multiple Linear Regression

Model	Unstandardized coeeficients		Standardized coeeficients	t	*p-value
	B	Std. error	Beta		
Age	2.176	1.742	0.225	1.249	0.221
Education	-11.439	21.706	-0.097	-0.527	0.602
Procedure	27.465	51.203	0.101	0.536	0.596
Anest duration	-0.793	0.674	-0.474	-1.177	0.248
Surgery duration	0.735	0.714	0.458	1.028	0.312
CPB duration	-0.585	0.774	-0.240	-0.755	0.456
Rewarm duration	2.305	1.524	0.408	1.512	0.141
Temperature rate	-1.940	2.351	-0.188	-0.825	0.416

* using multiple linear regression test, t-test

Factors that might correlated with impairment of PAL test were analyzed with simple linear regression with significant factors were included if *p*-value greater than 0.05.

Table 4.8: Associated Factors Related To PAL Test Impairment – Simple Linear Regression

Model	Coefficient	*p-value
Age	-4.985	0.279
Education	37.208	0.699
Procedure	-	-
Anesthesia duration	-0.360	0.694
Surgery duration	0.255	0.760
CPB duration	-1.066	0.488
Rewarm duration	-6.400	0.053
Rate of rewarm	-23.933	0.024

* using simple linear regression test, t-test

From table 4.9, the simple linear regression test were unable to differ type of procedure in impaired PAL subjects, as all of the subjects fall in the same procedure group. There was significant *p*-value noted with rate of rewarm with simple linear regression. Multiple linear regression proceed to determine present of significant correlation of impaired PAL with all of these variables.

Analyzing the PAL cognitive assessment value with multiple linear regression, there were also no significant correlation (p-value > 0.05) between PAL cognitive impairment with socio-demographic data and procedure characteristic.

Table 4.9: Associated Factors Related To PAL Test Impairment – Multiple Linear Regression

Model	Unstandardized coeeficients		Standardized coeeficients	t	*p-value
	B	Std. error	Beta		
Age	-2.317	4.472	-0.145	-0.518	0.623
Education	-29.974	113.590	-0.091	-0.264	0.801
Anest duration	-2.828	2.542	-0.910	-1.112	0.309
Surgery duration	3.118	2.498	1.102	1.248	0.258
CPB duration	-2.238	4.379	-0.424	-0.511	0.628
Rewarm duration	5.864	7.175	0.483	0.817	0.445
Temperature rate	-35.027	17.736	-0.874	-1.975	0.096

*using multiple linear regression test, t-test

For impairment in SST test, all the variables were analyzed with simple linear regression, accepting significant correlation with *p*-value greater than 0.05 before proceed with multiple linear regression.

Table 4.10: Associated Factors Related To SST Test Impairment – Simple Linear Regression

Model	Coefficient	p-value
Age	-8.701	0.361
Education	-4.034	0.945
Procedure	185.940	0.045
Anesthesia duration	0.108	0.884
Surgery duration	0.396	0.572
CPB duration	1.278	0.207
Rewarm duration	0.617	0.857
Rate of rewarm	7.249	0.695

*using simple linear regression test, t-test

Table 4.11 showed that from simple linear regression noted that type of procedure showed as significant correlation with impairment in SST test. However, other variables did not showed any significant correlation with this impairment. Further analysis with multiple linear regression done to determined the significant of it.

Multiple linear regression done to correlate SST analysis of cognitive function with socio-demographic and procedure variables, found that there were no significant correlation between them with *p*-value greater than 0.05.

Table 4.11: Associated Factors Related To SST Test Impairment – Multiple Linear Regression

Model	Unstandardized coeeficients		Standardized coeeficients	t	*p-value
	B	Std. error	Beta		
Age	1.049	4.361	0.083	0.241	0.832
Education	-155.600	89.877	-0.917	-1.731	0.226
Procedure	130.344	73.470	0.430	1.774	0.218
Anest duration	2.648	2.008	1.231	1.318	0.318
Surgery duration	-2.227	1.943	-1.078	-1.147	0.370
CPB duration	5.697	2.167	1.841	2.629	0.119
Rewarm duration	-18.093	13.201	-1.806	-1.371	0.304
Temperature rate	44.766	66.791	0.825	0.670	0.572

*using multiple linear regression test, t-test

CHAPTER FIVE

DISCUSSION

5.1 Demographic Characteristic

The demographic characteristics in this study include age, gender, race, education level and occupations.

Patients' age involved in this study, who had underwent CABG ranging from age 40 years old to age 75 years old. The youngest patients been subjected for CABG due to coronary artery disease in this study was 40 years old. Ko *et al* investigated coronary heart disease risk amongst Korean, noted that the prevalence of CHD risk factors increased in women with increasing age, especially after age 50, whereas no distinct tendency was observed in men with age, except for those with hypertension and diabetes mellitus which are known risk for CAD (Ko *et al.*, 2006).

According to Malaysia Health Indicator of 2010 report, there were total number of 52,145 patients were diagnosed to have ischemic heart disease upon discharge with the code of I20 to I25 according to ICD-10 disease coding system. With this number, the discharge rate of patients with ischemic heart disease per 100,000 population was 184.04 (Malaysia, 2010). World Health Organization (WHO) in its report Preventing Chronic Disease: a Vital

Investment states that 50% of the death secondary to chronic disease which includes cardiac disease was occurred prematurely in people under 70 years of age ((WHO), 2005). In comparison to findings from Global Registry Acute Coronary Events (GRACE), Malaysia Annual Report of the Acute Coronary Syndrome Registry in 2007 & 2008 found that Malaysian patients presented with ACS at a much younger age, which were less than 50 years old (Malaysia, 2009). While Malaysia NCVD-ACS registry in 2011, comparing with other registries had found that the subjects involved in the registry were much younger at presentation with the mean age of 59 ± 12 years from total of 3422 patients enrolled (Ahmad *et al.*, 2011) with overall incidence of coronary heart disease in Malaysia is estimated to be 141 per 100,000 population (Malaysia, 2009).

Majority of the subjects enrolled in this study were male in gender with 86% of them (n=37). This is not surprising as male gender is one of the non-modifiable risk factor for development of coronary heart disease, with increase of other modifiable risk factors for the establishment of this illness such as smoking is more prominent amongst man. Study conducted amongst Iranian from 2005 to 2010; found that out of 37,358 patients diagnosed with coronary artery disease via coronary angiography, majority were men with 11,995 of them were women. However, with the extensiveness of CAD, the frequency of recommendations for non-invasive modalities form the treatment of CAD was higher in the females (20.1% vs 18.6%, $P < 0.001$ (Abbasi *et al.*, 2012). With the close similarity to Malaysia, study conducted in India investigating incidence of CAD in 2008 found that the male to female ratio of patients with CAD was 10 : 1 (Jaswal *et al.*, 2008).

Study conducted by Agrinier *et al* investigating menopausal effect among women on coronary artery disease risk factor concluded that Framingham 10-year risk of CHD was higher in post-menopause, as compared with peri-menopausal individuals (5.1% vs. 5.0%, $p<0.05$) with the risk increases during the sixth decade. It has been explained by estrogens deprivation and also by the effect on lipid profile which is likely to occur in the peri-menopause period (Agrinier *et al.*, 2009).

It was not surprising that most of the patients in our study were Malays because they formed the majority of the population in this country followed by Chinese and Indians. According to Bureau of East Asian and Pacific Affairs, the proportions of races in Malaysia in 2010 was 53.3% were Malays, followed by Chinese, Aborigin, Indians and others with the percentage of 26.0%, 11.8% 7.7% and 1.2% respectively. Furthermore, this corresponds to 93% of Kelantan's population which was reported by Malaysian Department of Statistic in 2010 (department of statistics, 2010). In particular of race related risk for cardiovascular disease, Malaysian registry of NCVD-ACS conducted in 2006 enrolled 11 institution in Malaysia also found that race distribution of patients admitted for ACS symptoms with the proportion of Malay, Chinese, Indian and other races contributed 49%, 23%, 23% and 5% respectively (Ahmad *et al.*, 2011).

From this study, majority of the subjects enrolled had attained secondary education. This corresponds with data from Malaysia Educational Statistics Quick Facts in 2004 as Malaysian educational attainment of the adult population, 52.8% comprise of secondary educational level. The second most education level attained by participants in this study were primary

education, tertiary and no schooling with percentage of 27.1%, 12.8% and 7.3% respectively (Malaysia, 2011).

Most of the patients in our study work at farm field and skilled job with 60.4 % of them. Followed by pensioner with 25.6% . This is expected as incidence of CAD increase with age. Occurrence of CAD is higher in the elderly. Sjogren estimated higher coronary disease risk among farmers compared with white-collar workers. But during the analysis published in Lancet in 1996, the confounding factors such as age was not included (Sjogren, 1996). Jousilathi *et al* correlating level of fibrinogen with coronary heart disease risk in relation to type of occupation noted that women farmers may have been more exposed than women in other professions to factors leading into high serum fibrinogen and subsequently to increased coronary risk disease. However, in males, adjusted age analysis of serum fibrinogen concentration in males farmer did not differ from mean fibrinogen values of male white-collar and blue collar workers (3·28 ±SD 0·68, 3·32 ±SD 0·77, and 3·41 ±SD0·73, respectively) (Jousilahti *et al.*, 1997).

5.2 Medical And Procedure Characteristic

Majority of patients enrolled in this study were subjected for CABG with indication of 3 major coronary vessels occlusion from angiography, followed by LMS diseases which carry high risk of morbidity without surgical correction. Least number of indications for CABG in this study was CAD with concurrent valvular defects. Study conducted by Palazzuoli *et al* correlating Brain Natriuretic Peptide (BNP) level with narrowed number of coronary arteries based on angiography noted that 48.28% of subjects diagnosed with stable angina, unstable angina and non-Q wave MI had single coronary artery narrowing on angiography. Followed by two coronary arteries and 3 coronary arteries with percentage of 29.89% and 21.83 % respectively (Palazzuoli *et al.*, 2005). In total of 2936 patients with stable angina pectoris were enrolled in the Euro Heart Survey on Coronary Revascularization, 25 % of them were subjected for CABG. The coronary bypass surgery was preferred over percutaneous coronary intervention in multivessels disease or left main stem disease, as well as those with concomitant valvular heart disease (Breeman *et al.*, 2006).

Ninety three percent of our participants had underwent CABG alone as compared to 7% of them underwent CABG with valvular replacement or repair. Study evaluating operative mortality between 1,344,100 subjects underwent CABG, CABG/AVR or AVR after prior CABG in the Society of Thoracic Surgeons data found that operative mortality and morbidity was higher for a patient undergoing AVR after CABG than for a patient undergoing simultaneous CABG/AVR (Smith Iv *et al.*, 2004). However, the risk of developing permanent stroke or renal failure was about double for a patient undergoing surgery that involved AVR, either at the time of CABG or subsequently compare to CABG alone (Smith

Iv *et al.*, 2004). Smith *et al* had suggested in their study that CABG alone is superior at lower baseline aortic valve gradients in term of improvement in quality of life, with best management of CABG/AVR with the aortic valve gradient of over 30 mmHg (Smith Iv *et al.*, 2004).

Many epidemiological studies showed that diabetes, hypertension and hyperlipidemia are risk factors for CHD. It is not surprising that more than half of the subjects in this study had previously been diagnosed with this illness. Apart from that, renal disease as microvascular complication of the cardiovascular illness is also noted among individual who had been subjected for CABG in this study.

5.3 Cognitive Assessment Characteristic

In this study, cognitive assessment were assess with the used of CANTAB®. This cognitive tool is capable of evaluating few domains of cognition. The aspects of cognition that had been evaluated were comprehension, learning and reversal with the BLC and executive function via IED. Visual memory and new learning function of the brain were assessed with PAL; and SST used to evaluate decision making and response control of the participants.

The result of baseline cognitive assessment before CABG found that majority of the participants are capable to pass through the screening test of BLC. This BLC test is important as the induction test to assess patient comprehension prior to further assessment of executive function via IED. BLC test is designed to train the subject to follow an explicit instructional rule and to reverse a rule. Study conducted by Anita and her team examined preschool teachers' explicit print instructions during shared reading at schools. The study showed that explicit prints instruction contributed to children learning (McGinty *et al.*, 2012). Mean for baseline and even post CABG BLC test showed almost 100% in both condition. (99.6% ± 0.9; 99.7% ± 0.8). Therefore, all patients were proceed with IED test to elicit their cognition in the aspects of executive function, working memory and planning.

IED is a cognition domain test of executive function, working memory and planning. It assess rule of acquisition and reversal, featuring visual discrimination and attentional set shifting. This test is an analogue to a category change in Wisconsin Card Sorting Test. In this study,

we evaluated post CABG IED median total adjusted errors done compared to preoperative value in each subjects. An impairment was considered if there is 20 % increase in median total adjusted errors in IED task postoperatively. From the total of 40 participants that capable to complete both IED test before and after operation, 14 patients (35%) showed decline of this cognitive domain. It indicates that there was impairment of executive function post CABG with prevalence of it was 35%. However, 37.5% of the subject showed no impairment in IED test post-operatively. According *to* Elliot *et al*, this IED task is a sensitive test to frontal lobe dysfunction (Elliot *et al.*, 1995). Therefore, the dysfunction or with the present of significant deterioration in IED test postoperatively comparing to baseline assessment may signify possibilities of impairment or lesion in the frontal lobe functionally.

Multiple linear regression analysis done to evaluate factors that related to the result of IED impairment in post CABG patients, in correlation to the socio-demographic data that included age and education; found that there was no significant correlation between IED with age and education level of the patients ($p>0.05$). IED assessment was analyzed to find its correlation with type of procedure, anesthesia duration, surgery duration, CPB duration, rewarming duration and also rate of rewarming. However, these factors were not significantly correlated with impairment of IED performance.

PAL is an assessment of simple visual pattern and visuospatial associative learning. It contains both of delayed response procedure and conditional learning task. In order to have a successful result in PAL, it requires patent function of medial temporal lobe which responsible for frontal strategies and mnemonic processing (Jakala *et al.*, 1999). In this study,

we found that 35% of participants had impairment in this visual memory test. It is indicated by increment of total adjusted errors by 20% in PAL test postoperatively. However, in this study half of the participants (n=20) showed no impairment of PAL test after CABG. Fowler and colleagues in their study had reported that individuals with mild cognitive impairment with decline performance in PAL is one of the predicting factors for later progression to Alzheimers disease (Fowler *et al.*, 2002). Fowler also noted, supported with study by Taffe *et al* that poor performance in PAL test amongst questionable demented patient maybe the result of loss of muscarinic cholinergic receptors and/or to an impairment of cholinergic neurotransmission in the parahippocampal region (Fowler *et al.*, 2002; Taffe *et al.*, 2004). This impairment has also been supported by imaging technique as subjects with impaired PAL in early dementia who had presented with mild cognitive impairment showed dysfunction of the medial temporal lobe. In our study, as 35% of participants showed significant impairment of PAL test, it is been suggested that there is possibilities of anatomical brain dysfunction or lesion that might exhibit as impairment of PAL test.

In order to evaluate any significant risk factors of the impaired PAL postoperatively, multivariate analysis done to evaluate any correlation of this decline with patients' age, education level, type of procedure, duration for anesthesia, surgery, CPB and rewarming; and also rewarming rate. This analysis had concluded that there was no significant correlation of these factors with decline in PAL performance ($p > 0.05$). In contrast to large study conducted by Robbins & Rabbit et al, which showed a demonstrated decline of PAL with age (Robbins *et al.*, 1994; Rabbitt and Lowe, 2000). Our study did not suggest that age is one of the contributing factors of visual memory impairment in post CABG patient. In term of prevention or neuroprotection against dysfunction of visual-spatial cognition, Matthew *et al*

found that humanized monoclonal antibody directed against C5 complement component, Pexelizumab, had no effect on global measures of cognition, but may enhanced visual-spatial cognition (Mathew *et al.*, 2004).

SST is a test of response and motor inhibition, generally the reaction time. The outcome assessed in this study was the median SSRT on GO, which define as time in milisecond to press the button on the pad when there is no auditory signal.

Considering impairment of reaction time via SST if time taken post CABG for the task more than 20% of baseline reaction time; we noted that 27.5% (n= 11) of participants had impairment in this task post CABG. It can be concluded that subjects post CABG had impairment in reaction time with prevalence of 27.5%, based on significant difference of time taken during postoperative period. However, majority of individuals in this study with 60% of them (n=24) showed no changes in term of SST test before and after CABG. Aron *et al* had studied on frontal lesions patients found that the performance of SST dependent on intact right inferior gyrus (Aron *et al.*, 2003; Aron *et al.*, 2004). This also been supported with neuroimaging technique that response inhibition had been modulated by more extensive region includes orbitofrontal, anterior cingulated, dorsolateral and medial frontal, temporal and parietal cortices, the cerebellum and basal ganglia (Fineberg *et al.*, 2006). Therefore, it suggested that individuals with impairment of SST may shows similar changes in the brain function.

Despite of this derangement of reaction time in CABG patients, we are unable to find any significant correlation of reaction time dysfunction (p>0.05) with factors evaluated in this

study, which include patients age, education level, duration of anesthesia, surgery, CPB, rewarming and also rate of rewarming.

Overall, we noted that all three main domains of cognitive function that had been investigated in this study, showed incidence of cognitive impairment in patient post CABG at 1 week post-operation, with percentage of impairment noted in IED, PAL and SST were 35%, 35% and 27.5% respectively. However, in this study, majority of individuals showed no impairment in both IED and PAL post-operatively. While, in SST majority of them had no changes of SST before and after operation. This had been supported by numerous studies; indicate that both early and late post-operative cognitive decline is more likely after cardiac surgery than after non-cardiac surgery. As been reported by Newman and colleagues that significant cognitive decline noted in CABG patients with occurrence of 53% at discharge, 24% at 6 months an 42% after 5 years (Newman *et al.*, 2002). Constantine *et al* suggested from population based prospective study that cross-sectionally, CABG may be associated with better cognitive function in the first few years after surgery, and for more than 5 years it will be followed by delayed cognitive decline (Constantine *et al.*, 2006). Yuji Kadoi and colleagues found that the incidence of cognitive decline at 6 months in patient undergoing CABG was 24/88 (27.3%) (Kadoi and Fumoi, 2006).

In a big population-based study in 2006, assessing cognitive function in 5,092 samples, found that CABG group had greater decline in cognitive scores via MMSE during the first and second follow-up compared to baseline ($p= 0.0121$) (Constantine *et al.*, 2006). Ewa Ahlgren *et al* also noted in their study that there were 48% of patients underwent coronary artery

bypass showed cognitive decline after intervention (p= 0.01) as compared to control percutaneous coronary intervention group (10%). The study also noted that the CABG group had deterioration in the on-road driving test in parts like traffic behaviour (p=0.01) and attention(p=0.04) (Ahlgren *et al.*, 2003).

However, few studies comparing CABG with other non-cardiac surgery found there were similar occurrences of short-term cognitive dysfunction which may suggest it is not specific to CABG alone, but may also accompany other surgical procedures (Moller *et al.*, 1998). William-Russo *et al* compared outcomes in patients after CABG with outcomes in patients after total knee or total hip replacements found high incidence of cognitive decline in both group at 1 week and 6 months after surgery (Williams-Russo *et al.*, 1995).

In this study, we evaluated patients' cognitive function at interval of 1 week after CABG. This had been supported by Bruce *et al* as he reported in their study in 2007 that preexisting cognitive impairment in those patients underwent CABG had became significantly more impaired following 4-7 days of surgery. The study had compared the cognitive function among CABG patient with other valve repair or replacement and also robotically assisted valve repair (Bruce *et al.*, 2007). In a multi-institutional study by Wolman *et al* noted that the incidence of overt adverse neurologic outcome was approximately doubled in patients undergoing CABG that included intracardiac procedure compared with CABG alone (Wolman *et al.*, 1995). However, in our study, there was no significant correlation of type of procedure either CABG alone or CABG with valvular repair or replacement, with cognitive changes

After evaluating the parameters used in this study to elicit cognitive function postoperatively, it can be concluded that post CABG patients showed presence of cognitive impairment incidence post surgery in the early post operation; particularly in the aspect of visual memory test, executive function and reaction time. In this study, the higher incidence of cognitive impairment noted in the domains for executive function and visual memory by impairment of both IED and PAL test, with 35 percent of the subject had showed impairment of both tests postoperatively. However, this studies unable to suggest any significant factors that might govern these cognitive changes. Price *et al* examined the type and severity of cognitive impairment in elderly non-cardiac surgical patients, and had found that more subjects were impaired on the memory indexes (54%) relative to executive functions (34%) (Price *et al.*, 2008). Contrary to our study, we found that post CABG patients showed higher incidence of impairment in both visual memory via assessment with PAL (35%) and executive function with IED (35%) as compared to response inhibition task via SST (27.5%). Apart from that, William-Russo and colleagues in their study conducted in 1995 found that the main domain with the highest frequency of cognitive decline was memory at 6 months after surgery (Williams-Russo *et al.*, 1995).

5.4 Factors Related To Cognitive Changes

From this study, after evaluating few aspects that become possible contributing factors, we unable to correlate any significant factors that might contribute into cognitive decline post CABG.

Cognitive impairment is common in late life and this may occur due to normal process of aging. In a cross sectional study among Malaysian elderly found that the incidence of cognitive impairment in this age was as high as 24%. It contributed from dementia, age associated memory decline, depressive and anxiety related disorders (Krishnaswamy, 1995; Krishnaswamy, 1997). In relation to cognitive dysfunction postoperatively, we are unable to elicit any significant correlation between age and cognitive dysfunction. However, in the risk factor analysis of the ISPOCD I study, age was found to be a significant and independent risk factor. The incidence of POCD after 3 months was 7% in those aged 60-69, and 14% in those over 69 years of age (Moller *et al.*, 1998). In this study, the possibilities that we cannot evaluate age as significant factor for cognitive decline is because of inclusion criteria of patients in this group were ranging from 18 years old to 75 years old. The youngest patient participated in this group was 40 years old with the oldest was 75 years, and mean age was 58 years. Therefore, age as determining factors in this study was not as prominent, as the distribution of age limited to the maximum of 75 years old.

Level of education was also an important preliminary factor before operation because well-educated patients experienced less POCD after 1 week (Rasmussen, 2006). Lower educational level predicted the higher incidence of POCD. The significance of this concept is that subjects with greater cognitive reserves can sustain more neuronal los or pathological changes before exhibiting signs of clinically significant cognitive impairment (Bekker *et al.*, 2010). However, in our study we are unable to elicit any significant correlation of education level with cognitive dysfunction post CABG.

Other factors that might contributed into POCD are duration of anesthesia, respiratory complication, infectious complication and second operation (Rasmussen, 2006). However, in our study, there was no significant correlation of anesthesia duration and even surgery duration with postoperative cognitive decline.

Numerous modifiable factors have been reported to show association with risk for Alzheimers disease which can be preceded by mild cognitive impairment. Chronic diseases such as diabetes, elevated blood cholesterol level and depression have been associated with increased risk of Alzheimers disease. Several medication and lifestyle factors also been linked to a decreased risk for this problem; include low saturated fat consumptions, use of statins, educational attainment and participation in physical activity. However, there was no consistent associations were found for fatty acids, metabolic syndrome, blood pressure, obesity and body mass index, antihypertensive medications or gonadal steroids (Davigius *et al.*, 2010).

Numerous established studies from 1980s and 1990s have shown that the cognitive changes seemed especially prominent after surgery under cardiopulmonary bypass (Mikhailidis *et al.*, 1986; Pugsley *et al.*, 1994). In our study, the duration of cardiopulmonary bypass did not showed any significant correlation with each test of cognitive tool used in this study. In contrast to Ridderstolpe in their 4 years study among patient underwent cardiac surgery found that patient who had longer CPB time were at higher risk for early onset of cerebral complications ($p<0.001$) (Ridderstolpe *et al.*, 2002). However, meta analysis that include data from over 900 patients had confirmed that POCD rates after heart surgery with and without CPB were not significantly different in elderly patients at 1 year or at 5 years (Marasco *et al.*, 2008).

In this study, type of oxygenator used during conduct of CPB was membrane oxygenator. It applied to all of the participants that involved in this study during CPB, and therefore we unable to differ the cognitive changes with other type of oxygenator. Smith *et al* had studied on differences of oxygenator with cognitive changes and had found that reduced significant occurrence of emboli with membrane oxygenators as compared to bubble oxygenator, and suggested that reduced neuropsychological deficits in the membrane oxygenator group (Smith *et al.*, 1990).

With completion of this study, we noted that mean duration for rewarming phase during conduct of CPB was 12.26 mins, with the range of 4.34 min to 36.6 min. The rate of rewarming for every drop of 1°C ranging within 4.3 minutes to 36.7 min. Nancy in her article published in Cardiovascular Anesthesiology Journal, had suggested that rewarming must

proceed slowly, and the clinician may consider weaning at temperatures slightly below 37°C in patients at high risk of an ischemic event. She also suggested that it is critical to avoid hyperthermia during rewarming as it has deleterious effect to the brain (Nussmeier, 2005). During hypothermic CPB, hypothermia always initiated at the onset of bypass. Before bypass is terminated, patients are rewarmed, usually before the aortic cross clamp is removed. During the hypothermic phase, cerebral embolism is unlikely because the heart is excluded from the circulation by the aortic cross-clamp. The embolism most often occurs in the phase of warming of the brain, especially during or immediately after removal of the aortic cross-clamp. It has been suggested that too aggressive rewarming in an attempt to avoid the afterdrop in the temperature post CPB may lead to cerebral hyperthermia, and hyperthermia is deleterious to cerebral protection (Nussmeier, 2005). However, in our study we are unable to elicit any significant correlation of duration of rewarming and rate of rewarming with cognitive changes post CABG. Sahu *et al* in their study comparing neurocognitive deficit post CABG with rewarming at 33 °C and 37 °C had suggested that weaning from CPB at 33 °C is a useful strategy to lower the postoperative impairment of neurocognitive function (Sahu *et al.*, 2009).

There are few possible causative mechanisms that might lead into cognitive decline post CABG surgery that includes cerebral microembolism ischemia, hypoxia and inflammation. Zimpher *et al* suggested that long-term neurocognitive deficits in aortic valve replacement as the result of combined process of intra-operative damage and cumulative damaged caused by microemboli originating from prosthetic cardiac valves (Zimpfer *et al.*, 2006). Zimpher *et al* in their study among CABG patient in 2004 suggested that CABG with CPB may cause irreversible damage to cerebral tissue then resulting in significantly impaired neurocognitive

impairment. Suspected mechanism are impaired cerebral perfusion during CPB, postoperative systemic inflammatory response, and micro and macroembolism (Zimpfer *et al.*, 2004). They also noted that predictors of long term neurocognitive deficit were advanced age and cognitive deficit at 4-month follow up (Zimpfer *et al.*, 2004). The mechanism of elderly vulnerability towards cognitive dysfunction are advance sclerosis of ascending aorta which become possible source of micro and macroemboli during cross clamping and cannulation, and partial loss of cerebral autoregulation that results in cerebrovascular disease. There might also be due to decreased ability to recover and to compensate among elderly (Stump *et al.*, 1992).

In order to reduce the incidence or prevent the occurrence of post-operative cognitive decline (POCD), especially in cardiac surgery; there are various drugs that has been examined with regards to neuroprotective properties and potential prevention of it. A study conducted with perioperative piracetam had showed short-term neuroprotective effect for patients undergoing cardiac surgery under CPB, and persisted up to 6 weeks post cardiac surgery (Uebelhack *et al.*, 2003; Szalma *et al.*, 2006). Drugs that were found to be ineffective for POCD include calcium channel blocker (Legault *et al.*, 1996), thiamine and vitamin C (Day *et al.*, 1988), lidocaine (Wang *et al.*, 2002; Mitchell *et al.*, 2009), free radical scavenger (Ogasawara *et al.*, 2005), prostacyclin (Fish *et al.*, 1987) and statins (Matthew *et al.*, 2005).

Neurcognitive deficit is a drawback of coronary artery bypass grafting as it may reduce the merits of surgical intervention. Roach and colleagues had found in their study that cognitive dysfunction is associated with increased mortality (10%), a twofold increases in the length of

stay and a six-fold likelihood of discharge to nursing home (Roach *et al.*, 1996). These conditions are associated with dramatic increased of health care resources. From the patient perspective, the impact of the neurocognitive dysfunction is devastating as it has been shown to impair subjective working capacity, reduce in quality of life, job related abilities, productive working status and impair car driving abilities (Newman *et al.*, 2001; Ahlgren *et al.*, 2003). Therefore, the cerebral outcome of CABG especially towards cognitive dysfunction should be addressed to all patients who had been subjected for this procedure because of high prevalence of it and the devastating effects of the condition. Even though in our study, we are unable to recognize any correlating factors of this dysfunction, we hope for further research to evaluate on this aspects and emphasis on both the prevention and treatment of cognitive dysfunction post CABG.

CHAPTER SIX

CONCLUSION

Prevalence of coronary artery disease is high in Malaysia and many patients had been subjected for coronary bypass graft surgery (CABG) in order to correct the obstruction of coronary arteries. Despite improvement of symptoms post surgery, the effect of CABG on cognitive function is usually taken lightly by clinician. From this study, there is presence of cognitive impairment incidence in post CABG patients with the involvement of executive function and visual memory domain noted in 35% of the subjects. These conditions may cause devastating effect to the patient and also detrimental result to their quality of life. Thus, pre-procedural details should be informed to the patients prior to the surgery in term of anticipated neurocognitive changes post-operatively. Even though this study is unable to recognize any significant contributing factors related to cognitive dysfunction post CABG, we encourage future studies to look into this matter in order to implement preventive measure and possibly treatment of this problem. Limitation of this study is, it evaluates the cognitive changes in short term period rather than in long term period. Therefore, further studies should look into it and evaluate long term cognitive changes in this population as this may markedly impaired patients quality of life.

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APPENDIX 1

Collecting Data Form

A STUDY OF SHORT TERM COGNITIVE OUTCOME IN POST CABG PATIENT

Name: _____

Age: _____

Identification card no: _____

R/N: _____

Diagnosis: _____

Gender: ☐ Male ☐ Female

Race: ☐ Malay ☐ Chinese ☐ Indian ☐ Others

Education level:

☐ not schooling ☐ PMR/ SRP/ LCE ☐ Diploma/ Ijazah
☐ primary school ☐ SPM/ MCE ☐ Others

Occupation:

☐ senior officers & managers ☐ service workers & shops ☐ elementary occupations
☐ professionals ☐ skilled agricultural & fishery ☐ housewives
☐ technical & associates ☐ crafts & related trade workers ☐ unemployed
☐ clerical workers ☐ machine operators & assemblers ☐ unclassified

Co-morbid:

☐ Ischaemic heart disease ☐ Hyperlipidaemia ☐ Others
☐ Diabetes mellitus ☐ Renal failure
☐ Hypertension ☐ Bronchial asthma/ COAD

Pre-operative investigation:

Hb: _____ Na: _____
Hct: _____ K: _____

Baseline cognitive test date: _____

Date of operation: _____

Procedure: _____

Type of oxygenator: _____

	Time start	Time end
Anesthesia		
Surgery		
Cardio-pulmonary bypass		
Rewarming		

TEMPERATURE:	Pre-rewarming	Post-rewarming
- Nasopharynx		

Post-operative complication: _____

Extubation date: _____

Post-CABG cognitive test date: _____

APPENDIX 2

Information And Consent Form

LAMPIRAN A

MAKLUMAT KAJIAN

Tajuk Kajian : **KAJIAN MENGENAI KESAN JANGKA PENDEK FUNGSI KOGNITIF SELEPAS PEMBEDAHAN CORONARY BYPASS**

Nama Penyelidik : Dr Azlina Yusuf (MPM: 41921)

Professor Madya Dr Saedah Ali (MPM:31264)

Professor Madya Dr Wan Asim Wan Adnan (MPM: 22877)

PENGENALAN

Anda dipelawa untuk menyertai satu kajian penyelidikan secara sukarela mengenai kesan jangka pendek pembedahan Coronary Bypass terhadap fungsi kognitif. Kajian ini adalah untuk menilai fungsi kognitif sebelum dan selepas pembedahan Coronary Bypass, untuk menentukan sekiranya terdapat perubahan yang signifikan serta kadarnya, sama ada berkurang atau bertambah parameter kognitif. Di samping itu, ia juga untuk menilai dan menentukan domain kognitif serta faktor-faktor yang terlibat. Sebelum anda bersetuju untuk menyertai kajian penyelidikan ini, adalah penting anda membaca dan memahami borang ini. Sekiranya anda menyertai kajian ini, anda akan menerima satu salinan borang ini untuk disimpan sebagai rekod anda.

Penyertaan anda di dalam kajian ini dijangka mengambil masa sehingga 1 minggu. Seramai 43 pesakit akan menyertai kajian

TUJUAN KAJIAN

Kajian ini bertujuan adalah untuk menentukan sama ada, semasa minggu pertama selepas pembedahan Coronary Bypass, adakah terdapat pengurangan di dalam fungsi kognitif pesakit berbanding sebelum pembedahan. Selain itu, kajian ini juga ingin menilai faktor-faktor semasa pembedahan yang berkemungkinan berkaitan dengan penurunan fungsi kognitif selepas pembedahan tersebut.

KELAYAKAN PENYERTAAN

Doktor yang bertanggungjawab dalam kajian ini atau salah seorang kakitangan kajian telah membincangkan kelayakan untuk menyertai kajian ini dengan anda. Adalah penting anda berterus terang dengan doktor dan kakitangan tersebut tentang sejarah kesihatan anda. Anda tidak seharusnya menyertai kajian ini sekiranya anda tidak memenuhi semua syarat kelayakan.

Beberapa keperluan **untuk menyertai kajian ini adalah –**

- **Anda telah dijadualkan untuk pembedahan Coronary Bypass secara elektif.**
- **Anda mesti berumur 18 tahun dan ke atas , serta 75 tahun dan ke bawah.**

Anda tidak boleh **menyertai kajian ini sekiranya –**

- **Anda dijadualkan untuk pembedahan Coronary Bypass secara kecemasan.**

- Anda pernah melalui pembedahan Coronary Bypass sebelum ini.
- Anda pernah mengalami masalah mata.
- Anda pernah mengalami angin ahmar serta masih lagi kekurangan neurologi
- Anda mengalami masalah psikiatri yang signifikan
- Anda secara keseluruhannya tidak stabil

PROSEDUR-PROSEDUR KAJIAN

Semasa kemasukan anda ke wad untuk pembedahan coronary bypas yang telah dijadulkan, sekiranya anda bersetuju untuk turut serta di dalam kajian ini, fungsi kognitif dasar anda akan dinilai menggunakan penilaian berkomputer secara skrin-sentuh. Ujian ini akan mengambil masa lebih kurang 30 minit. Sementara itu, anda akan diminta memberikan maklumat mengenai masalah medikal, status pembelajaran dan status pekerjaan anda.

Pada tarikh yang telah ditetapkan untuk pembedahan, anesthesia dan surgeri yang dilakukan adalah mengikut standard. Semasa pembedahan, beberapa data akan direkodkan seperti jumlah masa pembedahan dan anestesia.

Sesudah pembedahan selesai, anda akan dirawat seperti biasa seperti pesakit yang lain juga.

Selepas enam ke 7 hari pembedahan, ketika anda telah secara medikal stabil dan mendapat ubat penahan sakit yang secukupnya; dan bersedia untuk discaj ke rumah, fungsi kognitif anda akan dinilai sekali lagi menggunakan alat yang sama.

RISIKO

Sekiranya anda menyertai kajian ini, anda mungkin mengalami beberapa risiko

Lawatan untuk menilai fungsi kognitif dasar anda sebelum pembedahan berkemungkinan menganggu anda dan boleh meningkatkan tahap kerisauan anda untuk melalui pembedahan.

Selain daripada itu, penilaian semula fungsi kognitif anda pada hari ke enam hingga ke tujuh selepas pembedahan, juga boleh sekali lagi menganggu anda, tetapi pihak kajian akan mempastikan tahap kesihatan anda telah dioptimakan dan anda diberi ubat penahan sakit secukupnya sebelum dinilai.

MELAPORKAN PENGALAMAN KESIHATAN

Jika anda mengalami apa-apa kecederaan, kesan buruk, atau apa-apa pengalaman kesihatan yang luarbiasa semasa kajian ini, pastikan anda memberitahu jururawat atau Dr. Azlina Yusuf (MPM: 41921) di talian 09-7676424 atau 016-4144989 secepat mungkin. Anda boleh membuat panggilan pada bila-bila masa, siang atau malam, untuk melaporkan pengalaman sedemikian.

PENYERTAAN DALAM KAJIAN

Penyertaan anda dalam kajian ini adalah secara sukarela. Anda berhak menolak untuk menyertai kajian ini atau anda boleh menamatkan penyertaan anda pada bila-bila masa, tanpa sebarang hukuman atau kehilangan manfaat yang sepatutnya anda perolehi.

Penyertaan anda juga mungkin boleh diberhentikan oleh doktor yang terlibat dalam kajian ini tanpa persetujuan anda. Sekiranya anda berhenti menyertai kajian ini, doktor yang terlibat di dalam kajian ini atau salah seorang kakitangan akan berbincang dengan anda mengenai apa-apa isu perubatan berkenaan dengan pemberhentian penyertaan anda.

MANFAAT YANG MUNGKIN [Manfaat terhadap Individu, Masyarakat, Universiti]

Prosedur kajian ini akan diberikan kepada anda tanpa kos. Anda mungkin menerima maklumat tentang kesihatan anda daripada pemeriksaan fizikal dan ujian makmal yang dilakukan dalam kajian ini. Hasil atau maklumat kajian ini diharapkan, dapat memberi manfaat kepada pesakit-pesakit pada masa hadapan. Anda tidak akan menerima sebarang pampasan kerana menyertai kajian ini. Namun sebarang keperluan perjalanan berkaitan dengan penyertaan ini akan diberi.

PERSOALAN

Sekiranya anda mempunyai sebarang soalan mengenai prosedur kajian ini atau hak-hak anda, sila hubungi;

Dr Azlina Yusuf (MMC: 41921)

Jabatan Anestesiologi & Rawatan Rapi,<Alamat Jabatan>

Pusat Pengajian Sains Perubatan,

USM Kampus Kesihatan

Tel: 09-7676424, 016-4144989

Sekiranya anda mempunyai sebarang soalan berkaitan kelulusan Etika kajian ini, sila hubungi;

Puan Mazlita Zainal Abidin

Setiausaha Jawatankuasa Etika Penyelidikan (Manusia) USM

Pelantar Penyelidikan Sains Klinikal, USM Kampus Kesihatan.

No. Tel: 09-767 2355 / 09-767 2352

Email : jepem@kk.usm.my

KERAHSIAAN

Maklumat perubatan anda akan dirahsiakan oleh doktor dan kakitangan kajian. Ianya tidak akan dedahkan secara umum melainkan jika ia dikehendaki oleh undang-undang.

Data yang diperolehi dari kajian yang tidak mengenalpasti anda secara perseorangan mungkin akan diterbitkan untuk tujuan memberi pengetahuan baru.

Rekod perubatan anda yang asal mungkin akan dilihat oleh pihak penyelidik, Lembaga Etika kajian ini dan pihak berkuasa regulatori untuk tujuan mengesahkan prosedur dan/atau data kajian klinikal. Maklumat perubatan anda mungkin akan disimpan dalam komputer dan diproses dengannya. Dengan menandatangani borang persetujuan ini, anda membenarkan penelitian rekod, penyimpanan maklumat dan pemindahan data seperti yang dihuraikan di atas.

TANDATANGAN

Untuk dimasukkan ke dalam kajian ini, anda atau wakil sah anda mesti menandatangani serta mencatatkan tarikh halaman tandatangan (Lihat contoh Borang Keizinan Pesakit di LAMPIRAN S **atau** LAMPIRAN G (untuk sampel genetik) **atau** LAMPIRAN P**).**

LAMPIRAN S

Borang Keizinan Pesakit/ Subjek

(Halaman Tandatangan)

Tajuk Kajian: **KAJIAN MENGENAI KESAN JANGKA PENDEK FUNGSI KOGNITIF SELEPAS PEMBEDAHAN CORONARY BYPASS**

Nama Penyelidik: Dr Azlina Yusuf (MPM: 41921)

Professor Madya Dr Saedah Ali (MPM:31264)

Professor Dr Wan Asim Wan Adnan (MPM: 22877)

Untuk menyertai kajian ini, anda atau wakil sah anda mesti menandatangani mukasurat ini. Dengan menandatangani mukasurat ini, saya mengesahkan yang berikut:

- **Saya telah membaca semua maklumat dalam Borang Maklumat dan Keizinan Pesakit ini** termasuk apa-apa maklumat berkaitan risiko yang ada dalam kajian **dan saya telah pun diberi masa yang mencukupi untuk mempertimbangkan maklumat tersebut.**
- **Semua soalan-soalan saya telah dijawab dengan memuaskan.**
- **Saya, secara sukarela, bersetuju menyertai kajian penyelidikan ini, mematuhi segala prosedur kajian dan memberi maklumat yang diperlukan kepada doktor, para jururawat dan juga kakitangan lain yang berkaitan apabila diminta.**
- **Saya boleh menamatkan penyertaan saya dalam kajian ini pada bila-bila masa.**
- **Saya telah pun menerima satu salinan Borang Maklumat dan Keizinan Pesakit untuk simpanan peribadi saya.**

Nama Pesakit **(Dicetak atau Ditaip)**	Nama Singkatan & No. Pesakit
No. Kad Pengenalan Pesakit **(Baru)**	No. K/P **(Lama)**
Tandatangan Pesakit atau Wakil Sah	**Tarikh** (dd/MM/yy) (Masa jika perlu)
Nama & Tandatangan Individu **yang Mengendalikan**	Tarikh **(dd/MM/yy)**

Perbincangan Keizinan (Dicetak atau Ditaip)

Nama Saksi dan Tandatangan	Tarikh **(dd/MM/yy)**

Nota: **i) Semua subjek/pesakit yang mengambil bahagian dalam projek penyelidikan ini tidak dilindungi insuran.**

LAMPIRAN G

Borang Keizinan Pesakit/ Subjek untuk *Sampel Genetik*

(Halaman Tandatangan)

Tajuk Kajian:	**KAJIAN MENGENAI KESAN JANGKA PENDEK FUNGSI KOGNITIF SELEPAS PEMBEDAHAN CORONARY BYPASS**
Nama Penyelidik:	Dr Azlina Yusuf (MPM: 41921) Professor Madya Dr Saedah Ali (MPM:31264) Professor Madya Dr Wan Asim Wan Adnan (MPM: 22877)

Untuk menyertai kajian ini, anda atau wakil sah anda mesti menandatangani mukasurat ini. Dengan menandatangani mukasurat ini, saya mengesahkan yang berikut:

- **Saya telah membaca semua maklumat dalam Borang Maklumat dan Keizinan Pesakit ini** termasuk apa-apa maklumat berkaitan risiko yang ada dalam kajian **dan saya telah pun diberi masa yang mencukupi untuk mempertimbangkan maklumat tersebut.**
- **Semua soalan-soalan saya telah dijawab dengan memuaskan.**
- **Saya, secara sukarela, bersetuju menyertai kajian penyelidikan ini, mematuhi segala prosedur kajian dan memberi maklumat yang diperlukan kepada doktor, para jururawat dan juga kakitangan lain yang berkaitan apabila diminta.**
- **Saya boleh menamatkan penyertaan saya dalam kajian ini pada bila-bila masa.**
- **Saya telah pun menerima satu salinan Borang Maklumat dan Keizinan Pesakit untuk simpanan peribadi saya.**

Nama Pesakit **(Dicetak atau Ditaip)**	Nama Singkatan & No. Pesakit
No. Kad Pengenalan Pesakit **(Baru)**	No. K/P **(Lama)**

Tandatangan Pesakit atau Wakil Sah	**Tarikh** (dd/MM/yy) Masa (jika perlu)
Nama & Tandatangan Individu **yang Mengendalikan Perbincangan Keizinan (Dicetak atau Ditaip)**	Tarikh **(dd/MM/yy)**
Nama Saksi dan Tandatangan	Tarikh **(dd/MM/yy)**

Nota: **i) Lebihan sampel kajian ini akan dilupuskan dan tidak akan digunakan untuk tujuan lain kecuali setelah mendapat**

kebenaran daripada Jawatankuasa Etika Penyelidikan (Manusia), USM.

ii) Semua subjek/pesakit yang mengambil bahagian dalam projek penyelidikan ini tidak dilindungi insuran.

LAMPIRAN P

Borang Keizinan bagi Penerbitan Bahan yang berkaitan dengan Pesakit/ Subjek

(Halaman Tandatangan)

Tajuk Kajian:	**KAJIAN MENGENAI KESAN JANGKA PENDEK FUNGSI KOGNITIF SELEPAS PEMBEDAHAN CORONARY BYPASS**
Nama Penyelidik:	Dr Azlina Yusuf (MPM: 41921) Professor Madya Dr Saedah Ali (MPM: 31264) Professor Madya Dr Wan Aasim Wan Adnan (MPM: 22877)

Untuk menyertai kajian ini, anda atau wakil sah anda mesti menandatangani mukasurat ini.

Dengan menandatangani mukasurat ini, saya memahami yang berikut:

- **Bahan yang akan diterbitkan tanpa dilampirkan dengan nama saya dan setiap percubaan yang akan dibuat untuk memastikan ketanpanamaan saya. Saya memahami, walaubagaimanapun, ketanpanamaan yang sempurna tidak dapat dijamin. Kemungkinan sesiapa yang menjaga saya di hospital atau saudara dapat mengenali saya.**
- **Bahan yang akan diterbitkan dalam penerbitan mingguan/bulanan/dwibulanan/suku tahunan/dwi tahunan merupakan satu penyebaran yang luas dan tersebar ke seluruh dunia. Kebanyakan penerbitan ini akan tersebar kepada doktor-doktor dan juga bukan doktor termasuk ahli sains dan ahli jurnal.**
- **Bahan tersebut juga akan dilampirkan pada laman web jurnal di seluruh dunia. Sesetengah laman web ini bebas dikunjungi oleh semua orang.**
- **Bahan tersebut juga akan digunakan sebagai penerbitan tempatan dan disampaikan oleh ramai doktor dan ahli sains di seluruh dunia.**
- **Bahan tersebut juga akan digunakan sebagai penerbitan buku oleh penerbit jurnal.**
- **Bahan tersebut tidak akan digunakan untuk pengiklanan ataupun bahan untuk membungkus.**

Saya juga memberi keizinan bahawa bahan tersebut boleh digunakan sebagai penerbitan lain yang diminta oleh penerbit dengan kriteria berikut:

- **Bahan tersebut tidak akan digunakan untuk pengiklanan atau bahan untuk membungkus.**
- **Bahan tersebut tidak akan digunakan di luar konteks – contohnya: Gambar tidak akan digunakan untuk menggambarkan sesuatu artikel yang tidak berkaitan dengan subjek dalam foto tersebut.**

Nama Pesakit **(Dicetak atau Ditaip)**	Nama Singkatan **atau** No. Pesakit

No. Kad Pengenalan Pesakit	**T/tangan Pesakit**	Tarikh **(dd/MM/yy)**

Nama & Tandatangan **Individu yang Mengendalikan Perbincangan Keizinan (Dicetak atau Ditaip)**	Tarikh **(dd/MM/yy)**

Nota: **i) Semua subjek/pesakit yang mengambil bahagian dalam projek penyelidikan ini tidak dilindungi insuran.**

ATTACHMENT B

RESEARCH INFORMATION

Research Title : A STUDY OF SHORT TERM COGNITIVE OUTCOME IN POST CABG PATIENT

Researcher's Name :Dr Azlina Yusuf (MPM: 41921)
Associate Professor Dr Saedah Ali (MPM:31264)
Associate Professor Dr Wan Aasim Wan Adnan (MPM: 22877)

INTRODUCTION

You are invited to take part voluntarily in a research study of short term cognitive function outcomes from the CABG surgery. This study will assess the cognitive function before and after the CABG surgery, in order to determine significance changes and the degree of it, either impairment or improvement of cognitive parameters. Apart from that, it also evaluates and determines the cognitive domain and factors governing it. Before agreeing to participate in this research study, it is important that you read and understand this form. If you participate, you will receive a copy of this form to keep for your records.

Your participation in this study is expected to last up to 1 week after the surgery. Up to 43 patients will be participating in this study.

PURPOSE OF THE STUDY

The purpose of this study are to determine if, during the first one week after CABG surgery, is there any significant reduction of cognitive function comparing to before the operation.Apart from that, this study also interested to determined factors during the operation that might related to cognitive decline after the surgery.

It is possible that information collected during this study will be analyzed by the sponsor in the future to evaluate cognitive function after CABG for other possible uses or other medical or scientific purposes other than those currently proposed.

QUALIFICATION TO PARTICIPATE

The doctor in charge of this study or a member of the study staff has discussed with you the requirements for participation in this study. It is important that you are completely truthful with the doctor and staff about you health history. You should not participate in this study if you do not meet all qualifications.

Some of the requirements to be in this study are:

- **You are planned for Coronary Arterial Bypass Grafting surgery electively.**
- **Your age must be 18 years old and above, and 75 years old and below.**

You cannot participate in this study if:

- **You are planning for Emergency Coronary Arterial Bypass Grafting surgery**
- **You had previous CABG done before**
- **You had history of visual impairment**
- **You had prior stroke with residual deficit**
- **You have significant psychiatric disorder**
- **You are in unstable general**

STUDY PROCEDURES

At your admission day for elective CABG surgery, if you agree to participate in this study, you will have a baseline cognitive function testing with computerized screen-touch battery test. The test will takes time about 30 minutes. In addition, you will be asked to provide information about your medical history, eductional and occupational status.

As you go for the operation on the scheduled date, the standardized anesthesia and surgery will be performed. While during the operation, few data will be recorded includes duration of surgery and anesthesia.

After the operation, you will be managed as normal standardized cardiac surgery patient.

Six to 7 days after the operation, when you are medically stable and have adequate pain control, and ready for discharge to home, your cognitive function will be tested again with the same computerized screen-touch battery test.

RISKS

There may be risks to you if you participate in this study.

Visit before the operation to test your baseline cognitive function might cause disturbance to you, and it might increased the anxiety of the surgery.

In addition to the risk named above, re-test of cognitive function on day six to 7 after the surgery, might also again cause disturbance to you but we will ensure that you are medically optimized and have adequate pain control prior to the assessment.

REPORTING HEALTH EXPERIENCES.

If you have any injury, bad effect, or any other unusual health experience during this study, make sure that you immediately tell the nurse or Dr. Azlina Yusuf [MMA Registration No.41921] **at 09-7676424 or 016-4144989. You can call at anytime, day or night, to report such health experiences.**

PARTICIPATION IN THE STUDY

Your taking part in this study is entirely voluntary. You may refuse to take part in the study or you may stop participation in the study at anytime, without a penalty or loss of benefits to which you are otherwise entitled. Your participation also may be stopped by the study doctor or sponsor without your consent.

POSSIBLE BENEFITS [Benefit to Individual, Community, University]

Study procedures will be provided at no cost to you. You may receive information about your cognitive function from the test to be done in this study. We hope that the outcome and information regarding this research will beneficial to future patients.

QUESTIONS

If you have any question about this study or your rights, please contact;

Dr Azlina Yusuf (MPM: 41921)

Department of Anesthesiology & Intensive Care,

School of Medical Science,

USM Health Campus

09-7676424, 016-4144989

If you have any questions regarding the Ethical Approval, please contact;

Puan Mazlita Zainal Abidin

Secretary of Research Ethics Committee (Human) USM

Clinical Sciences Research Platform, USM Health Campus.

Tel. No. : 09-767 2355 / 09-767 2352

Email : jepem@kk.usm.my

CONFIDENTIALITY

Your medical information will be kept confidential by the study doctor and staff and will not be made publicly available unless disclosure is required by law.

Data obtained from this study that does not identify you individually will be published for knowledge purposes.

Your original medical records may be reviewed by the researcher, the Ethical Review Board for this study, and regulatory authorities for the purpose of verifying clinical trial procedures and/or data. Your medical information may be held and processed on a computer.

By signing this consent form, you authorize the record review, information storage and data transfer described above.

SIGNATURES

To be entered into the study, you or a legal representative must sign and data the signature page [ATTACHMENT S or ATTACHMENT G (for genetic sample only) or ATTACHMENT P]

Patient/Subject Information and Consent Form

(Signature Page)

Research Title: A STUDY OF SHORT TERM COGNITIVE OUTCOME IN POST CABG PATIENT

Researcher's Name: Dr Azlina Yusuf (MPM: 41921)

Associate Professor Dr Saedah Ali (MPM: 31264)

Associate Professor Dr Wan Aasim Wan Adnan (MPM: 22877)

To become a part this study, you or your legal representative must sign this page. By signing this page, I am confirming the following:

- **I have read all of the information in this Patient Information and Consent Form** including any information regarding the risk in this study **and I have had time to think about it.**
- **All of my questions have been answered to my satisfaction.**
- **I voluntarily agree to be part of this research study, to follow the study procedures, and to provide necessary information to the doctor, nurses, or other staff members, as requested.**
- **I may freely choose to stop being a part of this study at anytime.**
- **I have received a copy of this Patient Information and Consent Form to keep for myself.**

Patient Name **(Print or type)**

Patient Initials **and** Number

Patient I.C **No. (New)**

Patient I.C **No. (Old)**

Signature of Patient **or Legal Representative**

Date **(dd/MM/yy)**

(Add time if applicable)

Name of Individual

Conducting Consent Discussion (Print or Type)

Signature of Individual

Conducting Consent Discussion

Date **(dd/MM/yy)**

Name & Signature of Witness

Date **(dd/MM/yy)**

Note: i) **All subject/patients who are involved in this study will not be covered by insurance.**

ATTACHMENT G

Patient/ Subject Information and Consent Form

(Signature Page)

Research Title: A STUDY OF SHORT TERM COGNITIVE OUTCOME IN POST CABG PATIENT

Researcher's Name: Dr Azlina Yusuf (MPM: 41921)

Associate Professor Dr Saedah Ali (MPM:31264)

Associate Professor Dr Wan Aasim Wan Adnan (MPM: 22877)

To become a part this study, you or your legal representative must sign this page. By signing this page, I am confirming the following:

- **I have read all of the information in this Patient Information and Consent Form** including any information regarding the risk in this study **and I have had time to think about it.**
- **All of my questions have been answered to my satisfaction.**
- **I voluntarily agree to be part of this research study, to follow the study procedures, and to provide necessary information to the doctor, nurses, or other staff members, as requested.**
- **I may freely choose to stop being a part of this study at anytime.**
- **I have received a copy of this Patient Information and Consent Form to keep for myself.**

Patient Name **(Print or type)**

Patient Initials **and** Number

Patient I.C **No.** (New)

Patient I.C **No.** (Old)

Signature of patient **or Legal Representative**

Date **(dd/MM/yy)**

(Add time if applicable)

Name of Individual

conducting Consent Discussion (Print or Type)

Signature of Individual

Conducting Consent Discussion

Date **(dd/MM/yy)**

Name & Signature of Witness

Date **(dd/MM/yy)**

Note: i) **All subject/patients who are involved in this study will not be covered by insurance.**

ii) **Excess samples from this research will not be used for other reasons and will be destroyed with the consent from the Research Ethics Committee (Human), USM.**

ATTACHMENT P

Patient's Material Publication Consent Form

Signature Page

Research Title: A STUDY OF SHORT TERM COGNITIVE OUTCOME IN POST CABG PATIENT

Researcher's Name: Dr Azlina Yusuf (MPM: 41921)

Associate Professor Dr Saedah Ali (MPM: 31264)

Associate Professor Dr Wan Aasim Wan Adnan (MPM: 22877)

To become a part this study, you or your legal representative must sign this page.

By signing this page, I am confirming the following:

- **I understood that my name will not appear on the materials published and there has been efforts to make sure that the privacy of my name is kept confidential although the confidentiality is not completely guaranteed due to unexpected circumstances.**
- **I have read the materials or general description of what the material contains and reviewed all photographs and figures in which I am included that could be published.**
- **I have been offered the opportunity to read the manuscript and to see all materials in which I am included, but have waived my right to do so.**
- **All the published materials will be shared among the medical practitioners, scientists and journalist world wide.**
- **The materials will also be used in local publications, book publications and accessed by many local and international doctors world wide.**
- **I hereby agree and allow the materials to be used in other publications required by other publishers with these conditions:**

- **The materials will not be used as advertisement purposes nor as packaging materials.**

- **The materials will not be used out of contex – i.e.: Sample pictures will not be used in an article which is unrelated subject to the picture.**

Patient Name **(Print or type)**	Patient Initials **or** Number

Patient I.C No.	**Patient's Signature**	Date **(dd/MM/yy)**

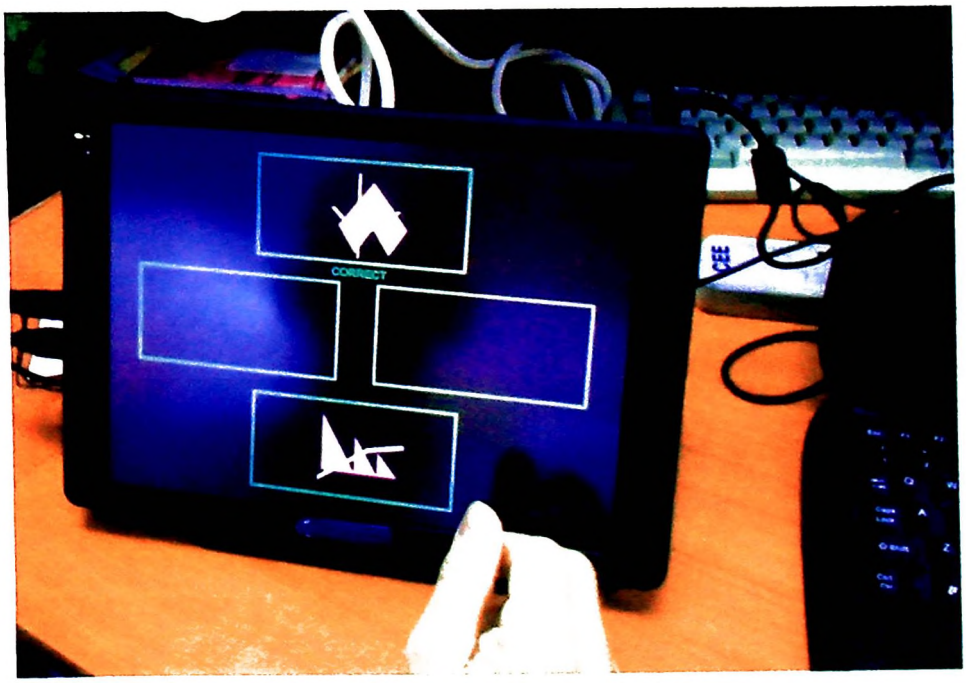
Name and Signature of Individual	Date **(dd/MM/yy)**

Conducting Consent Discussion

Note: i) **All subject/patients who are involved in this study will not be covered by insurance.**

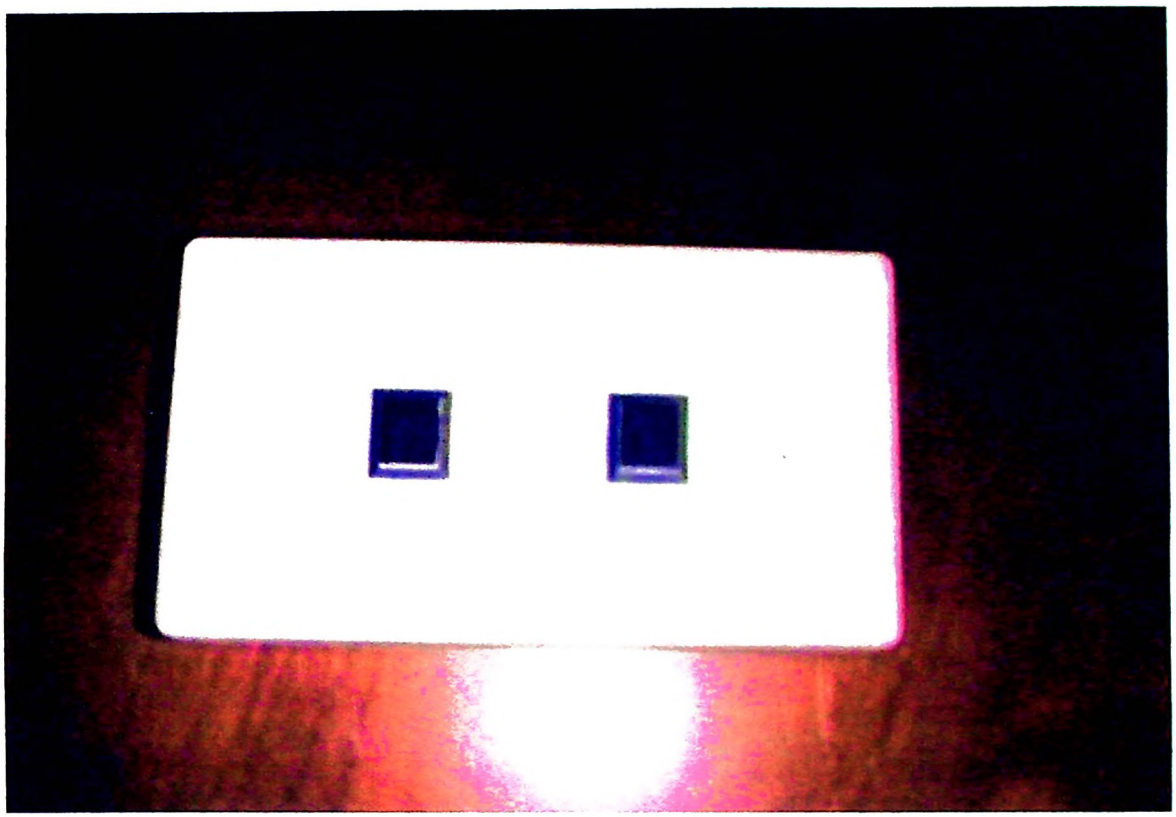
APPENDIX 3

CANTAB® Touch Screen Panel



APPENDIX 4

CANTAB® Press Pad



APPENDIX 5

Bedside Conduct Of CANTAB®