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Objective and subjective neuropsychological impairment and the relationship to depression, in randomized CPB and off-pump patients, following heart surgery

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This thesis entitled:
Objective and subjective neuropsychological impairment and the relationship to depression, in randomized CPB and off-pump patients, following heart surgery

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FRENCH SUMMARY

Les mécanismes impliqués dans la détérioration neuropsychologique suite à une chirurgie cardiaque sont peu connus mais ont été liés à des facteurs associés à la circulation extracorporelle (CEC), une technique utilisée lors du soutien circulatoire (pendant l'arrêt cardiaque) durant le pontage artéro-coronarien par greffe (PACG). Parallèlement, le PACG peut être exécuté sans CEC, en utilisant la technique à cœur battant (CB). Certains considèrent que ceux qui subissent un PACG et qui se plaignent de troubles neuropsychologiques, éprouvent plutôt de la dépression, tout en ayant des fonctions cognitives normales. Aucune étude n'a évalué l'impact du type de chirurgie (CEC ou à CB) sur le déclin neuropsychologique (objectif; subjectif) dans son interaction avec la dépression. Or, si la CEC est associée à la détérioration neuropsychologique suite à la chirurgie, la relation devrait être significativement plus forte entre les rapports cognitifs subjectifs et la performance cognitive objective dans le groupe à CEC. Conséquemment, l'influence de la dépression pourrait être plus importante chez ces patients du groupe à CB qui rapportent des troubles neuropsychologiques. Soixante-quatorze patients ont été distribués au hasard dans le groupe de CEC ou CB. Soixante-deux patients ont complété dix questionnaires (neuropsychologiques [objectifs, subjectif]; dépression) avant et 4 mois après la chirurgie. Certains tests neuropsychologiques ont enregistré des améliorations dans les deux groupes (RAVLT : $p=0.00031$, $p<0.0001$) ou uniquement dans le groupe à CB (Similarités : $p=0.0012$). Un déclin a été enregistré dans le groupe de CEC seulement, sans changement significatif entre les groupes (Grooved Pegboard:

p=0.0473). Aucune relation a été enregistrée entre le type de chirurgie et le déclin neuropsychologique (p=0.9999) suite à la chirurgie. Les patients dépressifs rapportent plus de plaintes de déclin neuropsychologique (p=0.0416) que les non-dépressifs. Parmi ceux qui rapportent une détérioration neuropsychologique plus importante, aucune relation a été enregistrée entre le déclin neuropsychologique et le type de chirurgie (p=1.000) et le niveau de dépression était similaire dans les deux groupes (p = 0.7207). Ces résultats suggèrent que la CEC n'est pas la cause majeure du déclin neuropsychologique suite à la chirurgie à PACG et que l'humeur peut favoriser l'autoévaluation positive de l'état de santé de l'individu.

Mots clés : Pontage artéro-coronarien – Dépression – Neuropsychologique – Objectif - Subjectif – Circulation Extracorporelle – Cœur Battant

ENGLISH SUMMARY

The mechanisms of postoperative neuropsychological (NP) impairment following heart surgery are poorly understood but have been linked to factors associated with Cardiopulmonary Bypass (CPB), a technique used to support the circulation while the heart is arrested for Coronary Artery Bypass Grafting (CABG). Alternatively, CABG can be performed without CPB, with the heart beating (off-pump technique). There is some evidence that post CABG patients that report NP disturbances are actually suffering from mood disorders such as depression instead of cognitive dysfunction. To date, no studies have evaluated the impact of the type of surgery (off-pump; on-pump) on NP decline (objective testing and subjective reporting) as it relates to depression. Moreover, if the CPB component of CABG is linked to NP decline, there should be a stronger relationship between subjective cognitive reporting and objective cognitive performance in the CPB group versus off-pump patients. Consequently, the impact of depression could be stronger in those off-pump patients that subjectively report a cognitive decline. A total of 74 patients were randomized into the CPB or off-pump group. Sixty-two patients completed both baseline and post-surgical testing trials (4 months after surgery). Eight neuropsychological tests, a depression scale, and a subjective test of neuropsychological outcome were administered to patients. Some improvements were recorded for RAVLT in both groups (B.H.: $p=0.0031$; CPB: $p < 0.0001$). Improvements in Similarities scores were significantly higher in the beating heart group only (B.H.: $p=0.0012$). Grooved pegboard scores decreased significantly in the CPB group ($p=0.0473$) with no change in the off-

pump group. Overall, there was no relationship between surgery type and NP impairment (p=0.9999). Post-operative depressed patients tended to subjectively report greater NP deterioration than non-depressed patients (p=0.0416). Amongst patients who reported the highest degree of NP impairment, there were no differences in NP impairment with respect to treatment type (p=1.000) and depression was similar in both treatment groups (p=0.7207). These results suggest that CPB may not be the major cause of NP impairment after CABG surgery. This research also suggests that a patient's mood may be an important variable that impacts the self-appraisal of the individuals' health status.

Keywords: - Cardiopulmonary – Coronary Artery Bypass Graft - Depression – Objective – Subjective -Neuropsychological Impairment

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LIST OF INITIALS AND ABBREVIATIONS

AD:	Alzheimer Dementia
BD:	Weschler Block Design Test
BDI:	Beck Depression Inventory
CABG:	Coronary Artery Bypass Grafting
CAD:	Coronary Artery Disease
CB:	*Coeur Battant*
CEC:	*Circulation Extracorporelle*
CFQ:	Cognitive Failure Questionnaire
CNS:	Central Nervous System
COWA:	Controlled Oral Word Association
CPB:	Cardiopulmonary Bypass
CVA:	Cerebro-Vascular Accident
CVLT:	California Verbal Learning Test
DV:	Dependant Variable
FAS:	Controlled Oral Word Association
	(F-A-S: Letters used in test)
ICU:	Intensive Care Unit
IRB:	Internal Review Board
IV:	Independent Variable
OPCAB:	Off-Pump Coronary Artery Bypass
MI:	Myocardial Infarction
NP:	Neuropsychological

PACG:	*Pontage Artéro-Coronarien par Greffe*
PNS:	Peripheral Nervous System
RAVLT:	Rey Auditory Verbal Learning Test
S:	Weschler Similarities
SAS:	Statistical Analysis System
SF-36:	Short-Form 36 item Health Survey
SDMT:	Symbol Digit Modalities Test
SRQ:	Self-Report Questionnaire
STS:	Society for Thoracic Surgery
WAIS-R:	Weschler Adult Intelligence Scale – Revised
WIS:	Weschler Intelligence Scale
WSP:	Weschler Digit Span

THE DEDICATION

This work is dedicated to the St-Michael's Hospital patients.

Without you this could not be.

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To dad, where ever you may be. Affectionately, thank you. You would have loved it.

LITTERATURE REVIEW

CABG – An overview and introduction

CABG is a surgical procedure offered to patients with coronary artery disease (CAD) to relieve angina, prevent heart attack (MI), and ultimately prolong life. The number of patients undergoing CABG has risen dramatically in recent years, making this the most commonly performed major surgical procedure with 650 000/year in the USA alone and 800 000 procedures worldwide per year. The success and widespread use of CABG is in part attributed to recent advances in cardiac surgery which has allowed a reduction in the risk of mortality and morbidity associated with the procedure (Haddock & al, 2003; Knipp & al, 2004; Murkin & al, 1999; Selnes & al, 1999; Symes & al, 2000).

Over the past 30 years, advances in surgical, anesthetic, and medical (perioperative) management have together improved surgical outcomes despite offering the operation to older and sicker patients (Khatri & al, 1999; Charlson & Isom, 2003). Advanced age appears to place patients at increased risk for cognitive decline, especially in those patients over 70 years of age (Mackensen & Gelb, 2004; Newman, & al, 1993; Symes & al, 2000; Townes & al, 1989; Tuman & al 1992). This may be related to occult cerebrovascular disease and/or microemboli, debris that can temporarily occlude intracranial vessels (Blauth & al, 1992; Newman & al, 1994; Stump & al 1992).

Populations of CABG patients also appear to be changing, which makes comparisons between studies difficult. Since 1974 the average age of patients undergoing CABG has increased from 52 years to 65 years of age in 1996. This trend is a reflection of the aging population and improvements in surgical technique and perioperative patient management that allow safer operations in older patients. Indeed, the situation is paradoxical; older patients benefit most from surgery as they are more likely to have advanced coronary artery disease, yet as a population they are at the greatest risk of postoperative morbidity and mortality. This larger risk is related to older patients being more likely to present with a greater number of comorbid risk factors, such as diabetes, hypertension and cerebrovascular disease (Symes & al, 2000).

With decreasing CABG related mortality over the years, the focus has shifted to morbidity, in an effort to improve quality of life outcomes. One such major morbidity following CABG is central nervous system (CNS) dysfunction. Of all of the adverse perioperative neurological outcomes, stroke is the most serious. Fortunately, due to technological and surgical improvements, the incidence of stroke is now reported to be as low as between 0.4% and 5.8% (Knipp & al, 2004; McKhann & al, 1997; Symes & al, 2000).

Consequently, the rate of post-CABG stroke being low, it is no longer sufficient as the sole index of CNS dysfunction. The focus has now shifted to neuropsychological (NP) impairment. Studies suggest that a considerable

proportion of all patients who undergo CABG sustain some degree of cerebral damage that manifests as mild cognitive impairment. In deed, as there is now a low risk of stroke following CABG, milder forms of cerebral damage have become a greater focus of concern. As a result, NP assessment has become more important within the domain of cardiac surgery. It is these less severe forms of neurologic injury which are now targeted for reduction in what has been described as an age of quality improvement (Stump & al, 1996; Symes & al, 2000).

NP tests are valuable tools in the assessment of brain dysfunction as they provide a method of systematically and quantitatively studying the behavioral expressions of this dysfunction (Lezac, 1995). The advantage of NP tests is that they are capable of detecting subtle changes in cognitive function (Symes, 2000). The neuropsychological effects of CABG surgery must be evaluated against a background of continuously changing surgical techniques, such as variations on the use of hypothermia, reductions in bypass time and considerable changes in equipment, all which have led to a reduction in morbidity following CABG, and specifically, a reduction in neuropsychological changes over time (Newman, 1989).

Although the cause of cognitive decline after CABG is likely multifactorial, two processes appear to be preferentially involved. The first process centers around the suggestion that cerebral damage arises as a consequence of

inadequate cerebral perfusion (insufficient blood flow to the brain) during surgery which leads, in turn, to ischaemic cell injury (insufficient blood flow to the cell). This may occur for a number of reasons, such as cerebrovascular occlusive disease (blocked vessels), hypotension (low blood pressure) or as a result of the incorrect placement of the aortic cannula (surgical tube bringing oxygenated blood from the heart lung machine back to the patient) such that blood flow up the blood vessels to the brain is suboptimal. The second process that has been identified as a possible cause of postoperative cerebral damage is linked to the accumulation of microemboli in the small blood vessels in the brain, thus impeding blood flow in these vessels. Air microemboli may be formed when air bubbles or particulate debris, generated by the CPB (Cardiopulmonary Bypass) machine becomes trapped in the blood (Ahonen & Salmenpara, 2004; Gillinov & al, 1991; Harris, 1993; Symes, 2000; Taggart & al, 1999; Taylor, 1993).

Incidentally, cognitive impairment also occurs after non-cardiac operations but is reported to be more frequent and severe after cardiac operations with CPB. Cognitive impairment after non-cardiac operations is usually due to patient-related factors (e.g. advanced age, ill health), whereas impairment that occurs after cardiac operations may be attributed to CPB (Hammeke, 1988; Smith, 1988; Treasure, 1989; Vingerhoets, 1997). The International Study of Postoperative Cognitive Dysfunction found that 26% of patients older than 60 years who underwent major abdominal or orthopedic surgery had cognitive

dysfunction one week after surgery. Major risk factors included older age, increased duration of anesthesia, and postoperative respiratory and infectious complications. In deed, age was a risk factor for persistent cognitive dysfunction: at 3 months, 14% of patients aged 70 years or older had cognitive impairment. Furthermore, CABG patients typically have extensive atherosclerosis (build-up of plaque in the inner lining of the artery) in multiple vascular systems and even "benign" invasive procedures in this population routinely produce detectable microemboli in the cerebral circulation (Mark & Newman, 2002)

In recent years, direct myocardial revascularization without CPB (off-pump operation), which reduces the surgical invasiveness, has gained interest (Bennetti, 1991; Calafiore, 1998; Diegeler, 1997). Coronary artery bypass graft (CABG) surgery was initially utilized without the use of cardiopulmonary bypass (CPB) or the "heart-lung machine" in the 1960's. However, following the advent and acceptance of CPB in association with the development of methods of myocardial protection (protection of the muscle wall of the heart), the on-pump (with CPB) technique was adopted instead, as it allowed operation on a non beating still heart. Forty years later, the off-pump technique is being resurrected due to new technological developments (that allow stabilization of a beating heart) and increasing scientific evidence that CPB is an independent risk factor for end organ injury, particularly brain injury, following heart surgery (Stump & al, 2001).

This off-pump procedure, which now accounts for over 20% of all CABG surgery performed in the United State and expected to reach 50% in 2005, has many associated benefits including reduced cost, reduced post-operative bleeding and a quicker recovery in comparison to patients undergoing traditional bypass surgery with CPB (Ascione & al, 1999; Calafiore & al, 1999; Cartier & al, 1999; Gu & al, 1998; King & al, 1997; Mack & al, 2001; Pfister & al, 1992; Puskas & al, 1998; Zenati & al, 1997). In the off-pump coronary artery bypass procedure, surgery is performed with the use of instruments to stabilize the coronary artery and surrounding surgical field. The heart continues to beat and the lungs continue to function throughout the operation, thus obviating the need for CPB (Stump & al, 2001). Since off-pump surgery is performed on the beating heart, CPB-related problems such as NP dysfunctions associated with microemboli formation or low blood flow to the brain should be reduced (Diegeler, 2000). Neurocognitive testing has an established role in assessing cardiac surgery outcomes, particularly in procedures where CPB is utilized to perform the operation. Such assessments have been in regular use since the 1960's and, through highlighting the presence of possible postoperative cerebral dysfunction, have contributed to the improvement of surgical techniques over this period (Slade & al, 2001).

There is increasing evidence pointing to an early deterioration in neuropsychological function after CPB (BhaskerRao & al, 1998; Borger & al,

2001; Carella & al, 1988; Chabot & al, 1997; Manspeizer & al, 2000; Mills & Prough, 1991; Pugsley & al, 1994; Selnes, 1999; Stump, 1999; Sylviris & al, 1998; Symes & al, 2000; van Dijk & al, 2000). These studies built on earlier research conducted by Shaw & al (1986) and Savageau & al (1982) which were the first studies to use both a comprehensive neurological and neuropsychological approach in the assessment of post-operative change (Lewis & al, 2004).

CABG and neuropsychological decline

As a part of a prospective study of neurological and psychological complications of CABG surgery, Shaw & al (1986) tested 298 patients before and after the operation using a battery of 10 standard psychometric tests. The main objective of these authors was to report on the early neuropsychological dysfunction one week following the operation. Two hundred and thirty-five patients (79% of the cohort) showed impairment in some aspect of cognitive function at the seventh day after the operation. Sixty-three patients (21%) showed no deterioration from levels before the operation in any of the 10 test scores. The authors also report that 123 of the patients whose scores deteriorated had no symptoms while in hospital. Twenty-three patients were considered by the authors to be overtly disabled by their intellectual functions during the period soon after surgery. The authors had concluded in their study that there was a high incidence of early cerebral impairment detectable by psychometric testing following coronary artery bypass graft surgery. However, they also added that often this was not of sufficient severity to cause serious concern to the patients or to interfere with their everyday activities in the hospital environment.

Savageau & al (1982), in their study of 245 patients, performed neuropsychological testing before, immediately following as well as 6 months after surgery. Although 28% of this group showed a deterioration in one or

more tests scores at the postoperative (ninth day) examinations as compared to their pre-operative scores, over 80% of these patients had returned to normal range by 6 months. Only 5% of patients showed consistent postoperative test scores deterioration both at 9 days and 6 months. The authors proposed that it seemed inappropriate to attribute these latter dysfunctions to the surgical episode per se. They offered rather that these findings underscored the need for further investigation of neuropsychological dysfunction following cardiac operations before interpreting the presence or absence of residual neuropsychological problems. Following these studies, several other investigations have examined NP outcome post CABG. The various studies that examine neuropsychological performance within one year following CABG are detailed below.

Lloyd & al (2000) conducted a prospective randomized trial in which the assessors of the outcome measures were blind to the treatment received. In this study, 60 patients without known neurological abnormalities undergoing coronary revascularization were prospectively randomized to 1 of 2 groups: 1) CPB (on-pump) or 2) Beating heart surgery (off-pump). NP performance was assessed pre-operatively and 12 weeks after the operation. The 2 groups had similar preoperative characteristics. No significant differences between the 2 groups (12 weeks post-operation) in the measure of NP outcome were reported. According to the authors, these results may support the hypothesis that in carefully selected, relatively young patients undergoing elective

operations with no previous history of neurological injury, modern CPB may cause a temporary functional, rather than long-term (12 weeks), detectable NP deterioration. The small study size raises caution on the interpretation of these results. Moreover, Diegeler & al (2000) in their study of a smaller sample group of 40 patients randomized in 2 surgical groups (on and off-pump procedures) have found that postoperative cognitive testing showed significant postoperative impairment in the CPB group when compared to the beating heart group. In contrast, Rankin & al (2003) in their study of NP performance of 34 randomized patients undergoing off-pump and CPB CABG found no NP change at 2.5 months postoperatively in either group.

For their part, Baker and his colleagues (2001) have studied NP outcome in patients up to 6 months post CABG. Elective patients requiring CABG surgery were randomized to receive either conventional CABG with CPB (14 patients) or off-pump surgery (12 patients). NP assessments (10 measures) were performed in the week prior to surgery, one week, and six months after surgery. NP test selection includes measures of memory, attention, and psychomotor speed. At the seven-day assessment there were no differences between the groups in the incidence of deficits on each NP measure. Similarly, there were no differences between the patients in each group when the number of tests per patient (displaying a deficit) was examined. The tests most susceptible to deficits in the CPB group were Pegs R, Trail Making B, and Digit Symbol Substitution. On the other hand, the most susceptible tests for

the off-pump group were verbal memory (CVLT Total, Long Free and Long Cued) and also Digit Symbol.

By avoiding CPB, the authors had initially anticipated that resultant NP dysfunction would be lessened. In fact, they state that their lack of expected findings were dissimilar to an earlier report (Murkin & al, 1999) from a non-randomized study which was highly suggestive of a substantial beneficial effect associated with surgery that avoided CPB (this study is detailed below). The authors therefore cite the small number of patients that were investigated (insufficient sample size) and possibly different lengths of CPB times as possible explanations for these results. However, the pattern of deficits found in each group does show some differences. At the initial postoperative assessment (1 week), the patients in the CPB group demonstrated a susceptibility to deficits in the cognitive domains of motor speed and dexterity, attention and visual-motor speed. Conversely in the off-pump group, the domain of verbal memory appeared to be most susceptible to early deficits.

The inability to demonstrate any difference in the number of NP deficits between the on-pump and off-pump groups may also be a function of the low number of bypass grafts (conduits used to route blood around the blockage in the diseased artery) performed in each group (mean number of grafts was 2.5 and 2.0), and thus shorter exposure to CPB in the on-pump group (mean CPB time 35.6 min.) because of less grafts. These findings support a previous study

by Andrew & al (1998) which demonstrated no clear NP benefit of off-pump surgery when compared to on-pump group when only a single graft was required; however, significant benefits were evident when the off-pump group was compared with patients with CPB undergoing multiple-grafts surgery, thus a longer time on CPB.

As declared earlier, Murkin & al (1999) reported on the results of 35 patients who underwent beating heart CABG as compared to 33 patients who received conventional CABG with CPB. There were no significant differences in age (61.8 vs. 57.7 years), weight (84 vs. 82 kg), or male/female ratios (25/8 vs. 30/5) between CABG and beating heart surgery patients respectively. They employed a battery of nine NP tests preoperatively, at 5 days and 3 months postoperatively. Cognitive tests included measures of verbal learning and memory, Rey Auditory Verbal Learning Test; visual memory, Benton Visual Retention Test; psychomotor speed and visual concept tracking, Trail Making Tests A and B; manual motor dexterity, Grooved Pegboard; executive functioning, Cowa Word Generation Test; as well as two measures of emotional functioning, State Trait Anxiety Inventory and Geriatric Depression Scale. A 20% decrease in change score, defined as the difference between preoperative and postoperative test scores, on 20% or more of tests was defined as "cognitive dysfunction".

Beating heart surgery patients demonstrated a significantly lower incidence of cognitive dysfunction at 5 days (66% vs. 90% respectively) and 3 months postoperatively (5% vs. 50% respectively) compared with conventional CABG surgery patients. Despite the small number of patients involved, the study seems to suggest that beating heart CABG may have a role in preventing, or at least reducing, the postoperative NP decline experienced by patients undergoing coronary revascularization for up to 3 months after CABG surgery (Ricci & Salerno, 2001). Both Manspeizer & al (2000) and Schmitz & al (2003) found similar results in their respective investigation as the Murkin & al (1999) study; neurocognitive dysfunction was reported to be significantly lower, up to 3 months postoperatively, than that of the conventional group. As well, Kilo & al (2001) found, in their study of 308 consecutive, unselected CABG patients, that the use of cardiopulmonary bypass was the only independent predictor of impaired cognitive brain function at 7-day and 4-month follow-up.

Taggart & al (1999), in their research of post-surgical NP outcome, reported on 25 patients undergoing CABG without CPB which in turn were matched with 50 patients undoing CABG grafting with CPB. There was no randomization of patients, nor was the examiner blind to the regimen of the patient. Each patient was submitted to a battery of 10 standard tests of NP function before surgery, at discharge and at 3 months after surgery. At discharge, most NP tests had deteriorated in both CPB and off-pump groups. In both groups, 4 tests had deteriorated significantly and an additional test result (delayed recall)

had worsened significantly in the CPB group only. At 3 months, all but one test (visual search) in the CPB group had returned to or exceeded baseline performance.

Although the absence of improvements in any test on repeated examination might in itself represent some degree of impairment, this should apply to both groups and therefore would not invalidate the comparison between the groups. Also, considering that the group without CPB also had less severe coronary artery disease and shorter operating times make these observations more striking. The lack of randomization and a small study size combined with the fact the examiner was not blinded to the experiment makes it difficult to draw founded conclusions. The authors strongly stipulate that the similar patterns of early decline and late recovery of cognitive function in patients undergoing CABG on and off-pump and the lack of significant difference between the absolute or change scores between the groups on any of the tests suggests that CPB is not the major cause of post-operative cognitive impairment. Other studies have found similar results (Knipp & al, 2004; Townes & al, 1989; Wimmer-Greinecker & al, 1998).

Bruggemans & al (1995) have attempted to correct some of the methodological problems associated with studying the NP functioning following CPB. They focused on the learning effects (repeated measuring) as well as distress to test performance. These confounding variables were controlled by

including the spouse of the patient who is presumably exposed to the same potential stressors associated with the operation (test procedures, hospital stay, etc.). The NP tests were administered 2 weeks preoperatively and 1 week, 1 month, and 6 months postoperatively. Each patient was then compared with his or her spouse at each postoperative interval, and the group as a whole was compared with the spouse control group as a whole at each postoperative interval (Slade & al, 2001). For recent memory, patients' scores showed a significant deterioration at one month after CABG surgery compared with the scores of spouses. The effect had not disappeared at 6 months postoperatively. Psychomotor speed and verbal fluency deteriorated significantly at one week postoperatively with incomplete recovery at 6 months.

In recent years, Fearn & al (2001) have also attempted to include a control group (elderly urologic patients undergoing general anesthesia without CPB) in their study of cerebral injury and cognitive deficits after cardiac surgery (CABG patients with CPB). Although the 2 groups are dissimilar in sample size and mean age of patients (mean age in the control group for the 19 patients was 74; mean age in the study group for the 70 patients was 60), the results are comparable to the above mentioned Bruggemans & al (1995) study in that cognitive deficits were still present up to 6 months after heart surgery.

Several studies have also evaluated the long-term (defined in this study as one to five years) NP deficits when utilizing CPB and have found the CPB patients at an increased susceptibility of an affected NP performance. A number of those studies assess the NP parameters by studying CPB patients only (without comparing this technique to the off-pump); some of the studies were conducted before this recent trend to perform off-pump surgery (mid nineties). It was not until recently that, as a result of the wide popularization of beating heart CABG, the interest of many investigators has shifted toward this new approach to coronary surgery, in an attempt to objectively disclose the real advantages and disadvantages of avoiding CPB during CABG operations (Ricci & Salerno, 2001). Thus, the long-term post-surgical NP outcome is explored in the following studies.

In 1989 Willner & Rodewald examined 66 patients undergoing coronary artery bypass surgery with a mean age of 55 years. This study was conducted to consider whether the neuropsychological deficits observed at 8 weeks after surgery persisted up to 12 months after surgery. This investigation found that NP deficits endure up to 12 months following heart surgery. However, in this research, an analysis of the bypass time between those patients showing deficits at 12 months and those without, indicated a significantly longer bypass in the group with neuropsychological deficits. In addition, the duration of the operation was found to be longer in those patients with deficits. The authors also found in their study that patients with NP impairment were significantly

older than those without deficits. This study contrasts with an additional prospective investigation of 135 patients who underwent CABG and received a comprehensive neuropsychological assessment 2 weeks before the operation and 3, 12 and 24 months after the operation (Klonoff & al, 1989). In their research, no discernable neuropsychological impairments were found after the operation. Most patients returned to their preoperative status 3 months after bypass surgery. Further improvements were found 12 and 24 months after the operation.

A recent study by Van Dijk & al (2002) examined a randomized population of patients into one of two groups, off-pump (n=142) and on-pump surgery (n=139). In this study, cognitive dysfunction was determined by a standard battery of 10 neuropsychological tests (Rey Auditory Verbal Learning; Grooved Pegboard; Trail Making Tests Part A and B; Sternberg Memory Comparison; Line Orientation Test; Stroop Color Word Test; Continuous Performance Task; Self-ordering Tasks; Visuo-spatial Working Memory; Symbol Digit Modalities Test) administered before and after surgery by psychologists blinded to the patients' treatment assignment. Patients who received their first CABG surgery without CPB had improved cognitive outcomes 3 months after the procedure. However, effects were limited and became negligible at 12 months.

The authors have explained these limited results at 1 year in part by a relatively young group of patients (mean, 61 years) with less advanced

coronary artery disease and with limited comorbidity. Patients in the trial were at substantially lower risk for complications in general and for cognitive dysfunction in particular than the patients routinely undergoing OPCAB (off-pump coronary artery bypass) in the United States. For example, comparing the study cohort with the Society for Thoracic Surgery (STS) Registry cohort of OPCAB reveals that the trial patients averaged 5 years younger than the STS patients, had less advanced coronary artery disease, and had less extra-coronary vascular disease. If a more representative group had been studied, the incidence of cognitive dysfunction would likely have been significantly higher than the 29% observed at 3 months and the power of the study to detect a benefit of OPCAB would have been enhanced (Mark & Newman, 2002). However, Lee & al (2003) reported on the cognitive outcome of 60 randomized patients (on and off-pump) tested before the operation as well as 2 weeks and 1 year after surgery. Using the same categorical definition of cognitive decline as a 20% decline in 20% of neurocognitive tests performed, they found that off-pump patients performed better on the Rey Auditory Verbal Learning Test at both 2 weeks and 1 year post surgery, whereas on-pump performance was statistically unchanged for all cognitive measures. The authors interpreted this lack of improved performance over time, in the on-pump group, as a relative cognitive decline or deficit in the ability to learn this test and concluded that off-pump surgery may be less injurious to cognitive function than CPB.

Selnes and his colleagues (2001) have presented longitudinal results in order to determine the long-term (preoperative to 5 years postoperative) and late (1-5 years postoperative) changes in cognitive tests performance in patients after CABG. A group of 102 patients (originally 172) completed preoperative and follow-up cognitive testing (all patients underwent CPB; no control group was utilized). A battery of NP tests assessing 8 cognitive domains were administered: 1) verbal memory: Rey Auditory Verbal Learning Test; 2) visual memory: Rey Complex Figure (delayed recall) and Symbol Digit (paired recall); 3) language: Boston Naming Test; 4) attention: Digit Span (forward and backward); 5) visuo-construction: Rey Complex Figure; 6) psychomotor speed: Symbol Digit and written alphabet; 7) motor speed: Grooved Pegboard (dominant and non-dominant hand); and 8) executive function: Stroop Test. The Center for Epidemiologic Studies Depression Scale, a 20-item self-report questionnaire was administered as a screening instrument for depression.

The results of the study show that cognitive test performance between the baseline (preoperatively) and 5 years (postoperatively) has a 2-stage course. Except for visuo-construction, performance from baseline to 1 year tended to improve for most cognitive domains. By contrast, from 1 year to 5 years, performance declined for most cognitive domains. Thus, when comparing preoperative scores (baseline) and 5 year follow-up, the 2 domains for which performance at 5 years were significantly worse than that at baseline, were visuo-construction and psychomotor speed.

It has been suggested that for CABG candidates, cognitive function at baseline might be impaired because of long-standing cardiac disease (Vingerhoets & al, 1997), so that postoperative improvements in test scores might reflect a true improvement in cognitive function, perhaps as a consequence of improved cardiovascular functioning. In this study, patients with lower baseline scores tended to improve more between baseline and 1 year. However, it was not determined if this improvement could reflect true progress in cognitive function, as opposed to practice effect or even regression toward the mean.

In the absence of a control group, a specific causal relation between CABG and late cognitive decline cannot be established. There is nevertheless some indirect evidence of a possible link between late cognitive decline and CABG. When scores at 5 years were compared with performance at baseline, one of the cognitive domains with significant decline was visuo-construction. There is some indication that the changes observed in visuo-construction after CABG may not be coincidental. A common neuro-anatonomical correlate of visuo-constructional deficits includes the posterior parietal regions of the cerebral hemispheres (Brazis & al, 1990). This is also an area of the brain that is believed to be particularly vulnerable during or after cardiac surgery. For example, Barbut and his colleagues (1998) reported that 53% of patients who had strokes after cardiac surgery had infarts in the posterior parietal region.

As outlined earlier, the mechanisms by which CPB might cause brain injury are generally believed to be related to hypo-perfusion, microemboli, or both, but there is no obvious link between any of these mechanisms and a progressive or delayed decline in specific cognitive domains. However, it has been suggested that hypo-perfusion followed by re-perfusion during CPB surgery may initiate in some patients a cascade of events that subsequently lead to the development of neuronal injury (Edmunds, 1997).

Interpretation of the findings of this study is limited by several factors, including the lack of availability for follow-up of some patients during the 5 year study period. The educational level of subjects who did not complete follow-up testing was lower than that of subjects who completed the follow-up. Therefore the results of the study may have been biased by selective attrition of subjects with the lowest cognitive performance at baseline. Further longitudinal studies with control groups are also needed to determine whether the observed late changes in cognitive test scores are the result of normal aging in a population with cardiovascular risk factors, of the CPB operation itself, or of some combination of these and other factors.

Newman & al (2001) studied the course of cognitive change up to five years following CABG with emphasis on the effects of postoperative decline on long-term cognitive function. NP tests were performed preoperatively (baseline), before discharge, at six weeks, six months, and five years after CABG surgery

on 261 patients (all patients underwent CPB). Assessments were performed using a well-validated battery of five NP tests (Benton Revised Visual Retention Test; Digit Span (WAIS-R); Digit Symbol (WAIS-R); Randt Memory Test; Trail Making Test). Cognitive decline was evident in 53 percent of the patients at discharge; the incidence decreased to 36 percent at six weeks and 24 percent at six months. Despite this early improvement, at five years the incidence of cognitive decline was 42 percent (i.e. late decline). Whereas the cognitive function of patients without NP impairment at discharge remained above the baseline level five years after surgery, patients who had impairment at discharge showed a marked decline from baseline function five years later. This study, like most other studies of cognitive outcomes after CABG, did not include a control group thus opening up other possibilities of late decline such as the effect of aging on the brain (Selnes & McKhann, 2001). It does however suggest that patients who experience immediate cognitive decline (approximately 50 percent of the CABG surgery patient population) are at increased risk for long-term cognitive impairment and a reduced level of overall cognitive function. As well, patients in this study were operated on from 1989 to 1993, with a different standard of care specific for that period, thus limiting extrapolation to patients undergoing CABG with current techniques.

Some critics of the Newman & al (2001) study, namely Taggart & al, 2001, have stated that there is substantial evidence that postoperative cognitive decline is not unique to cardiac surgery but is also common after other forms

of major surgery. The authors also stipulate that they have documented a similar pattern of cognitive decline and recovery in patients undergoing coronary surgery with and without CPB and suggested that stress of anesthesia and surgery in general must also play a substantial role. Newman & Blumenthal (2001) have replied based on the International Study of Post-Operative Cognitive Dysfunction (Biomed European concerted action program [in European countries and in the USA] involving 1218 elderly patients who have undergone an operation under general anesthesia) and commented that although neurocognitive decline does occur following other major surgeries, the impairments take place at a much lower rate than that associated with cardiac surgery (Moller & al, 1998). They do not rule out the role of general anesthesia and overall surgical stress in neurocognitive dysfunction. Nevertheless, they affirm that their study clearly illustrates a correlation between early postsurgical neurocognitive decline and late neurocognitive deterioration.

Furthermore, Ricci & Salerno (2001) stipulate that this above mentioned investigation demonstrates that conventional CABG performed on CPB is associated with a substantial risk of protracted neurobehavioral decline, the magnitude of which is significantly greater than that observed in the age-matched general population. Contrary to what was hypothesized, in the vast majority of patients such decline does not appear to be either transient or

reversible, since as many as 42% of the patients still displayed significant cognitive deficits at five years from the operation.

A recent longitudinal study of cognitive function also investigated cognitive change 5 years after coronary artery bypass surgery. Stygall & al (2003) examined NP performance on 107 participants using 11 tests, preoperatively and 6 days, 8 weeks, and 5 years after surgery. The overall NP change score declined at 6 days, showed some recovery at 8 weeks, and declined again at 5 years. An increased number of microemboli recorded during surgery, NP deterioration in the days following CABG, and degree of recovery between 6 days and 8 weeks were identified as predictors of change in NP outcome at 5 years following CABG. This suggests that even over a 5-year period, operative damage is detectable. By comparison, the participants in the Newman (2001) study were divided into those who showed a decline 6 days after surgery and those who did not. Cognitive decline was defined as a drop of at least one standard deviation in one of the four factors determined by factor analysis of the NP battery and by change in a composite NP index. At 5 years the group that showed a decline at 6 days continued to show a poorer NP performance. Change in the composite NP index was predicted by, among others, older age, less education, and the extent of NP decline at 6 days. Selnes & al (2001) used change scores between baseline and 5 years and found statistically different changes in two of eight cognitive domains. In both of these studies, limited assessments were made of the surgical procedures and of the occurrence of

microemboli, often considered the major determinant of NP changes after CABG.

In this study, each test score was treated as an outcome, and factor analysis (Newman & al, 2001) or conceptually defined constructs of domains (Selnes & al, 2001) were not applied to the data. The NP tests were individually examined. In two of the tests there was a small improvement at 5 years, whereas all other tests showed a decline. The variety of cognitive functions reflected in the tests that showed decline at 5 years suggests that many NP functions are vulnerable following CABG. This study also suggests that microemboli in CABG are important in relation to cognitive change even over a 5-year period after the operation; alternatively this decline may reflect a more general disease process that evolves over the intervening 5 years.

As seen above, numerous studies have made attempts to quantify cognitive changes associated with the use of cardiopulmonary bypass, but only a few studies in recent years have incorporated a control group, and even fewer have included a control group in the measure of long-term neurocognitive deficits. Zimpfer and associates (2004) studied neurophysiologic and cognitive changes in a group of patients undergoing coronary artery bypass grafting (CABG) surgery with those of a control group of inpatients on the internal medicine service. After CABG, neurocognitive function was serially reevaluated at 7-day (n = 104), 4 months (n = 100), and 3-year follow-up (n = 88).

Neurocognitive function was objectively measured by means of cognitive P300 evoked potentials (activation of a widespread network of cortical structures, including association areas in the parietal, temporal and prefrontal cortex and the hippocampus) and with standard psychometric testing.

They conclude largely on the basis of the P300 evoked potential changes, that the CABG patients have persistent neurocognitive impairment when retested at 7 days, 4 months, and 3 years post-surgery. According to Selnes (2004) the interpretation of these long-term evoked potential changes after CABG (and those of previous other studies involving traditional cognitive outcome measures) requires caution, because of the "decline" seen at 3 years this may not necessarily be directly or causally related to the use of cardiopulmonary bypass itself. It is possible that the 3-year changes reflect new events in the brain secondary to progression of underlying cerebrovascular disease. Alternatively, other studies using magnetic resonance imaging have documented that new silent lesions may occur in as many as one third of patients between 3 and 12 months after bypass surgery. A notable limitation of this study is that the present data is only valid for highly selected elective low risk patients undergoing coronary artery bypass grafting and cannot be extrapolated to the standard population of patients undergoing CABG. A second limitation is that although patients undergoing coronary artery bypass grafting were matched with their nonsurgical controls with regard to age and

sex, they were not matched, however, for other risk factors related to increased morbidity following CABG.

A study cohort of 52 subjects of an initial 91 patients who underwent CABG on an elective basis served as their own control as they were submitted to neuropsychological testing pre and post-surgically as well as at follow-up (5 years post surgically). This study conducted by Mullges & al (2002) found that patients, after elective CABG surgery, did not show a late decline of cognitive abilities as compared to preoperative scores. The majority of their patients had improved cognitive test scores at 5 years, and only a small group (13%) had mild cognitive decline. A significant shortcoming of the study is the complete lack of information about 22% of the original patients and incomplete information of an additional 21%, which may introduce a bias toward better outcome. This was also a highly select healthy population with a low 5-year mortality rate (4%), reflecting the preoperative exclusion of patients in poor condition. Another potential source of bias was introduced by the initial patient selection and is the exclusion of patients for reasons of obvious brain dysfunction or any emergency surgery. Additionally, the baseline cognitive performance reported in this study appears to be higher than the baseline scores of previously reported cohorts. This may be due to higher education levels, but may also be attributable to other factors more difficult to assess, such as duration or severity of coronary artery disease. Despite its short comings, this study does demonstrate that late cognitive decline is not a

necessary outcome after CABG at least in highly selected healthy patients (Selnes & McKhann, 2002).

In contrast, others have reported cognitive decline following CABG in the 3 to 5 year post-surgical period (Selnes & al, 2001; Newman & al, 2001; Stygall & al, 2003 & Zimpfer & al, 2004) where others within their prospective longitudinal post-surgical neuropsychological performance studies have reported that previously accounted cognitive decline is transient and reversible at one (van Dijk & al, 2002), or even two years (Klonoff & al, 1989) post surgery, with noted exceptions at the one-year mark (Lee & al, 2003; Willner & Rodewald, 1989). Even so, the etiology of the long-term cognitive decline as affirmed in these investigations remains unclear. Selnes & McKhann (2001) have suggested that there could potentially be a biphasic course to cognitive change after surgery – an immediate postoperative decline followed by improvement and then a possible subsequent late decline. It does however remain unclear if the possible early and late decline are different manifestations of the same underlying mechanism or if they are two separate phenomena. Moreover, the authors suggest that patients with late decline tend to be older and to have less education. These observations raise the possibility that the late decline in cognitive performance may very well be multi-factorial despite alternate explanations, such as the natural aging process of the brain.

Implications of subjective neuropsychological outcome and depression

Recent advances in surgical techniques (exposure of the target coronary artery), as well as the development in improved stabilization devices (tools that stabilizes the beating heart during the off-pump operation), have allowed an increase in off-pump procedures (Diegeler, 2000). This rising incidence of off-pump procedures has sparked interest in comparing the NP outcomes in CABG patients who had their operation with CPB versus those without (off-pump group) thereby isolating CPB as a possible independent risk factor. Parallel to these findings is an emergence of alternate theories related to the observed NP decline and that stipulates that many patients with NP complaints (subjective reports from the patient of cognitive difficulties) following heart surgery are instead suffering from emotional disturbances, such as depression, rather than NP impairments per se (Vingerhoets, 1995). These studies are few in numbers and don't differentiate between CPB and off-pump patients.

One such study by Newman & al (1989) compared both subjective reports of cognition and NP test performance in 62 patients one year after CABG. Their results showed no correlation between reported complaints by the patient and NP assessments of deficits in any of the cognition domains evaluated postoperatively. However, patients who reported subjective complaints tended to have significantly higher levels of depression. It was concluded that mood

state plays an important role in the reporting of cognitive deficits after surgery, and that volunteered information regarding the deterioration of a patient's cognitive abilities does not reliably reflect assessed postoperative cognitive performance. It was therefore hypothesized that raised levels of depression lead patients to magnify everyday normal failures of cognition and, consequently, judge their performance as having deteriorated.

In 1995, Vingerhoets & al attempted to reinvestigate the findings of Newman & al (1989). They used a larger group of cardiac patients (90 patients) as well as a more extensive checklist of subjective complaints and NP tests in a 6 months post surgical assessment. Both these studies used three category choice answers in a semi-structure interview format to assess the patient's subjective report of cognition function. In agreement with the results of Newman, the study concluded that there is little relationship between self-reported changes in cognitive function and objective cognitive performance. As well, patients who reported deterioration in cognition after surgery were found to have higher levels of depression.

Recognizing that it is not uncommon for patients to complain that their cognitive abilities are reduced following heart surgery, Khatri & al (1999) also reinvestigated the relationship between these variables. Measures of NP function, mood and perceived cognitive abilities were administered the day before surgery as well as 6 weeks postsurgery. While subjective reports of

cognitive change are often elicited by surgeons and other staff engaged in the clinical care of patients, it is clear that the observed deficits are often not volunteered by the patient and if they are, they may not reflect the actual changes that would be observed with formal assessment (Newman, 1989). In their study, the authors utilized the *Cognitive Difficulties Scale* (McNair & Kahn, 1983) to assess the perceived cognitive abilities. Each item is rated on a 5 point Likert Scale indicating the frequency of a given cognitive problem. There was a total of 170 patients (average age: 61 years old) undergoing CABG. Although objective measures of impaired cognitive performance following CABG were not associated to perceived cognitive difficulties, the presence of depression was related to the perception of cognitive functioning.

The preceding studies indicate that subjective complaints of NP deficits do not necessarily correlate with objective NP testing. The most important determinant of a patient's subjective reporting of cognitive change following CABG is the current mood state of that patient. In particular, levels of depressed mood are significantly associated with the likelihood of complaints of cognitive deterioration. This finding is not surprising, given the difficulty of making judgments regarding ones cognitive performance and is consistent with individuals with depressed mood having a greater salience of their memories of cognitive failure (Newman, 1989). If, as seen previously, CPB is being increasingly associated to objective NP impairment in comparative studies with off-pump procedures, it becomes important to clarify if this

potential dichotomy between the two techniques (in terms of objective NP impairment) also reflects a stronger representation of subjective reporting of NP impairments conveyed by the patient undergoing CPB. Therefore, this project will address, among other matters, the following question: Are both surgical techniques affected equally by mood in the reporting of subjective NP impairment irrespective of a potentially stronger objective NP inefficiency linked to CPB?

As previously outlined, depression can influence patients' reporting of NP dysfunction. Additionally, the expected strong association between CPB and objective NP testing may diminish the role of mood (i.e. depression) in subjective reporting in the CPB group. Assessing depression (especially its impact relative to these surgical techniques) will enable addressing the potential adverse effect of the patient's morale and could lead to efforts in modifying behaviors that would otherwise impede normal recovery from CABG (Khatri & al, 1999). The ability to treat mood disorders is underscored by the fact that in this population, depression tends to persist if left untreated and contributes significantly to medical morbidity and mortality after myocardial infarct (MI) which is independent of medical risk factors for poor outcome (Burg & Abrams, 2001; Burg & al, 2003). In fact, depression has been found to be uniquely related to prolonged hospitalization, delayed recovery and difficulty returning to a normal life after surgery. Finally, depression, either before or after surgery, is an important independent predictor of re-

hospitalization and death up to 2 years after CABG, and should be carefully monitored and treated if necessary (Blumenthal & al., 2003, Selnes & McKhann, 2002). It appears that it is advantageous to focus on efforts to identify depression in patients suffering from chronic diseases (Shroder, 2004). Detection and recognition of risk factors for depression will enable health care professionals to better advise and counsel patients preoperatively about these various risks associated with this particular type of surgery.

In addition to the previously cited formal studies, anecdotal reports by surgeons of increased subjective reporting of cognitive disturbances emanating from the CPB population compared to the off-pump group has begun to surface (Mack, 2004; Selnes & McKhann, 2001). Curiously, in contrast, a recent prospective study (Keizer & al, 2003) examined the difference in reporting self-assessed cognitive failures one year postoperatively in 81 randomly assigned patients undergoing off-pump (N=45) and on-pump (N=36) surgery. A control sample of 112 age-matched healthy subjects was also included in this study. Their findings suggest that CABG does not result in a substantial proportion of patients with subjectively experienced cognitive decline one year after the procedure, irrespective of the type of surgical technique (on-pump versus off-pump). Again the number of patients in each group is too small to draw hard conclusions.

The initial focus (hypothesis 1) of this project was to prospectively randomize patients to a CPB and off-pump group to compare differences in cognitive outcome, if any, at 4 months following CABG operation. Secondly (hypothesis 2 & 3), this study examined the relationship between objective and subjective NP functioning as well as the contribution of depression in the perception of NP impairment 4 months after surgery for both surgical techniques combined. Third, the levels of subjective cognitive complaints were compared in on-pump versus off-pump patients (hypothesis 4). Finally, the fifth and sixth hypothesis explored the relationship between subjective and objective complaints as well as depression in the comparison of the two treatment groups (CPB and off-pump). Hypothesis 5 and 6 represents uncharted areas of research where each surgical technique was considered as possible outcome predictors of NP decline and depression. The underlying assumption is based on the rationale that since the on-pump technique should experience a higher incidence of cognitive deficit, the "complainers" within the CPB group are more likely to have NP impairment in comparison with the "complainers" within the off-pump group.

HYPOTHESES

1. The beating heart surgery technique will have significantly lower objective NP impairment in comparison with CPB 4 months after surgery.

2. There will be no significant relationship between self-reported changes in NP function and objective NP performance, 4 months after surgery, for both groups combined.

3. Patients with subjective reports of NP deterioration after surgery will have higher levels of depression, 4 months after surgery, both groups combined.

4. The CPB group will have significantly higher subjective NP reports of deterioration than the off-pump group 4 months after surgery.

5. Subjects with the highest self-reported changes in NP scores in the CPB group will be more likely to have NP impairment than the subjects with the highest self-reported changes in NP scores in the off-pump group, 4 months after surgery.

6. Subjects with the highest self-reported changes in NP scores in the off-pump group will be more likely to be depressed than the subjects with the highest self-reported changes in NP scores in the CPB group, 4 months after surgery.

METHODOLOGY

Participants

This study was conducted at St-Michael's Hospital, a university teaching hospital affiliated to the University of Toronto. A total of 74 subjects were recruited. Sixty-two patients completed both set of testing trials (pre-surgical and 4 months after surgery). This pool of subjects was comprised of males and females of all ages randomly selected into one of two types of CABG surgery, CPB (conventional) and off-pump (beating heart). Please refer to Appendix VII to view the details pertaining to inclusion and exclusion criteria for eligible subjects in this study. All patients gave written informed consent to participate in this study. The patients undergoing CPB surgery were given the same consent form as the patients undergoing off-pump surgery.

Material

Neuropsychological Test Battery:

Rey Auditory Verbal Learning Test (RAVLT – Rey, 1964; Taylor, 1959) This easily administered test measures immediate memory span, provides a learning curve, reveals learning strategies – or their absence, elicits retroactive and proactive interference tendencies and inclination to confusion or confabulation on memory tasks, measures both short-term and long-term retention following interpolated activity and allows for a comparison between retrieval efficiency and learning.

For trial I, the examiner reads a list (A) of 15 words at a rate of one per second. The examiner writes down the words recalled in the order in which they are remembered. The examiner rereads the list (trial II), then instructs the subject to say as many words as he can remember, including the words said the first time. The list is reread for trial III, IV, and trial V, using trial II instructions each time. On completion of trial V, the examiner then reads the second word list (B), again writing down the words in the order in which the patient says them. Following trial (B), the examiner asks the patient to recall as many words from the first list as possible (trial VI). The word list (C) is available should either list (A) or (B) be rendered unusable (interruptions,

improper administration). A 30-minute delayed recall trial (VII) gives information on how well the patient recalls what was once learned.

The score for each trial is the number of words correctly recalled. A total score, the sum of trials I through V, can also be calculated. Test re-test reliability correlation coefficients after one year were in the .38 to .70 range (Lezak, 1995; Spreen & Strauss, 1998). Appendix I includes a copy of the above mentioned test.

Trail Making Test (TMT – Reitan, 1956) This test consists of two parts, A and B. The subject must first draw lines to connect consecutively numbered circles on one work sheet (Part A) and then connect the same number of consecutively numbered and lettered circles on another worksheet by alternating between the two sequences (Part B). The subject is urged to connect the circles "as fast as you can" without lifting the pencil from the paper. The examiner points out errors as they occur, so that the patient could always complete the test without errors, and bases the score on time alone.

Lower scores (i.e. faster times) indicate better cognitive function. This is a test of complex visual scanning involving motor speed as well as attention and concentration. Reliability coefficients vary considerably, with most above .60 but several in the .90s (Lezak, 1995; Spreen & Strauss, 1998). Appendix II includes a copy of the above mentioned test.

Grooved Pegboard (Klove, 1963) This test that assesses motor coordination, consists of a small board containing a 5 x 5 set of slotted holes angled in different directions. Each peg has a ridge along one side requiring it to be rotated into position for correct insertion.

It is part of the Wisconsin Neuropsychological Test Battery and the Repeatable Cognitive-Perceptual-Motor Battery. The score represents the time to completion. The test re-test reliability is substantial (r = .82) (Lezak, 1995; Spreen & Strauss, 1998).

Controlled Oral Word Association (FAS – Spreen & Strauss, 1991) This test assesses the speed as well as the ease of verbal production. The subject is asked to produce orally as many words as possible beginning with a given letter in a limited period of time (one minute). F, A, and S are the most commonly used letters for this popular test. In the FAS set, F has the lowest, and S has the highest dictionary frequency. The subject is instructed to exclude proper nouns, numbers, and the same word with a different suffix.

The 1-year re-test reliability coefficient recorded was .70 (.70 for F; .60 for A; .71 for S). The score, which is the sum of all acceptable words produced in the three one-minute trials, is adjusted for age (Lezak, 1995; Spreen & Strauss, 1998).

Symbol Digit Modalities Test (SDMT – Smith, 1975) Above 110 blank squares, each paired with a nonsense symbol, is a printed key that pairs each of these nonsense symbols with a different number. The task is to fill in the blank spaces with the number that is paired to the symbol above the blank space as quickly as possible for ninety seconds. This not only enables the patient to respond with the more familiar act of number writing, but also allows a spoken response trial. When in accordance with the instructions, the written administration is given first. The examiner can use the same sheet to record the patient's answers on the oral administration by writing them under the answer spaces.

The test primarily assesses complex scanning and visual tracking with the added advantage of providing a comparison between visuomotor and oral responses. Manual speed and agility contribute significantly to SDMT performance. The score in both written and oral administration of the test is the number of correct substitutions in each 90-second interval. Test-retest reliabilities range from r = .76 to .80 (Lezak, 1995; Spreen & Strauss, 1998). Appendix III includes a copy of the above mentioned test.

Wechsler Adult Intelligence Scale – Revised (WAIS-R – Wechsler, 1981) This is an individually administered clinical instrument designed to assess the intellectual ability of adults ranging from 16 through 89. Some units of the test

require verbal responses from the subject, and others require the subject to manipulate test materials to demonstrate performance ability (Lezak, 1995). Out of the 14 existing subtests, three have been selected for this study:

Wechsler Digit Span Test (DSp) This subtest is classified as part of the "verbal section" . This test is commonly used for measuring span of immediate verbal recall as well as attention and concentration. This test requires subjects to repeat a series of digits that have been orally presented to them both forward and, in an independent test, in reverse order. When a sequence is repeated correctly, the examiner reads the next longer number sequence, continuing until the subject fails a pair of sequences or repeats a nine-digit sequence correctly. The forward and backward repetition tasks are combined into a single score representing the number of correctly repeated digit sequences for both tasks. Test re-retest reliability ranges from .66 to .89 (Lezak, 1995). Appendix IV includes a copy of the above mentioned test.

Wechsler Similarities (S) This test is an examination of general mental ability and verbal concept formation. The subject must explain what each of a pair of words has in common. The word pairs range in difficulty from the simplest ("orange – banana"), to the most difficult ("praise – punishment"). The test begins with the first item for all subjects and is discontinued after four failures. Items are passed at the two-point level if an abstract generalization is given and at the one-point level if a response is a specific concrete likeness. Test re-

test reliability coefficients range from .70 to .80 (Lezak, 1995). Appendix IV includes a copy of the above mentioned test.

Wechsler Block Design Test (BD) This subtest is part of the "performance" or non-verbal section. This test measures visuospatial organization. This is a construction test in which the subject is presented with red and white blocks, four or nine, depending on the item. Each block has two white and two red sides, and two half-red half-white sides with the colors divided along the diagonal. The task is to use the blocks to construct replicas of two block constructions made by the examiner and seven designs printed in a smaller scale. The four block designs have one-minute time limits and the nine-block designs two-minute limits. The subject can earn one of two bonus points for speed on selected items (credits); the score is the total number of points based on time limits for each trial. Reliability coefficients reported in the test manual and also based on split-half comparisons run at .83 to .89 (Lezak, 1995).

Definition of Neuropsychological Impairment

Cardiac patients will act as their own control. A decrease of 20% on 20% of these tests will be considered to represent neuropsychological impairment. The principal advantage of this definition is that it can identify individuals who have significant deficits despite overall improvements in group-mean scores that are secondary to the practice effect.

This definition is most commonly used in the literature and has been recommended at an international consensus conference for studies of cognitive impairment for post-surgical cardiac patients. As well, the above mentioned battery of NP tests represents assessment tools recommended in the consensus conference on the evaluation of neurobehavioral outcomes after cardiac surgery operations (Mahanna & al, 1996; Murkin, 1995).

Perceived Cognitive Function Test

The Cognitive Difficulties Scale (McNair & Kahn, 1983) This tool is a 39-item self-report measure that assesses perceived problems with short-term and long-term memory, concentration, attention and psychomotor coordination. Each item is rated on a 5 point Likert scale indicating the frequency of a given cognitive problem, ranging from 0 (not at all) to 4 (very often). The total scale score ranges from 0 to 156 reflecting the subjects' perceived level of cognitive function.

The test-retest reliability score is r = .77. Representative items include: "*I have trouble recalling names of people I know*"; "*I make mistakes in writing, typing, or operating a calculator*"; "*I cannot keep my mind on one thing*". This scale has been previously validated on CABG patients (Khatri & al, 1999). Appendix V includes a copy of the above mentioned test.

Mood Assessment Test

Beck Depression Inventory (BDI – Beck, Ward, Mendelson, Mock & Erbaugh, 1961) This tool has been previously utilized to measure depressive symptoms in a target population of subjects following heart surgery (Timberlake & al, 1997). This is a 21 item self-administered inventory that reflects severity scores for 13 cognitive-affective symptoms and 8 somatic symptoms related to depression. A micro-computer printout indicates the severity of the depressed mood, lists major symptom complaints, and shows a table response.

The internal consistency evaluated by split-half reliability is of 0.86. The BDI is a brief measure that offers the added advantage of measuring the severity of depression. A typical question in this test is: "*I do not feel sad*": *0* – "*I feel sad*": *1* – "*I am sad all the time I can't snap out of it*": *2* – "*I am so sad or unhappy that I can't stand it*": *3*. Appendix VI includes a copy of the above mentioned test.

Study design

This is a prospective randomized clinical study. This thesis project was created in conjunction with an existing study designed to compare the rate of graft patency (time to graft blockage – evaluated using standardized angiographic techniques) and NP impairment 4 months post-operatively between a group of CABG surgery patients undergoing traditional CPB with cardiac arrest (on pump) versus those undergoing coronary bypass surgery while the heart continues to beat (off pump). The information collected from the participants has benefited both studies performed on this pool of patients. Some information collected exceeded the scope of this current thesis project but has been outlined below to provide an accurate and complete representation of the implications of this study.

The sponsor for this study was Medtronic (700 Central av. NE, Minneapolis, MN). The subjects were not paid for participation in this study and did not receive any direct benefits over those derived through normal standard of practice at St-Michael's hospital. The investigators did not receive an honorarium for participation in the study. The investigators were not employed as consultants for the study sponsor. The investigators may however provide teaching and training support related to the study; any honorarium received for these services will be deposited in the St-Michael's research account. The

investigators have no proprietary interest in the devices used in this study. The funds will be used for publication, travel and office fees, operating room related expenses as well as angiograms and carotid duplex ultrasounds for the patients. There is an agreement between the investigator and the sponsor regarding use, publication and disposal of data. The investigator agreed to complete and submit all required case report forms in a timely manner, report all study patient deaths, adverse events, IRB actions (review boards) and protocol deviations.

All patients referred for elective CABG surgery were screened for eligibility for the study. Eligible patients met specific inclusion/exclusion criterias (outlined in Appendix VII) and were eligible for either surgical procedure. Patients meeting these criterias were flagged and the surgeon discussed the study with the patient at their pre-surgical assessment. After meeting with their prospective surgeon, the research coordinator met with the potential study subjects in order to answer any additional questions and to obtain informed consent from the patients interested in participating (see Appendix VIII). Appendix XI provides the reader with a copy of the St-Michael's REB (Research Ethics Board) approval letter for the current study.

Upon entrance into the study, demographic, medical and anthropometric information were collected from the patient's chart. A medical history including past cardiac history, history of ischemic events (unstable angina, heart attack),

location and extent of coronary artery occlusion, current medication use as well as the presence of comorbid diseases (i.e. diabetes, hypertension) were recorded. Also, the duration of use of any cholesterol lowering medications was recorded as these medications may affect plaque stability and therefore the risk of embolus (a "wandering" blood clot). In addition, all subjects underwent a carotid Doppler ultrasound prior to surgery. Demographic data included age, sex, education, race and smoking status. Anthropometric data included current height and weight as well as any recent changes in weight (see Appendix VII for a sample of the Case Report Forms filled out on every patient).

Selection of patients eligible to be included in this study was determined solely at the discretion of the surgeon. Some patients were deemed poor candidates for beating heart procedures largely on the basis of ventricular function or coronary anatomy. These patients were excluded from the current study. Patients who were good candidates for beating heart surgery were randomly assigned, at the time of enrollment, to one of two surgical procedures: 1) bypass surgery using traditional or conventional on-pump techniques (CPB) or 2) bypass surgery done off-pump while the heart continues to beat. Randomization was done with the assistance of the University of Toronto Statistical Consulting Service (electronic randomization – SAS generation number system). Randomization was also adjusted such that patients with 1)

age greater than 70 years, 2) diabetes, were equally split between the two groups.

Further adjustments occurred such that each individual surgeon performed an equal number of each of the two procedures. Patient randomization information was provided to the surgeon. Patients were monitored so that they could be excluded from the study if at any time during surgery the surgeon felt that it was in the best interest of the patient. The reason for any change in randomized surgical procedure would have been recorded. Participants were also asked to provide information regarding the presence of angina or any other ischemic events, including any additional surgical interventions or hospitalizations that may have been required in the interim period between surgery and the 4-month follow-up visit.

Perceived cognitive abilities, NP assessment and mood evaluation were conducted within 7 days prior to surgery, in conjunction with routine pre-admission visit, as well as 4 months post-operatively. A certified psychometrist (a member of the stroke team at St-Michael's hospital), who was blinded as to the nature of the surgery that each patient has undergone, performed these evaluations. The angiographer also remained blinded as to the nature of the surgical technique used. The surgical and related procedures performed in this study satisfied current Canadian and Ontario legislations and regulations.

RESULTS

Demographic Comparison

A total of 62 patients were enrolled in the study at St-Michael's Hospital over approximately a 2 year period, from October 2001 through July 2003. The following table contains a summary of the demographic characteristics of the beating heart and conventional surgery groups, including gender, education, age, race and first language.

The significance of these comparisons is contained in the column entitled "Statistical Significance". Any comparisons which result in a p-value less than 0.05 are considered to be statistically significant at a 95% confidence level. Group comparisons were performed using a chi-square test (for categorical measures such as gender and level of education) and a 2-sample t-test for continuous measures. Categorical responses are represented by the percentage response (and number of cases in parentheses) and continuous measures are represented by their mean +/- standard deviation (SD).

Table I: Demographics

	Surgery Type		Statistical Significance
	Beating Heart	**Conventional**	
Number of cases	31	31	n/a
Gender	Male – 97 % (30) Female – 3 % (1)	Male – 90 % (28) Female – 10 % (3)	p=0.3597 *
Education	< 12 yrs – 34 % (9) Grade 12 – 23 % (8) 12-15 yrs – 19 % (6) 16+ yrs – 24 % (8)	< 12 yrs – 26 % (8) Grade 12 – 19 % (6) 12-15 yrs – 31 % (9) 16+ yrs – 24 % (8)	p=0.7125
Age (yrs)	40-49 – 10 % (3) 50-59 – 27 % (8) 60-69 – 40 % (12) 70+ - 23 % (8)	40-49 – 7 % (2) 50-59 – 49 % (15) 60-69 – 28 % (9) 70+ - 16 % (5)	p=0.2580 *
Race	White – 86 % (26) Non-white–14 % (5)	White – 93 % (29) Non-white – 7 % (2)	p=0.4827 *
First language	English – 61% (19) Not English–39 % (12)	English – 69 % (22) Not English –31 % (9)	p=0.4912

* Due to the small frequency of some responses, Fisher's Exact test was used instead of a chi-square test

The subject population was male dominated in gender (97 % in the beating heart group and 90 % in the conventional group). The largest percentage of patients (34%) in the beating heart group had an education level of 12 years and under, and the conventional group (31%) was at a range of 12 to 15 years of education. The highest percentage of patients in the beating heart group (40%) was between the ages of 60 and 69 years, the conventional group (49%) was between the ages of 50 and 59 years. The study was predominantly represented by a white population (86% in the beating heart group and 93% in the conventional group) where the first language was principally English (61% in the beating heart group and 69% in the conventional group). Based on the above table we see no evidence of demographic differences across the two treatment groups.

Twelve patients out of the original 74 (6%) did not complete the follow-up questionnaires. The reasons cited included work related difficulties (1), distance to and from the testing site (2), did not want to take part in the follow-up angiogram (x-ray of blood vessels) examination (2), loss of contact with the patient (1) and no reasons stated (6).

Delay calculations between testing visits

Calculations were based on only the subjects who had both objective and subjective data as well as depression scores. Below are the times in days between visits:

Total cohort – Average days between tests = 122.5

Minimum = 59

Maximum = 479

Beating heart (off-pump) – Average days between tests = 128

Minimum = 59

Maximum = 440

Conventional (CPB) – Average days between tests = 121

Minimum = 84

Maximum = 479

Statistical significance between the treatment groups: p=0.9505. The two treatment groups, CPB and off-pump, averaged 4 months (approximately 123 days) between testing visits.

Baseline Calculations

The following table contains a summary of the baseline scores (objective NP tests, subjective scores, and depression scores) for the beating heart and conventional treatment groups. Baseline group differences were assessed through a series of independent sample t-tests and the results are summarized in the column entitled "Statistical Significance". The results are displayed in the table below.

Table II: Baseline scores

Test	**Beating Heart (mean +/- SD)**	**Conventional (mean +/- SD)**	**Statistical Significance**
Subjective test	33.6 +/- 15.7	39.1 +/- 19.2	p=0.2876
RAVLT	75.9 +/- 13.3	78.3 +/- 14.1	p=0.4431
Trail making test	145.9 +/- 62.6	143.5 +/- 50.6	p=0.8514
Symbol digit modalities	93.9 +/- 20.0	96.7 +/- 23.4	p=0.5629
Grooved pegboard	180.7 +/- 35.0	176.5 +/- 38.9	p=0.6169
Block design	25.0 +/- 8.4	27.1 +/- 9.5	p=0.2948
Verbal fluency	51.1 +/- 18.1	52.7 +/- 16.6	p=0.6760
Similarities	18.2 +/- 4.9	19.0 +/- 5.0	p=0.4938
Digit span	14.5 +/- 4.5	13.7 +/- 4.0	p=0.4468
BDI	6.6 +/- 4.4	7.7 +/- 5.5	p=0.3138

We can see from the above table that no significant differences across the two treatment groups were present at baseline.

Hypothesis testing

Hypothesis 1 – The beating heart surgery technique will have significantly lower objective NP impairment in comparison with CPB 4 months after surgery

In order to test this hypothesis, the degree of improvement per NP test was calculated. For tests in which higher scores indicated greater performance (i.e. RAVLT, Symbol Digit Modalities, Weschler Block Design, Verbal Fluency, Weschler Similarities, and Weschler Digit Span), these change scores were calculated as 100% x (follow up-baseline)/baseline. For tests in which higher scores indicated poorer performance (i.e. Trail Making Test and Grooved Pegboard), improvement was calculated as 100% x (baseline-follow-up)/baseline.

Subjects who did not respond to one or more component of any given test were not scored for that particular test (change scores would not make sense if the responses are based on a different number of items). Subjects who did not have scores for each of the eight NP tests were not included in this component of the analysis. Any subjects with 2 or more change scores of 20% (i.e. indicating a 20% decrease on 20% or more of the tests) were classified as impaired (NP), while all other subjects were classified as non-impaired (binary result – NP impairment or not).

Analyzing the parametric data (test scores) by means of these binary results allows for a clear definition of NP impairment (20% decrease on 20% or more tests – NP impairment or not). Although the results could have been analyzed as a series of continuous outcomes, the optimal statistical correspondence to the impairment definition in this study is interpreted through these binary results.

A multiple logistic regression was then performed with treatment group, age, and the interaction between treatment and age included as explanatory factors in the model. NP impairment (Dependant Variable (DV)) was the outcome measure. Statistical significance (p value at 95%) will be obtained with multiple IV's: 1) Age (regardless of treatment, are you better in one age group) 2) Treatment (regardless of age, are you better in one treatment group) 3) Interaction (does effectiveness of treatment depend on age of patient). For the purpose of this analysis, age was classified into four age groups (40-49 years; 50-59 years; 60-69 years; 70 + years). The results of this test are summarized in the following table:

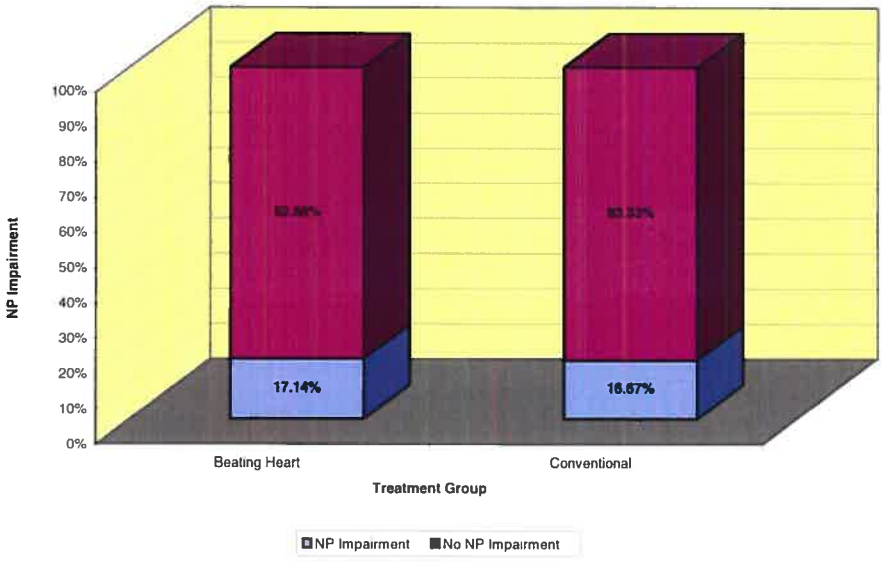
Table III: Logistic regression results

Parameter	% Impaired (n)	Chi-square	Degrees of Freedom	Statistical Significance
Overall model	16.9% (12)	6.59	7	p=0.4725
Age group	40-49 – 0.0% (0) 50-59 – 14.8% (4) 60-69 – 15.4% (4) 70+ - 30.8% (4)	1.02	3	p=0.7953
Surgery type	Beating Heart – 17.1% (6) Conventional – 16.7% (6)	<0.01	1	p=0.9999
Age x Surgery	BH 40-49 – 0% (0) BH 50-59 – 22.2% (2) BH 60-69 – 6.7% (1) BH 70+ - 37.5% (3) C 40-49 – 0.0% (0) C 50-59 – 11.1% (2) C 60-69 – 27.3% (3) C 70+ - 20.0% (1)	2.79	3	p=0.4251

Based on the above table we see no evidence of a relationship between surgery type and NP impairment or of a relationship between patient age and NP impairment. Detailed analysis between surgery type and NP impairment for each individual age group ((40 to 49 years of age; 50 to 59 years of age; 60 to 69 years of age; 70 years of age and older) is displayed in Appendix X. Although some of the highest concentration of NP impairment appears in the 60 to 69 years of age and 70 and older subgroups, in both treatment groups, no evidence was found to suggest a significant relationship between these variables.

A histogram illustrates these above mentioned results (see below):

Figure 1: Treatment vs. NP impairment



Terminology: Beating heart is synonymous to off-pump and conventional is equivalent to CPB or on-pump.

The figure illustrates the similar outcome between the two treatment groups; there is no significant difference between the 2 groups.

Summary of test scores by group at baseline and 4-month follow-up

The following table contains a summary of each of the test scores (mean +/- SD) by treatment group at baseline and 4-month follow-up. Changes in scores across time within treatment groups were tested using a paired t-test, while changes across groups were tested using a 2-sample t-test.

Table IV: Summary of test scores by treatment group over time

Scale	Group	Baseline Score (+/- SD)	4 Month Score (+/- SD)	Significance of change by group	Significance of change between groups
RAVLT	Beating Heart Conventional	75.8 +/- 13.3 78.3 +/- 14.1	82.1 +/- 14.8 89.1 +/- 16.0	p=0.0031 p<0.0001	p=0.1736
Trail making test	Beating Heart Conventional	145.9 +/- 62.6 143.5 +/- 50.6	150.5 +/- 63.9 149.8 +/- 52.1	p=0.6094 p=0.3021	p=0.9845
Symbol digit modalities	Beating Heart Conventional	93.9 +/- 20.0 96.7 +/- 23.4	93.4 +/- 23.3 99.5 +/- 23.1	p=0.7935 p=0.1217	p=0.0929
Grooved pegboard	Beating Heart Conventional	180.7 +/- 35.0 176.5 +/- 38.9	179.2 +/- 41.0 168.6 +/- 42.2	p=0.7148 p=0.0473	p=0.1706
Block design	Beating Heart Conventional	25.0 +/- 8.4 27.1 +/- 9.5	26.6 +/- 8.6 28.6 +/- 9.2	p=0.1345 p=0.1746	p=0.9137
Verbal fluency	Beating Heart Conventional	51.1 +/- 18.1 52.7 +/- 16.6	51.6 +/- 18.8 51.8 +/- 16.6	p=0.7335 p=0.5593	p=0.3973
Similarities	Beating Heart Conventional	18.2 +/- 4.9 19.0 +/- 5.0	19.7 +/- 3.8 19.9 +/- 5.1	p=0.0012 p=0.1907	p=0.0284
Digit span	Beating Heart Conventional	14.5 +/- 4.5 13.7 +/- 4.0	14.6 +/- 4.4 14.3 +/- 4.3	p=0.7127 p=0.1344	p=0.6478
BDI	Beating Heart Conventional	6.6 +/- 4.40 7.7 +/- 5.50	5.9 +/- 4.2 6.4 +/- 4.9	p=0.4753 p=0.2467	p=0.5676
Subjective test	Beating Heart Conventional	33.6 +/- 15.7 39.1 +/- 19.2	35.4 +/- 19.0 50.5 +/- 29.3	p=0.8831 p=0.7564	p=0.3795

Based on the above table, we can see that RAVLT scores changed significantly in both the beating heart and conventional groups during the course of the study. Grooved pegboard scores decreased significantly in the conventional group but did not change over time in the beating heart group. Similarities scores increased significantly in the beating heart group but remained relatively constant in the conventional surgery group. The improvement in similarities scores was significantly higher in the beating heart group than in the conventional surgery group.

Hypothesis 2 – There will be no significant relationship between self-reported changes in NP function and objective NP performance, 4 months after surgery, for both groups combined

In order to test this hypothesis, a series of scatterplots and correlations were performed to assess the nature and strength of the relationship between the 4-month changes in objective test scores and the 4-month changes in total subjective test scores. The results of these correlations are summarized in the table below.

The center column of this table contains the correlation coefficient. These statistics range in value from +/- 1, with larger absolute values indicating a stronger relationship. A correlation coefficient of 0 indicates no relationship between the corresponding pair of variables.

The third column in this table contains the statistical significance of the association. Any correlations which result in a p-value of less than 0.05 suggest that the two measures are more related than we would expect them to be by chance alone. (Note that a significant correlation does not necessarily indicate a strong association – generally speaking, a correlation coefficient with an absolute value of 0.70 or higher is evidence of a fairly strong association

between the corresponding pair of measures). The IV is the objective NP assessment and the DV is the subjective NP evaluation. The p value is established at 95%.

Table V: Correlations of changes in subjective and objective test scores

Objective Measure	**Correlation with Subjective**	**Statistical Significance**
Similarities	r=0.17	P=0.3094
Trail making test	r=0.11	P=0.4944
Verbal Fluency	r=-0.27	P=0.0926
Digit Span	r=0.06	P=0.7349
Block Design	r=0.10	P=0.5519
Symbol Digit Modalities	r=0.14	P=0.3939
Grooved Pegboard	r=-0.06	P=0.7319
RAVLT	r=-0.28	P=0.0807

Based on the above table we see no strong evidence of a relationship between changes in the subjective and objective test scores. These findings were tested more thoroughly through a series of linear regression analyses (to assess further the degree of the relationship), and are summarized in the following table:

Table VI: Linear regression of changes in subjective and objective test scores

Objective Measure	**F-Statistic**	**Degrees of Freedom**	**Statistical Significance**
Similarities	1.13	1,35	P=0.2956
Trail making test	0.40	1,35	P=0.5306
Verbal Fluency	1.77	1,35	P=0.1914
Digit Span	0.15	1,35	P=0.6963
Block Design	0.45	1,35	P=0.5045
Symbol Digit Modalities	0.06	1,35	P=0.8090
Grooved Pegboard	0.03	1,35	P=0.8561
RAVLT	4.03	1,35	P=0.0523

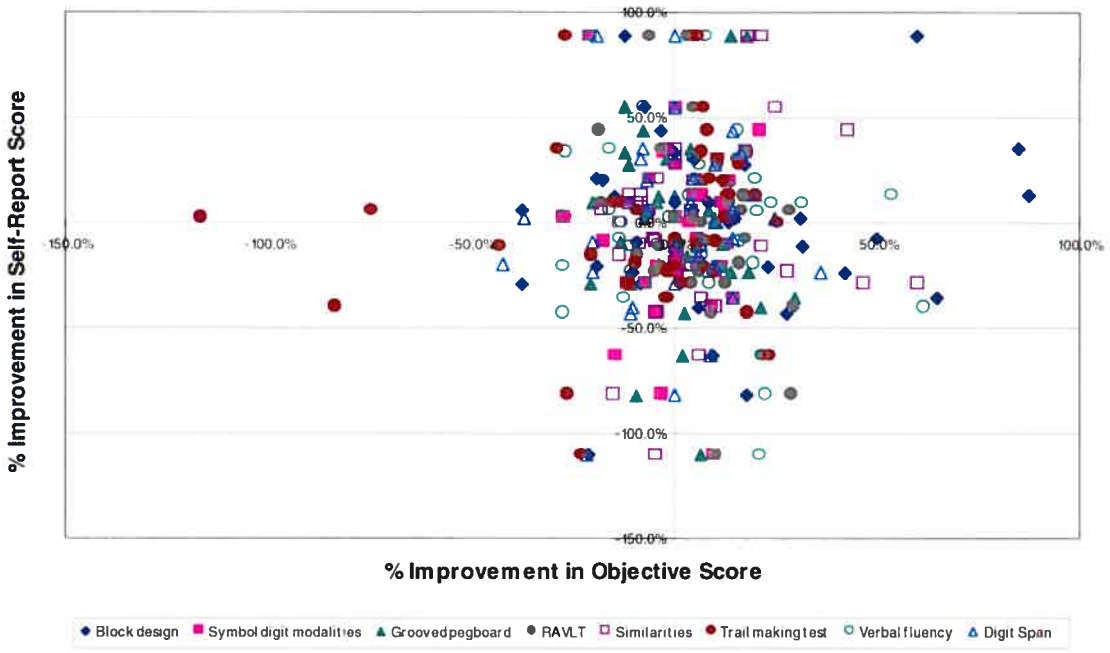
Based on the above series of tests, we see that there may in fact be an INVERSE association between self-reported subjective scores and changes in the RAVLT (greater subjective improvements correspond to poorer RAVLT improvement scores) although this finding did not quite reach statistical significance.

Correlations were performed separately for each age group (40-49 years; 50-59 years; 60-69 years; 70 + years) between RAVLT and the subjective

neuropsychological test scores to further investigate the detected trend (See Appendix X). Based on the results, we see no evidence to suggest that the strength of the association between RAVLT scores and subjective test scores vary across age groups. Again, these results should be interpreted with caution due to the small sample size involved in the analysis.

A scatter plot illustrates the above mentioned results (see below):

Figure 2: Self-reported vs. objective NP performance



Positive %'s indicate an improvement in scores, while negative %'s indicate deterioration. As illustrated by this graph, no significant relationship between the objective and subjective scores was found.

Hypothesis 3 – Patients with subjective reports of deterioration after surgery will have higher levels of depression, 4 months after surgery, both groups combined.

In order to test this hypothesis, a correlation analysis was performed to assess the relationship between 4-month changes in subjective scores and Beck Depression Inventory (BDI) total scores at 4 months. The results of this test found a moderate, negative association ($r=-0.32$, $p=0.0416$) suggesting that subjects whose subjective scores deteriorated over time tend to have higher depression levels. This finding was tested more thoroughly through a linear regression analysis (to determine the degree of relationship among the variables) and is summarized in the following table. The IV is depression and the DV is subjective NP evaluation. The p value is established at 95%.

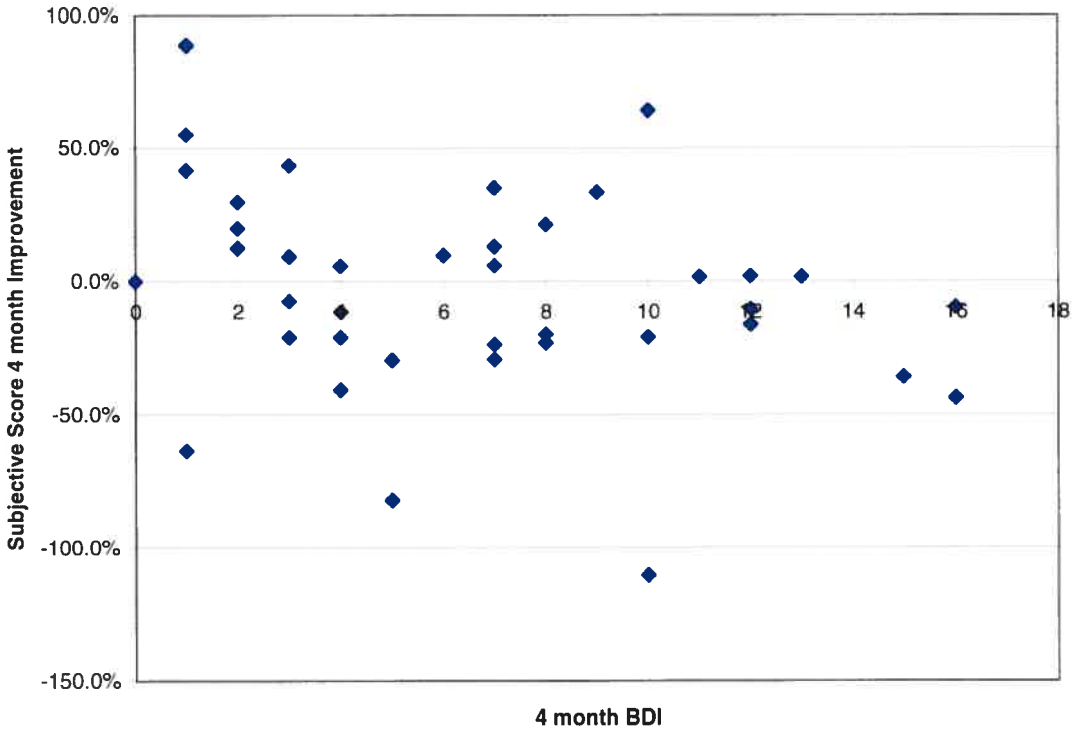
Table VII: Linear regression of changes in subjective and depression test scores

Explanatory Variable	**F-Statistic**	**Degrees of Freedom**	**Statistical Significance**
Depression at 4 months	4.45	1,38	p=0.0416

The linear regression results confirm the results of the correlation analysis and provide evidence to suggest that patients with higher depression levels at 4 months tend to report greater NP deterioration than those with lower depression levels.

A graph illustrates the above mentioned results (see below):

Figure 3: Self-reported deterioration vs. depression



Positive %'s indicate an improvement in scores, while negative %'s indicate deterioration. Here we see a mild, negative trend which is what we would expect.

Additional correlations of change were performed separately, for each age group (40-49 years; 50-59 years; 60-69 years; 70 + years) between subjective scores and depression to further investigate the relationship between the variables (see Appendix X). The results of the Ancova found no evidence to suggest that subjective deterioration scores and depression results are associated with age. The larger age grouping of 50 -59 years (31 subjects of a 62 subject cohort) detected a trend toward significance ($p = 0.0714$) without reaching statistical significance.

Hypothesis 4 – The CPB group will have significantly higher subjective NP reports of deterioration than the off-pump group 4 months after surgery.

In order to address this issue, a t-test was performed to assess the degree of change in subjective NP scores within each treatment group to determine if there is a significant difference between CPB and off-pump groups. The IV is the treatment and the DV is the subjective NP assessment. The results of this test are summarized in the following table:

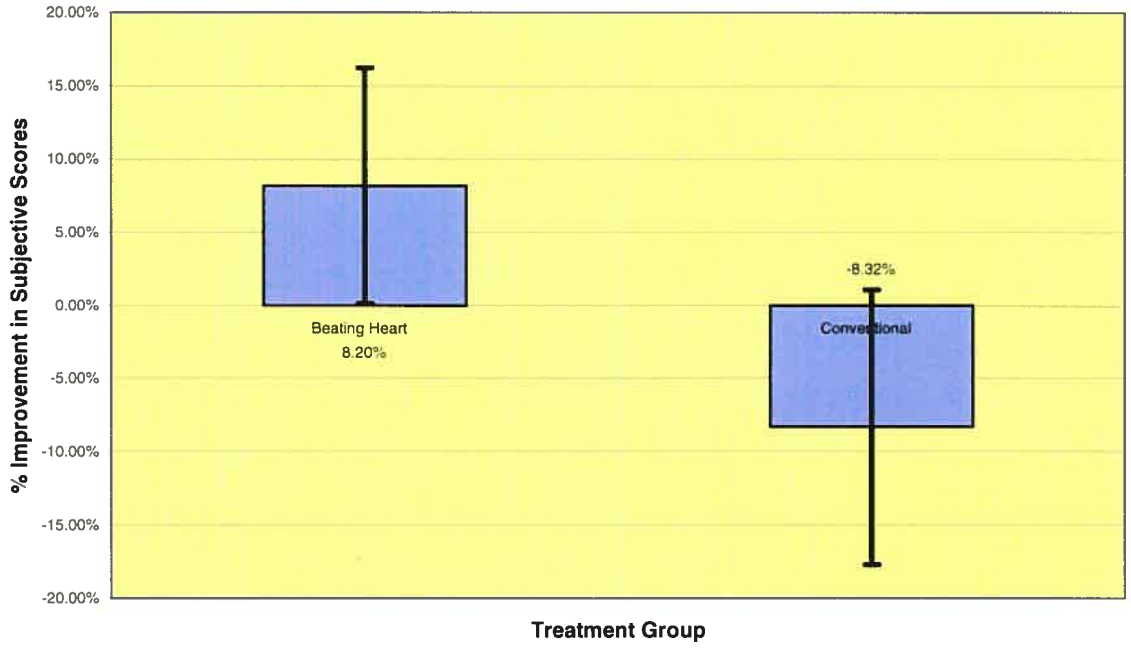
Table VIII: T-test of changes in subjective test scores vs. treatment

Group	Deterioration % +/- SD	t-statistic	Degrees of Freedom	Statistical Significance
Conventional	8.20% +/- 43.2%	1.32	39	p=0.1929
Beating Heart	-8.32% +/- 36.1%			

Based on the results of this test, there is an apparent trend that did not reach statistical significance on the degree of reported change in subjective scores across the two treatment groups even though on average the beating heart group showed an actual improvement on NP scores while the conventional surgery group reported a mild deterioration.

A box plot illustrates below the above mentioned results:

Figure 4: Self-reported deterioration vs. treatment group



Terminology: Beating heart is synonymous to off-pump and conventional is equivalent to CPB or on-pump.

Positive percentages on the y-axis indicate an improvement, while negative scores indicate deterioration. The trend in improvement for the beating heart group as well as the trend in deterioration for the CPB group is illustrated in this graph.

Additional correlations of change were performed separately, for each age group (40-49 years; 50-59 years; 60-69 years; 70 + years) between subjective scores and treatment to further investigate the relationship between the variables (see Appendix X). Based on the results of these tests, there is no evidence to suggest that the degree of reported change in subjective scores differs across the two treatment groups after controlling for age.

Hypothesis 5 – Subjects with the highest self-reported changes in NP scores in the CPB group will be more likely to have NP impairment than the subjects with the highest self-reported changes in NP scores in the off-pump group, 4 months after surgery.

In order to address this hypothesis, the 50% of subjects within each treatment group who reported the greatest extent of NP impairment were identified. The median was located (lining up all subjects) to determine the "high complainers" (50% = high complainers). All other subjects were not included in this analysis. Fisher's exact test was then performed among these subjects with the highest self-reported degrees of NP impairment, in order to determine whether the proportion of subjects with objective NP impairment differs across treatment group. (Note: Fisher's exact test was chosen instead of a chi-square test due to the small frequency of subjects with NP impairment in this subset of the data. Chi-square requires a sample size of at least 5 subjects per cell, while Fisher's exact test does not have any minimum sample size requirements).

Although Fisher's exact tests basically test for association without any underlying assumptions of directionality, the IV can be considered to be the treatment group, and the DV, objective NP impairment. Subjective NP

impairment (high complainers) is what we are subsetting our data by (similar logic to inclusion/exclusion criteria for clinical studies). The p value is established at 95%.

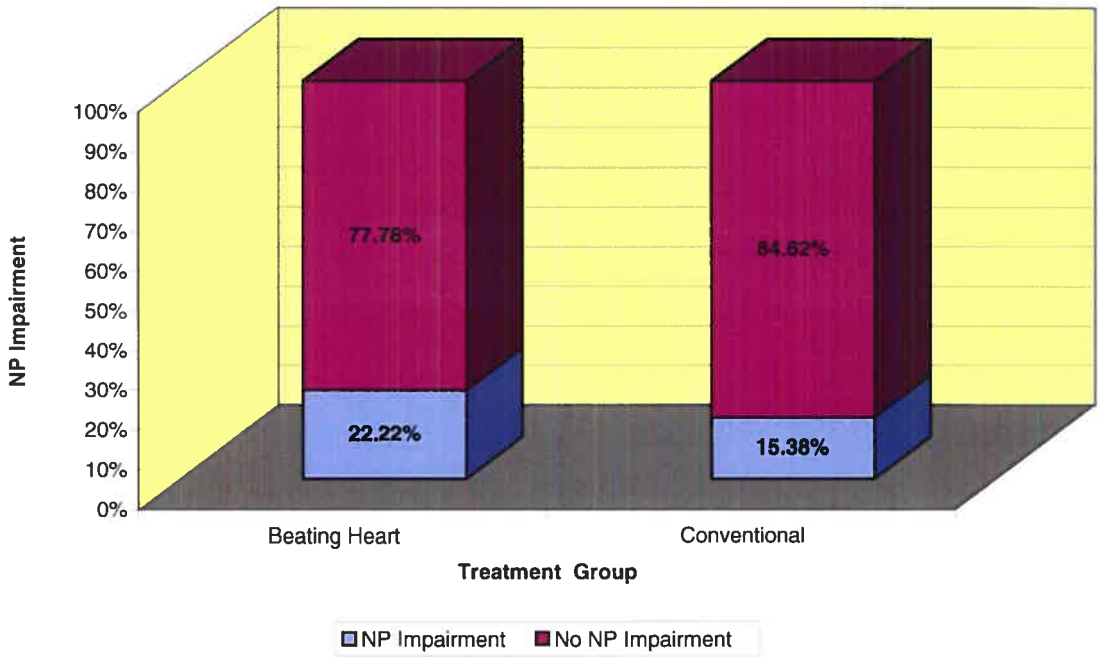
In this analysis, 22.2% (2) of the subjects in the beating heart group were found to have NP impairment, compared to 15.4% (2) of the subjects in the conventional surgery group. This finding was not statistically significant (p=1.0000). These results are displayed in the following table:

Table IX: NP impairment vs. treatment group

NP Impairment	Group		Total
	Beating Heart	Conventional	
No	77.8% (7)	84.6% (11)	81.8% (18)
Yes	22.22% (2)	15.38% (2)	18.2% (4)

A histogram illustrates below this outcome between the 2 treatment groups:

Figure 5: Treatment group vs. NP impairment (among the 50% of subjects per group with the highest subjective reports of NP impairment)



Terminology: Beating heart is synonymous to off-pump and conventional is equivalent to CPB or on-pump.

This histogram illustrates the similarity between the 2 treatment groups; no evidence of a relationship was found between the beating heart group and the conventional group among the patients with the highest scoring NP complaints.

The relationship between age and objective NP impairment, self-reported NP change as well as treatment group was investigated (see Appendix X). Fisher's exact test was then performed among subjects with the highest self-reported degrees of NP impairment, broken out by age group, in order to determine whether the proportion of subjects with objective NP impairment differs across the CPB and off-pump group. No significant relationship was found between objective NP impairment, self-reported changes, age, and treatment group.

Adjustment of % of subjects retained for H5

Additional analysis was performed on H5 (and on H6, which will be detailed subsequently) to attempt adjusting the % of subjects retained for each series of tests. Our goal is to use the subjects with the highest self-reports of NP impairment. Originally, we had selected 50% of the subjects from each group. The analysis tests were once again performed while selecting only the top 5%, 10%, and 25% of subjects (with the highest self-reports of NP impairment) in each group. Regardless of which cutoff % was used, the test results did not detect any significance.

This was tested using the Fisher's exact test which yields only a p-value – no test statistic. The results are as follows:

Table X: NP impairment by treatment group

Self-reported NP impairment cutoff	**Percentage with objective NP impairment**		**Statistical Significance**
	Beating Heart	Conventional	
5%	0.0% (0)	66.7% (2)	p=0.4000
10%	33.3% (1)	40.0% (2)	p=1.0000
25%	16.7% (1)	25.0% (2)	p=1.0000
50%	22.2% (2)	15.4% (2)	p=1.0000
100%	15.8% (3)	19.1% (4)	p=1.0000

All of these tests revealed no significant results.

Hypothesis 6 – Subjects with the highest self-reported changes in NP scores in the off-pump group will be more likely to be depressed than the subjects with the highest self-reported changes in NP scores in the CPB group, 4 months after surgery.

To test this question, the 50% of subjects within each treatment group with the highest self-reported levels of NP impairment were once again used as the study sample. The median was located to determine the "high complainers". These patients were then classified as depressed or normal based on their 4-month BDI values. Fisher's exact test was performed in order to determine whether any association between treatment and depression exists among this sub-group. Although Fisher's exact test basically checks for association without any underlying assumptions of directionality, the IV can be considered to be the treatment group, and the DV, depression. Subjective NP impairment (high complainers) is what we are subsetting our data by. The p value is established at 95%. Interestingly, it can be argued that depression could have been treated as a continuum and therefore assess whether the average depression scores differ significantly across the two treatment groups. However, the optimal statistical correspondence to the depression definition in this study (as per BDI criteria) is interpreted through the following categorical results:

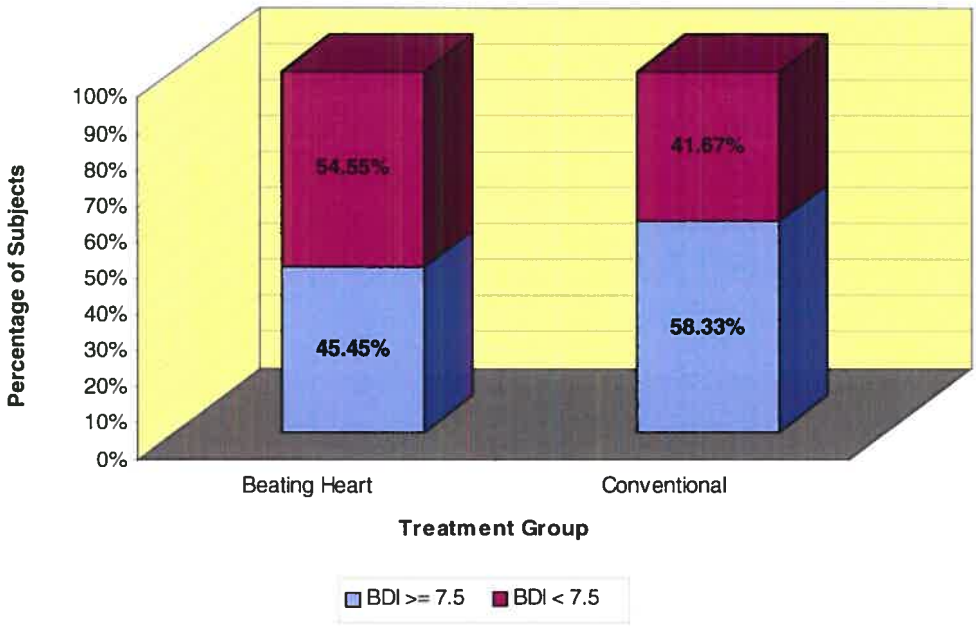
Table XI: Depression vs. treatment group

Depression	**Group**		**Total**
	Beating Heart	Conventional	
No	54.5% (11)	41.7% (10)	48.1% (21)
Yes	45.5% (5)	58.3% (7)	51.9% (12)

In this analysis, 45.5% (5) of the subjects in the beating heart group were found to be depressed, compared to 58.3% (7) of the subjects in the conventional surgery group. The results of the test found no evidence of a relationship between depression and treatment group (p=0.6843).

A histogram illustrates below this outcome between the 2 treatment groups:

Figure 6: Treatment group vs. depression (among the 50% of subjects per group with the highest subjective reports of NP impairment)



Terminology: Beating heart is synonymous to off-pump and conventional is equivalent to CPB or on-pump.

This histogram illustrates the similarity between the 2 treatment groups; no statistical difference was found between the beating heart group and the conventional group among the patients with the highest scoring NP complaints.

The relationship between age group and depression, subjective deterioration as well as treatment group was investigated (see Appendix X). Fisher's exact test was performed in order to determine whether any association between treatment and depression exists among this sub-group of high NP complainers within each age group. No significant evidence of a relationship between age group, depression, subjective deterioration, and treatment group was found.

Adjustment of % of subjects retained for H6

Additional analysis was performed on H6 (and H5, as presented previously) to attempt adjusting the % of subjects retained for each series of tests. Our goal for this hypothesis is to use the subjects with the highest self-reports of NP impairment. Originally, we had selected 50% of the subjects from each group. The analysis tests were once again performed while selecting only the top 5%, 10%, and 25% of subjects (with the highest self-reports of NP impairment) in each group. These patients were then classified as depressed or normal based on their 4-month BDI values. Regardless of which cutoff % was used, the test results did not detect any significance.

This above mentioned hypothesis was tested using the Fisher's exact test in order to determine whether any association between treatment and depression exists among these sub-groups. The results of these tests are summarized in the following table:

Table XII: Depression by treatment group

Self-reported NP impairment cutoff	**Depression**		**Statistical Significance**
	Beating Heart	Conventional	
5%	0.0% (0)	66.7% (2)	p=0.4000
10%	0.0% (0)	40.0% (2)	p=0.4643
25%	14.3% (1)	50.0% (4)	p=0.2821
50%	45.5% (5)	58.3% (7)	p=0.6843
100%	30.0% (6)	43.5% (10)	p=0.5282

All of these tests revealed no significant results.

Power calculations

The following table contains a summary of the sample size required to make our observed effect sizes become statistically significant. These calculations were performed separately for each hypothesis (with the exception of H2 which tests for a lack of difference between the treatment groups) at a 95% confidence level and with 80% power.

Table XIII: Power calculations

Hypo-thesis	**Comments**	**Total Required Sample Size**
H1	The proportion of patients with NP impairment in each of the two groups was completely identical. No sample size will make this into a statistically significant difference.	n/a
H3	Results of current analysis are already significant, implying sufficient power with current sample size.	n/a
H4	77-109 subjects required per treatment group.	154-218
H5	518 subjects required per group, groups based on 50% of subjects within each treatment group.	2,064
H6	1,247 subjects per group, each group based on 50% of subjects in each treatment group.	4,988

H1: We found exactly the same proportion of impaired subjects in each group. Increasing the sample size cannot help reach statistical significance. NP impairment was split almost completely evenly across the 2 treatment groups which suggest that the required sample size will need to be increased to the highest degree to make the difference become significant. Currently at an alpha level of 0.05 (which is standard), the study has only 5% power to detect a difference in the rate of NP impairment across the 2 treatment groups. In order to reach 80% power (which is standard), it would require 99 822 subjects per group.

H2: Null hypothesis – won't expect to find a relationship between the variables.

H3: This hypothesis is significant. We therefore have sufficient power.

H4: Here 77 – 109 subjects per treatment group would be needed (for a total of 154-218 subjects) in order to make the observed effect become significant.

H5: A total of 518 per group, for a total of 1032 subjects would be required. It must be noted that this test is based only on those with the highest NP impairment scores, so actual sample required would be twice this or 2064.

H6: A total of 1247 per group is required to make this hypothesis significant. Both groups combined need 2494 patients and since this comprises only half of the sample, 4988 patients would be needed.

DISCUSSION

Demographic Comparisons

A significant proportion of the patient population, in both surgical groups, was male. Although the demographic pool of subjects did represent fewer females, studies focused on cardiac surgery patients will generally incur a strong male population which is representative of this cardiac patient population. Neither gender, education, age, race nor first language were significantly different between the two surgical groups. In this study, 31% of patients in the conventional group and 39 % in the beating heart group did not have English as a first language. As this could potentially affect patient understanding of a testing session, there was no significant statistical difference between the conventional and beating heart group for this variable, thus canceling any potential skewed influence in either group. Both treatment groups averaged a four month delay period between testing visits. There was no significant difference between the two surgical groups in the time between each assessment session.

Hypothesis testing

Hypothesis 1 – The beating heart surgery technique will have significantly lower objective NP impairment in comparison with CPB 4 months after surgery

This study addressed several criteria's of patient exclusion in its investigation of 62 patients randomized into either CPB or off-pump surgical groups. Patients who were on medication that effect CNS or PNS such as anti-psychotics or anti-epileptics were excluded. The study also controlled for hypertension, excessive alcohol use (over 14 drinks per week), history of neurological disease (previous CVA, psychotic disorders, Parkinson's, brain tumors, epilepsy, head injury with impaired cognition, Alzheimer's, essential tremor) as well as any change (dose/type) in anti-depressant medication during the course of the study. Any patient admitted for a CABG re-operation or any patient unable to provide informed consent or incapable to read or comprehend English was excluded from the research. Moreover, all patients 70 years of age and older and who suffer from diabetes, were equally split between the 2 groups. (See Appendix VII - Case Report Forms - for complete exclusion list). The baseline scores indicated no significant differences before surgery between the two treatment groups, the beating heart and the conventional group.

In the perspective that the neuropsychological measures are administered in an objective context and cognitive performance was assessed through a blinded examiner, our postulated hypothesis was that the surgical group in the off-pump group would perform significantly better than the CPB group by having undergone beating heart surgery, and therefore avoiding CPB. In this study, no significant differences emerged from the relationship between surgery type and NP impairment or of an association between patient age, treatment group and NP impairment in the context of the above mentioned exclusions. This supports the assertion that post-surgical neuropsychological impairment may not be strictly associated to CPB as alleged through previous research.

The power statistics revealed that NP impairment was split almost completely evenly across the 2 treatment groups. This suggests that the required sample size would need to be increased to the highest degree to make the difference become significant. In deed, currently at an alpha level of 0.05 (which is standard), the study has only 5% power to detect a difference in the rate of NP impairment across the 2 treatment groups. In the context of this research, in order to reach 80% power (which is standard), it would require approximately 100 000 subjects per treatment group.

The results of the current study are consistent with previous research that question CPB as the source of post CABG neuropsychological impairment

(Baker & al, 2001; Lloyd & al, 2000; Malheiros & al, 1995; Malheiros & al, 1999; Rodig & al, 2000; Taggart & al, 1999; Townes & al, 1989; Wimmer-Greinecker & al, 1998). Through the literature, several suggestions have been outlined as possible alternate explanations to the role of CPB on postoperative neuropsychological decline. Taggart & al (1999) have suggested generalized tissue injury as a possible contributing effect. Previous findings have supported that patients undergoing major non-cardiac operations have showed cognitive dysfunction. It has also been suggested that the effects of the anesthesia regimen can be involved in post-surgical neuropsychological decline. However, the studies cannot, thus far, distinguish between the effects of surgical injury from those of anesthesia. Nevertheless, it has been recognized that anesthesia can produce short-term cognitive dysfunction (Taggart & al, 1999).

By avoiding CPB it was generally anticipated that resultant neurocognitive dysfunction would be lessened but in our sample group this was not the outcome. One significant but marginal decrease in consecutive test scores was noted for the Grooved Pegboard in the conventional group ($p = 0.0473$); it did not reach statistical significance when compared to the beating heart group ($p = 0.1706$) although the beating heart group did trend slightly towards a decreased score but non-significantly. A larger study cohort may have contributed to exacerbate this difference between the two groups and therefore highlight the Grooved Pegboard as a test with a stronger and distinctive significant margin in the conventional group.

In the current study population, there was no significant decline in neuropsychological outcome between the 2 treatment groups, CPB and off-pump, in the consecutive individual tests scores. Nevertheless, the Grooved Pegboard, a test of psychomotor speed, fine motor control, and rapid visual-motor coordination (Mitrushina & al (1999)) may represent a cluster of neuropsychological capacities more significantly affiliated with CPB related effects and outcomes.

A significant improvement was noted between baseline and post-surgical testing for the Similarities test, where the beating heart group showed significant improvement over the conventional group ($p = 0.0284$). RAVLT for both groups had marked significant improvements within each group between the pre and post testing sessions (beating heart: $p = 0.0031$; Conventional: $p < 0.0001$). This improvement did not reach statistical significance when comparing the observed change between the groups ($p = 0.1736$).

A learning effect as well as regression towards the mean cannot be excluded considering the significant postoperative improvement outcomes after 4 months. As well, attrition levels can potentially skew results in that the population of patients that continues with the study could be a considerably motivated group. The patients that were absent through attrition may have

registered weaker scores in their postoperative test scores. However, this does seem unlikely since the attrition score was registered in this study at 6%.

Improved health (reduced or absent angina [chest pain of cardiac origins]) after the operation may have contributed to some of the superior follow-up scores; cognitive function at baseline may have been impaired because of long-standing cardiac disease. Additionally, beating heart patients do tend overall to spend less time in the operating room and intensive care unit as compared to the conventional group who also tend, for their part, to experience more major complications such as bleeding and unstable angina (Stump & al, 2001). The significance of change in the improvement score for the Similarities test in the beating heart population may very well reflect a group having experienced overall improved health as well as lower complication rates as detected through this form of verbal concept formation testing. As reported by Lezak (1995), for example, the Similarities test tends to be more sensitive to the effects of brain injury, regardless of localization, than the other WIS verbal tests. Although both the conventional and beating heart group reported some improvements on the Similarities test, the beating heart group's improvement was significant over the CPB group. The beating heart group may have faired significantly better on this neuropsychological test as it has been associated in previous research to have a lesser risk of developing microemboli intra-operatively when compared to CPB (Taggart & al, 1997). However, Spreen & Strauss (1998) have reported that the RAVLT test is

sensitive to neurological impairment. Following the observation that both groups have significantly improved their RAVLT test scores following surgery, this may challenge the latter proposition that the conventional group may singularly have distinctive and exceptional neuropsychological challenges when compared the beating heart group. Following this premise, it would have been expected that the improvement would have been superior in the beating heart group as well, which is not what was observed in this study. Overall, this highly selective population (see inclusion/exclusion list – Appendix VII) combined with a smaller sample size may have provided results less comparable to other study cohorts in previous research. This may have resulted in filtering out patients at higher risk for NP impairment. Additional studies with less stringent inclusion/exclusion criteria's and larger sample groups are needed for further clarification.

A frequently reported association with poor NP outcome, according to Newman (1989), is the age of the patient. The author stated that patients over the age of 60 were especially at an increased vulnerability. The author also reported that the patients with neuropsychological deficits were significantly older than those without. These findings are similar to those reported for more severe neurological damage. There have been, however, some large studies which have failed to find any particular association with age (Shaw & al, 1987; Shaw & al, 1987). In this study, there were no reported significant differences between the various age groups in NP impairment, even though some of

highest concentration of neuropsychological impairment occurred in the patients 60 years of age and older. This discernable stronger representation never reached statistical significance in this study.

Hypothesis 2 – There will be no significant relationship between self-reported changes in NP function and objective NP performance, 4 months after surgery, for both groups combined

Overall, as anticipated, there is no discernable evidence of a relationship between objective measures of neurocognitive performance and perceived cognitive abilities. Rabbitt & Abson (1990) have argued that tested individuals may have very limited conscious access to their own cognitive process as the authors explored the possible methodological and empirical difficulties in the use of Self-Report Questionnaires (SRQ). In deed, their judgments about their cognitive competence may reflect socially conditioned beliefs about memory and other cognitive functions as much as their personal ability. Moreover, people may not encompass the ability to activate their insights into their own competence, or into the cognitive lapses they suffer or the errors they make. Individuals' view of their own cognitive efficiency, of the numbers or kinds of errors and lapses which they make, and of the causes of these lapses, will change with the environments to which they must adapt.

The lack of predictive value of the subjective neuropsychological questionnaire on the objective performance can also lye in the marked difference between neuropsychological laboratory tasks and everyday-life demands. It can be that these discrepancies are indicative of the dissimilarity between the experimental conditions and everyday life; this laboratory context may induce a limitation

where there is only a vague correspondence to real life. Perhaps there are insufficient comparable standards simply because of a lack of important and substantial parallels between the two forms of testing. Controlled testing conditions apply certain limitations to potential comparable environments and enhance restrictions in the contrast of these two forms of neuropsychological questionnaires. Parallel to this is the suggestion that the questions in the self-report test may not reflect the patients' current lifestyles. It may be that the investigation targets a lifestyle not relatable to this particular population of cardiac patients.

Finally, a potential pervasive problem with SRQ, whatever their degree of insight on their own cognitive process, in that people cannot assess their own efficiency in absolute terms. They can only make relative comparisons assessing their competence against their perceived ability to cope with the particular demands or against the performance of people they know well, therefore assessing incompatible domains to objective neuropsychological tests.

This therefore illustrates that Self-Report Questionnaires (SRQ) may tell us a number of things about individuals without reliably picking up on objective differences in their everyday competence. It is therefore probable that the subjective tool used in this study is not as sensitive as the objective neuropsychological battery used on this population of subjects. The inverse

correlation could also reflect an inherent weakness in the measuring tools utilized in this study. Future use of SRQ should consider these potential limitations in the interpretation of the subjective questionnaires.

Additional analysis did reveal a slight inverse trend between RAVLT, a test score of the objective neuropsychological test battery, and the overall subjective neuropsychological test score, although this particular finding never reached statistical significance. While these results must be assessed with caution as they represent a slight tendency, perhaps this outcome is detecting a sub-clinical population that tends to report an overall subjective impression of neuropsychological progress, while the RAVLT scores seemingly trend towards deterioration, and vice versa.

The RAVLT measures immediate memory span, provides a learning curve, reveals learning strategies, or their absence, elicits retroactive and proactive interference tendencies as well as tendencies to confusion or confabulation on memory tasks, measures both short-term and longer-term retention following interpolated activity, and allows for a comparison between retrieval efficiency and learning (Lezak, 1995). It has been demonstrated that certain sub-population of patients can effectively perform more poorly on the RAVLT than others. For example, patients with dementia of the Alzheimer type (AD) show more impairment on the RAVLT than patients with head injury or AIDS. Although this study has controlled for Alzheimer's disease, the diagnosis

process can be lengthy, where many patients can go on undetected for an extended period of time. This most common form of dementia among an older population affects part of the brain that involves thought, memory and language, the very aspects involved in the RAVLT. In addition, it is also plausible that the tentative results reflect a sub-clinical population of patients afflicted by a condition known as multi-infarct dementia, which results from the accumulating affect of small strokes, and may produce Alzheimer's-like symptoms which frequently can occur in patients having undergone heart surgery (Taylor, 1999). In this case, the patient's own subjective assessment of his neurocognitive functioning could be impaired. However, this can only be evidenced through MRI testing, data unavailable for this population of subjects (Edmunds, 1997). Additionally, when each age group was tested separately for the assessment of a potential relationship between RAVLT and subjective neuropsychological in order to further investigate the detected trend, no evidence was found to suggest any association for any of these sub-group clusters, perhaps again because of a smaller sample size (made even smaller by separating the cohort into smaller age groups).

Hypothesis 3 – Patients with subjective reports of deterioration after surgery will have higher levels of depression, 4 months after surgery, both groups combined.

Post-surgical depression has emerged as a predictor of the perception of cognitive difficulty in this study. The findings echo previous results (Khatri & al, 1999, Newman, 1989 & Vingerhoets & al., 1995) in post-surgical CABG patients in deed suggesting a significant relationship between depression and perception of cognitive condition.

It has been suggested in previous research (Keizer & al, 2003) that a self-rating questionnaire may be more related to the everyday-functioning emotional state rather than to the objectively discerned cognitive abilities. This could help elucidate, in part, why the subjective neuropsychological reports in this study (hypothesis 2) did not correlate with the objective neuropsychological data but does, however, correlate with depression levels (hypothesis 3).

In contrast, Newman (1989) has attempted to explain the relation between depression and perceived neuropsychological impairment by suggesting that negative mood can contribute to perceptions of poor health. This particular cluster of patients assessed with depressed mood would exhibit a distinctive

tendency to focus more extensively on their cognitive failures and consequently evaluate their cognitive status more negatively.

This statement is supported by the cognitive-behavioral theories relative to depression. It has been suggested that negatively biased cognition is a core process in depression (Ingram & Holle (1992) & Ingram & Hollon (1986)). In deed, they advocate that individuals who are depressed will tend to formulate cognitive distortions and either amplify negative events or minimize positive ones. This process is reflected in the "cognitive triad of depression"; depressed patients typically have a negative view of themselves, of their environment, and of the future. They tend to view themselves as worthless, inadequate, unlovable, or deficient. Depressed patients view their environment as overwhelming, as presenting insuperable obstacles that cannot be overcome, and as continually resulting in failure or loss. Depressed patients continuously distort their interpretations of events in that they maintain negative views of themselves, the environment, and the future. These distortions represent deviations from the logical process of thinking used typically by people (Barlow, 2001).

An important predisposing factor for many patients with depression is the presence of early schemas. Beck (1976) has emphasized the importance of schemas in depression, and provided the following definition: "A schema is a (cognitive) structure for screening, coding, and evaluating the stimuli that

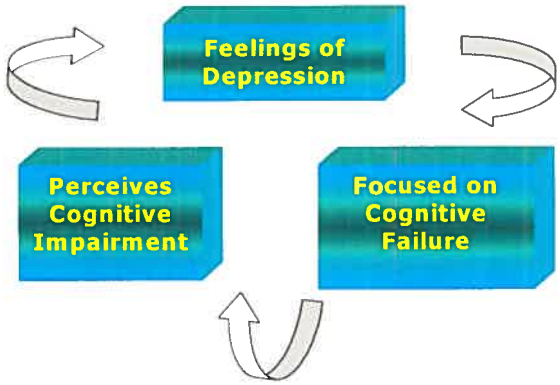
impinge on the organism... on the basis of the matrix of schemas, the individual is able to orient himself in relation to time and space and to categorize and interpret experiences in a meaningful way." (Page 283)

In further specifications of the notion of the schema, Beck & al (1990) have added that "in the field of psychopathology, the term schema has been applied to structures with a highly personalized idiosyncratic content that is activated during disorders such as depression...Thus, in clinical depression, the negative schemas are in ascendancy, resulting in a systematic negative bias in the interpretation and recall of experiences as well as in short-term and long-term predictions, whereas the positive schemas become less accessible. It is easy for depressed patients to see the negative aspects of an event, but difficult to see the positive. They can recall negative events much more readily than positive ones. They weigh the probabilities of undesirable outcomes more heavily than positive outcomes." (Page 32)

Khatri & al (1999) have suggested that conversely, perceived cognitive impairment may also play an important role in the development and maintenance of depressed moods. It may be that patients who perceive cognitive impairment may feel more depressed. Indeed, people who perceive poor health often feel more depressed. It is therefore likely that a negative feedback-loop of perceived cognitive impairment and depressed mood is operative in such a way that a person who feels depressed may focus more on

his or her cognitive failures, perceive cognitive impairment, feel more depressed, and continue to magnify cognitive errors, thus maintaining a mood state consistent with their perception of health. The figure below illustrates this theory:

Figure 7: Negative feedback loop



This finding has further relevance since the follow-up examinations, between doctor and patient, will reveal through the patients' account their current health status; this will influence, in part, the physicians' subsequent medical report. It must therefore be considered by the health care staff that depressed mood can be implicated in the assessment and reports of the patient's neuropsychological symptoms and therefore can alter their perception and ultimately influence their health status.

Isen & al (1978) have previously underscored that what is commonly called mood and most often thought of as an emotional state may very well have a cognitive dimension and may even be more appropriately conceptualized as a cognitive state. On the other hand, one should consider the possibility that mood itself consists in, or is a product of, those very cognitive changes. Nevertheless, from this study it is not possible to identify which of these variables heads the other but it does appear that, based on our current results measured in this study, depression and subjective neuropsychological assessment emerge as interactive.

However, when Keizer & al, 2003, examined the relationship between depression as measured with the mental health scale of the SF-36 questionnaire (Short Form Health Survey questionnaire) and CFQ (Cognitive Failure Questionnaire) scores, the authors only found a weak relationship ($r = 0.174$; $p = 0.043$). Therefore, different mechanisms may be implicated in the analysis of cognitive functioning in post-surgical CABG patients and in the way this particular measure is assessed. Conversely, it must also be noted, that this current research, in its own findings, did report a significant but weak relationship between the two variables of depression and subjective neuropsychological disorder. All the discussed related outcomes must be considered in light of this limitation.

Separate analysis was performed on individual age groups between subjective NP scores and depression results and found no evidence of an association between these variables. However, the results must be interpreted with caution. By breaking the population down into smaller groups (smaller sample size) based on 4 age groups, it has reduced the sample size (and consequently the power) substantially. In deed, the larger age grouping of 50 -59 years (31 subjects of a 62 subject cohort) was the only age group that detected a trend toward significance ($p = 0.0714$) while the overall hypothesis was significant ($p = 0.0416$). In separating the cohort into smaller groups, no significant age sub-group emerged from the analysis, at the exception of a trend toward significance which was represented by half of the total group of subjects (31 out of 62 subjects). The loss of significance in the age groups is likely related to the loss of statistical power. The subdivided patient cohort may no longer have the power required to detect a significant difference.

Parallel to these findings, it can be argued that self-reported NP changes (as tested by the Cognitive Difficulties Scale) and depression (as tested by the BDI) are mutually linked, which can create a self-fulfilling prophecy effect and can risk a bias of non-falsifiability. Based on the separate age group calculations it is interesting to note that while the overall association between these two measures was significant, this outcome was lost in the sub-analyses broken into age groups (aside from one trend toward significance). It appears that in these particular research conditions, these two variables are falsifiable.

Hypothesis 4 – The CPB group will have significantly higher subjective NP reports of deterioration than the off-pump group 4 months after surgery.

Objective neuropsychological tests are utilized under optimal laboratory conditions, and tend to induce specific test-related strategies while invoking minimal distraction and stress. Self-report subjective tests have been developed with the objective of overcoming the limitations of laboratory paradigms in assessing everyday cognitive competence (Keizer & al, 2003). Subjective judgments of change in cognitive function are difficult to make, but they are important in that these constitute the complaints that some patients make at follow-up clinics (Newman, 1989). Nevertheless, the results of this study found no significant difference in self-reported cognitive failures between patients undergoing on-pump and off-pump CABG. These results are consistent with the Keizer & al (2003) study who report no evidence suggesting that the level of reported change in the subjective measure varies between the two groups, on and off-pump. However, these results are not compatible with the anecdotal statements from previous research of increased neuropsychological complaints emanating from the CPB population (Mack, 2004, Selnes & McKhann, 2001). These anecdotal reports may very well have been based on unselected patients and may include patients with higher risk factors for NP impairment, whereas in this study, there were important exclusion criteria perhaps filtering out patients at risk for NP impairment.

Additionally, after controlling for age, no evidence was found to suggest that the level of self-reported cognitive change is significantly different between the conventional (CABG) and the off-pump surgical group. However, after dividing the subjects into separate age groups, the sample size was reduced considerably; this limitation must be considered when interpreting these results.

On the other hand, the results do show a trend towards improvement for the beating heart group on the subjective scores whereas in the CPB treatment group there was noted deterioration. The subjective questionnaire is directly related to an individual's decision to precisely and correctly respond to the various questions. It is therefore sensitive to various levels of accuracy. As stated by Rabbitt & Abson (1990), subjective self-ratings may not reflect absolute levels of everyday competence, but only the relative success of individuals' adaptation to specific environments. In practice, the beating heart patient tends, on average, to spend less time in the Intensive Care Unit (ICU) as well as on the floor, tends to receive fewer blood transfusions and spends less time on the ventilator post-surgically than the CPB patient. Overall, the off-pump patient tends to experience a quicker recovery relative to the CPB patient (Ascione & al, 1999; Calafiore & al, 1999; Carter & al, 1999; Gu & al, 1998; King & al, 1997; Mack & al, 2001; Pfister & al, 1992; Puskas & al, 1998; Zenati & al, 1997). In this context, the post-surgical CPB patient is more likely to be confronted with his cognitive shortcomings than the off-pump patient.

Although these patients were blinded to the type of surgery they received, and therefore were not influenced in one way or another to endorse or deny their subjective experience, they may however have recognized the quality and progress of their recovery and may have been influenced indirectly by these considerations. The individuals' judgment about his cognitive competence may reflect socially conditioned beliefs about cognitive function and outcome, relative to specific contexts, as much as their personal ability (Rabbitt & Abson, 1990; Rodig & al, 1999). Hence, as beating heart patients may have been experiencing an overall better than anticipated recovery and may have anticipated suffering more impairment than they did, their expectation may have biased their response to the subjective questionnaire accordingly.

The self-report measure is based upon a general assumption that symptom reporting is a function of information transfer. That is, according to Putzke & al (2001), individuals (a) notice their behavior, (b) store that information in memory, (c) attend to and comprehend the information request, (d) retrieve and incorporate the appropriate information, and (e) decide to relay an accurate representation of the resulting information. This practice is therefore an intricate and multifaceted process which encompasses many levels of integration and assimilation. The self-report measure is an integral component of psychological assessment, research and treatment but must implicitly be considered in light of these constraints.

Overall, the results of this study for hypothesis 4 show that the beating heart group was found to improve marginally, while the conventional group became slightly worse (8.3% improvement in the beating heart group versus 8.2% of deterioration noted in the CPB group). Through power calculations performed on these results, it has also been noted that a sample of 77-109 subjects per treatment group (for a total of 154-218 subjects) would be required to make the observed effect become significant. It can therefore be anticipated, that with a larger sample size, this current observed trend (improvement in the beating heart group and deterioration in the conventional group) could have reached statistical significance.

Hypothesis 5 – Subjects with the highest self-reported changes in NP scores in the CPB group will be more likely to have NP impairment than the subjects with the highest self-reported changes in NP scores in the off-pump group, 4 months after surgery.

The literature suggests that since we are seemingly separating those who are more likely to encounter neuropsychological decline (conventional) from those who are less likely (beating heart), it would be expected to find a stronger association of subjective neuropsychological disorders with the conventional group. However, there was no significant difference between the two treatment groups. The power calculations (in the results section) also reveal that the two treatment groups are so closely matched, that it would entail 518 subjects per group to attain a significant difference between the two groups. Both groups combined require 1032 patients and since this comprises only half of our sample, it would require 2064 patients overall.

In the statistical definition of the highest self-reported change in NP impairment, it was initially determined that 50% would classify and designate this assigned population. This was an arbitrary choice. It had therefore become necessary to adjust the % of subjects retained for each series of tests in order to verify if this definition had imposed a restriction on the data analysis findings. The objective, in order to test this hypothesis, was to utilize the patients with the highest self-reports of NP impairment. Initially, 50% of

the subjects were used from each group; three additional % were selected and the analysis was carried out once again while selecting only the top 5%, 10%, and 25% of subjects with the highest self-reports of NP impairment in each treatment group. Although there appeared to be a slight trend toward significance for the most selective cutoff point (5%) when compared to the other cutoff points, the test results did not detect any significance.

In order to explore the potential impact of various age groups and their implication regarding neuropsychological impairment, additional calculations were performed among the subjects with the highest self-reported degree of NP impairment, broken into various age groups, in order to determine whether the proportion of subjects with objective NP impairment differs across treatment and age groups. These findings revealed no significant relationship between objective NP impairment, self-reported changes, age, and treatment group. However, the statistical power was considerably reduced by grouping further the sample size into smaller clusters. The interpretation of these results must consider this limitation.

Hypothesis 6 – Subjects with the highest self-reported changes in NP scores in the off-pump group will be more likely to be depressed than the subjects with the highest self-reported changes in NP scores in the CPB group, 4 months after surgery.

Based on the literature, the premise was that the two treatment groups reflected different levels of anticipated association with neuropsychological decline; the CPB group was more likely to be linked to elevated levels of neuropsychological decline than the off-pump group. Based on this projected alliance, it was not only projected to find a stronger association between subjective and objective NP decline in the CPB group when compared to the off-pump group (Hypothesis 5), but it was also expected that the impact of depressed mood would be significantly lessened in the reporting of subjective NP impairment in the CPB group when compared to the off-pump group (Hypothesis 6). No evidence was found to support a relationship between depression and treatment group in the subject population reporting the highest neuropsychological complaints.

The power calculations revealed that the CPB group and the off-pump group are statistically comparable in that it would require 1247 subjects per group to attain a significant difference between the two groups. Both groups combined would require 2494 patients and since this comprises only half of our sample, it would involve an overall amount of 4988 patients. Based on these

calculations it does appear that, in these similar research conditions, a reasonably larger sample would not yield a different result in subsequent studies.

Initially it was arbitrarily determined that the statistical definition of the highest self-reported change in NP decline would be established at 50%. This classification was adjusted in order to verify if this categorization had imposed any limitation in compiled results. Three additional % categories were chosen in order to respond to our statistical goal of including the group of patients with the highest subjective NP impairment. The analysis was carried out once again while selecting only the top 5%, 10%, and 25% of subjects with the highest self-reports of NP impairment in each treatment group. Irrespective of the level of adjusted % of inclusion selected, the test results did not detect any significance.

However, it does appear that if we are more selective in choosing patients with high self-reports of NP deterioration (5%), the results on the test become very non-significant ($p=0.400$) when compared to 25% which yielded a value of $p=0.2821$. This may be because our sample size is larger when we do not limit ourselves to the top 5% or 10% of our subjects and so we have more statistical power. It is therefore suspected that these findings are mainly due to the power issue i.e. more significance was found when we include more patients because we have more statistical power to detect the difference.

The impact of various age groups was also analyzed in order to explore the impact of advancing age on these variables and to determine whether any association between treatment and depression exists among this sub-group (50% of subjects within each treatment group and age group combination with the highest self-reported levels of NP impairment). No evidence of a relationship between age group, depression, subjective deterioration, and treatment group was found. Again, the results must be interpreted with caution as the further grouping of patients into smaller age-clusters reduces the statistical power significantly in this study.

Overall, it appears that surgery type does not serve as a predictive variable when considering subjective neuropsychological reports from the patient. It was anticipated through this research that a post-surgical NP complaint from a patient could yield separate associations based on the type of surgery the patient had undergone. It could have been anticipated that if a patient had undergone beating heart surgery and complained of NP decline, depression may have been the more likely associative variable implicated. Complaining of NP decline following conventional surgery would have been more likely associated with objective NP challenges rather than depression. This was not verified in this study perhaps because the high risk patient population (more typically associated with CABG surgery) was selected out based on the exclusion criteria for this study.

Implication for health psychology

The distinctive goal of this current research was to explore the implication of on-and-off pump CABG surgery as a predictive outcome variable of depression based on the level of subjective neuropsychological complaints. Surgery type was not found to be a predictive variable of mood outcome based on stronger subjective neuropsychological complainers in this study. However, there was a significant relation between mood and subjective NP impairment. In deed, negative mood was associated with perception of poor neuropsychological outcome. Effectively, this research suggests that a patient's mood may be an important variable that impacts the self-appraisal of the individuals' health status. Interventions that focus on reducing emotional distress such as depression could potentially lead to an improved perception of the patient's cognitive abilities following CABG. The importance in treating mood disorders is also underscored by the fact that depression has been previously associated with less exercise, failure to use social support resources as well as poor adherence to lifestyle recommendations and medical treatment, including medication management (Charlson & Isom, 2003; Jiang & al, 2002; Ziegelstein, 2001). In the cardiac patient population, it would then be advantageous to identify depression at its earliest stage and to intervene accordingly.

In light of the previously stated benefits of targeting depression, anticipation and prevention of mood disorders is of paramount importance in order to offset the adverse potential effects. Replication of this study with a larger sample (perhaps a multi-center trial) over a longer follow-up period may also help untangle some of the statistical trends and tendencies noted in this study. The specific inner workings of depression and its impact on the post-surgical recovery period is of prognostic importance in order to continuously advance treatment strategies offered to patients requiring CABG.

RESEARCH LIMITATIONS

Inevitably, the contributions of a study must be considered in light of its limitations. Nonetheless, these particular limitations combined with the findings of the present research allow for future opportunities of complimentary research.

The study population in this research project included patients referred to the cardiac surgery service for elective CABG surgery and who were screened for eligibility for the study based on inclusions/exclusions factors (see Appendix VII). The study was therefore based on restricted guidelines in the selection of the subject population. The results of this research are consequently only valid for elective patients with a comparable age range undergoing coronary artery bypass grafting and cannot be extrapolated to patients undergoing other than elective isolated coronary artery bypass grafting surgery with comparable inclusion/exclusion factors. In deed, by pre-selecting the research population within these guidelines, it may be that we enrolled a population of patients undergoing CABG that was biased toward those with a better outcome. The unbiased and unrestricted CPB patient may be at higher risk of experiencing neuropsychological decline following CABG.

The self-report questionnaire (SRQ) category was utilized in this study. Depending on the subject matter areas being investigated, the outcome may be prone to some inaccuracies as a result of less than precise recall, lack of information, or discomfort with self-disclosure. As well, subjective test scores

of neuropsychological outcome are provided through one tool with the goal to measure several neuropsychological dimensions (attention, concentration, memory, motor skills, etc.). Overall objective neuropsychological test score, in this study, is provided through several individual tests. This limitation must be considered when comparing these measures. Additionally, a study of postoperative outcomes that consist of a comprehensive neuropsychological (objective, subjective) and depression test battery almost certainly implies a certain selection bias. The research population undergoing this succession of various cognitive as well as mood assessments must be comprised of individuals ready and able to complete the diverse tasks in a post-surgical recovery period.

The collection of data in this study was performed over a 2 year period, between October 2001 and July 2003, producing a snapshot of cardiac patients undergoing CABG surgery during that particular period of time. Cardiac surgery skills and techniques are continuously improving and will modify over time in response to surgical advances. Future attempts at contrasting this particular study to upcoming research must consider this limiting factor.

This study performed a preoperative as well as postoperative testing session. This is conducive to learning through repeated measures, recognized as the "practice effect". It is an established fact that repeat-testing on neurocognitive

tests leads to change in performance independent of any changes in underlying function or capacity (Slade & al, 2001). A considerable learning potential is highly undesirable. There are other factors involved in repeat testing including those resulting from fatigue or boredom, which can have the opposite effect. One way in which this problem can be overcome is by utilizing parallel forms of the tests where they are available. This approach does not deal entirely with the problem because practice effects occur with the specific processes as well as the specific content of tests. In the case of studies in which patients are randomly assigned to the experimental or control conditions to investigate procedures for improving outcome, it is not necessarily so crucial. The issue becomes increasingly important in clinical group studies in which patients serve as their own control. Previous research has examined the implication of a non-surgical control group and found no evidence of improvement or decline in the follow-up test scores (McKhann & al, 1997). A learning effect cannot be excluded however considering the improvement results found in this investigation for some individual neuropsychological assessments.

Regression towards the mean is a statistical phenomenon whereby extreme baseline scores become less extreme after repeated examination, even though a "true change" in the subject scores has not occurred during the course of the study (Taggart & al, 2001). Regression towards the mean alone can result in a greater proportion of patients who performed very well at baseline and

subsequently be classified as cognitively impaired (at the 4 month post-operative testing session); in the absence of a relevant control group it is likely that it was the patients who performed well at baseline that constituted the largest proportion of those classified as impaired at discharge, and hence any systematic change could be due to regression towards the mean. However, the possibility of regression effects towards the mean values as potential influence on the results may very well be minimal; none of the 2 surgical groups recorded a more extreme performance at the pre-surgical testing session. The baseline calculations revealed that there were no significant differences across the two treatment groups.

This project was created in conjunction with an existing study and did not include a control group in its design. Although the patients were randomly assigned into the two types of surgery, the control group would have enabled a better command of the effects of outside variables on the outcome. Randomization does however tend to achieve balance between the groups in terms of various variables, such as age and education. This is optimally achieved in larger groups, which is not always attainable in practice. In deed, without control, experimental results can be dominated by influences such as the details of the experimental arrangement, the selection of subjects, and the placebo effect. The result can be bias. Several types of control groups have been suggested in the past. A group of patients undergoing another type of surgery can control for surgical effects, distress, anxiety, anesthesia and

trauma. However, since morbidity does tend to be elevated in these surgical populations as well, this type of control group is not optimal and will not fully control for practice effect (Slade & al, 2001). A spousal control group does provide an additional option but does not however necessarily control for such variables as age and education and also introduces a gender confound, where the control group would tend to be predominantly female in gender since overall more men than woman undergo heart surgery. A third possibility, however, not entirely easily achievable, is a friend control subject group with similar age, gender and education which could possibly remedy more optimally for the practice effect.

This particular study was comprised of 62 patients. It is conceivable that a larger sample size is desirable in such a study. In effect, some hypotheses have detected trends without ever attaining significance in their results (such as the fourth hypothesis recording a trend in the improvement of the subjective neuropsychological scores for the beating heart group and a deterioration for the conventional treatment group). It can be argued that a larger sample may have impacted the results. According to the power calculations, hypothesis 4 for example, could have benefited from an increased study cohort. In this case, 77 to 109 subjects per treatment group would have been required (for a total of 154-218 subjects) in order to make the observed effect become significant.

Patient attrition is a factor that can potentially influence the outcome of a study. In this research, the attrition was of 6%. Nevertheless, patients who drop out off studies are usually the patients with the worse preoperative cognitive and psychological status (Haddock & al., 2003). Moreover, these patients may have dropped out because of depression. This attrition albeit small, may have influenced the outcome results.

FUTURE RESEARCH AND CONSIDERATIONS

Several avenues and approaches for future research can be considered. There is an increased need to combine and integrate the results of the independent clinical trials of the various studies on post CABG neuropsychological decline. Each trial has provided various results of the impact of CABG surgery on neuropsychological decline. The comparison between the different studies is currently complex (various sample size, a range of neuropsychological measures, etc.) which promotes the necessity to create a pool of results from the separate investigations. A comprehensive meta-analysis could statistically combine the results of the various investigations in order to produce a set estimate of the outcome variable of interest and achieve statistical integration of different studies.

As stated previously, Selnes & McKhann (2001) suggested the existence of a two-phase course to neuro-cognitive decline after CABG surgery – an immediate post-surgical decline followed by progress and then possibly followed by late decline. It should be determined whether these early and late cognitive declines following CABG surgery are dissimilar manifestations of the same underlying mechanism or if they are two separate events. By means of control group, these future studies would have to control for a range of variables such as the normal aging of the brain. The current results of this research may reflect, in this particular cohort, the trend in "progress" stated by

these authors. If such mechanisms of late decline are revealed, measures of prevention targeted to at risk populations can be exercised.

Future research could examine the Alzheimer sub-clinical population and its particular impact on post CABG neuropsychological outcome. It is well documented that neuropsychological deterioration can be effected by age and its related variables. Subsequent research should isolate the various age-related variables potentially affecting the outcome results.

Future studies could examine in greater detail the impact of education following CABG on an individuals' neurocognitive function. It could be valued to better identify potential resistance patterns to neuropsychological decline associated with various levels of learning. Previous studies have mostly outlined the demographics of the population in terms of its levels of education. However, the impact of higher education on post-surgical cognitive outcome has yet to be extensively examined as a predictive outcome variable.

Although, no overall significant NP decline was associated with the CPB group in this research, many studies have reported significant results on individual NP tests over time, including this investigation. It may become important to identify individual tests across various studies which increasingly contribute to the trend toward significant outcome. Future research could then focus on these individual tests that evoke a tendency to record significant changes

across the treatment groups and further examine this pattern of sensitivity in recording significant changes across surgical groups.

Future studies should incorporate assessments of patient's quality of life; in investigations indicating even partial deterioration of cognitive function (through the specific decline of one or several neuropsychological tests), it remains unclear how this affects their quality of daily life and activities as well as responsibilities (for example, housework, independent living, etc.). Furthermore, factors such as prolonged recovery and hospitalization as well as compliance level as a direct consequence of post-surgical neurocognitive performance should be investigated. An evaluation of the ability of the health care system to identify and deal with these outcomes is also needed.

Considering the results obtained in this study, several research limitations referring to the use and interpretation of subjective results have been enumerated, especially in light of its comparable nature to objective testing (Rabbitt & Abson (1990)). Recognition of the limitations of existing questionnaires is a first step towards improving our methodologies to yield useful data about individual differences in everyday competence. Future research is needed to further elucidate this limitation.

The findings of the present study provided additional evidence of the relationship between perception of poor neuropsychological outcome and

negative mood. However, the apparent complex and associative nature of the relationship between depression and subjective neuropsychological outcome implies consideration for other possible causes of cognitive complaints. Personality instruments should be included as part of future reflections in the study of these variables.

As stated in previous sections of this report, the fourth hypothesis could have benefited from increased statistical power in order to reach significance in that approximately 77 to 109 subjects per treatment group would have been required (for a total of 154-218 subjects) in order to make the observed effect become significant. Additionally, this highly selective study population, as outlined through the inclusion/exclusion criteria (Appendix VII), may have filtered out patients with higher risks linked to NP decline (objective, subjective) as well as depression. Perhaps future research could explore a sample of patients more representative of the patient population actually undergoing CABG surgery.

These various suggestions can assist in leading to new approaches in addressing fundamental questions regarding the interaction of the many variables explored in this study.

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APPENDIX I

REY AUDITORY VERBAL LEARNING TEST

(REY, 1964)

Rey Auditory Verbal Learning Test (RAVLT) 12/01/94
Form 2 (Learning List C)

Pre Post F-up

Name: _____

Date: _____

	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5
1.	violin ___	violin ___	violin ___	violin ___	violin ___
2.	tree ___	tree ___	tree ___	tree ___	tree ___
3.	scarf ___	scarf ___	scarf ___	scarf ___	scarf ___
4.	ham ___	ham ___	ham ___	ham ___	ham ___
5.	suitcase___	suitcase___	suitcase___	suitcase___	suitcase___
6.	cousin ___	cousin ___	cousin ___	cousin ___	cousin ___
7.	earth ___	earth ___	earth ___	earth ___	earth ___
8.	stairs ___	stairs ___	stairs ___	stairs ___	stairs ___
9.	dog ___	dog ___	dog ___	dog ___	dog ___
10.	banana ___	banana ___	banana ___	banana ___	banana ___
11.	town ___	town ___	town ___	town ___	town ___
12.	radio ___	radio ___	radio ___	radio ___	radio ___
13.	hunter ___	hunter ___	hunter ___	hunter ___	hunter ___
14.	bucket ___	bucket ___	bucket ___	bucket ___	bucket ___
15.	field ___	field ___	field ___	field ___	field ___

TOTAL _____ _____ _____ _____ _____

Total Score

Form 2 (List D, Recalls C, and Recognition)

	List D (Interference)		List C (After Interf.)		List C (20-min Del Rec.)		
1.	orange	____	violin	____	violin	____	
2.	table	____	tree	____	tree	____	
3.	toad	____	scarf	____	scarf	____	
4.	corn	____	ham	____	ham	____	
5.	bus	____	suitcase	____	suitcase	____	
6.	chin	____	cousin	____	cousin	____	
7.	beach	____	earth	____	earth	____	
8.	soap	____	stairs	____	stairs	____	
9.	hotel	____	dog	____	dog	____	
10.	donkey	____	banana	____	banana	____	
11.	spider	____	town	____	town	____	
12.	money	____	radio	____	radio	____	
13.	book	____	hunter	____	hunter	____	
14.	soldier	____	bucket	____	bucket	____	Total 5 trials: ____
15.	padlock	____	field	____	field	____	Delayed recall: ____
	total	____	total	____	total	____	Recognition: ____

RECOGNITION

scarf	____	television	____	doctor	____	**town**	____
leaf	____	rock	____	soldier	____	beach	____
stairs	____	toad	____	**radio**	____	cork	____
frog	____	chin	____	chest	____	corn	____
table	____	**ham**	____	donkey	____	lunchbox	____
banana	____	piano	____	pear	____	bus	____
hospital	____	**field**	____	**cousin**	____	train	____
suitcase	____	soap	____	grass	____	uncle	____
peel	____	**tree**	____	**dog**	____	**violin**	____
book	____	city	____	gloves	____	star	____
blanket	____	**hunter**	____	hotel	____	spider	____
padlock	____	orange	____	**bucket**	____		
earth	____	money	____	sofa	____	Total	____

bold = List C

underline = List D

Rey Auditory Verbal Learning Test (RAVLT) 12/01/94
Form 3 (Learning List F)

Pre Post F-up

Name: _____

Date: _____

	Trial 1		Trial 2		Trial 3		Trial 4		Trial 5	
1.	doll	___	doll	___	doll	___	doll	___	doll	___
2.	mirror	___	mirror	___	mirror	___	mirror	___	mirror	___
3.	nail	___	nail	___	nail	___	nail	___	nail	___
4.	sailor	___	sailor	___	sailor	___	sailor	___	sailor	___
5.	heart	___	heart	___	heart	___	heart	___	heart	___
6.	desert	___	desert	___	desert	___	desert	___	desert	___
7.	face	___	face	___	face	___	face	___	face	___
8.	letter	___	letter	___	letter	___	letter	___	letter	___
9.	bed	___	bed	___	bed	___	bed	___	bed	___
10.	machine	___	machine	___	machine	___	machine	___	machine	___
11.	milk	___	milk	___	milk	___	milk	___	milk	___
12.	helmet	___	helmet	___	helmet	___	helmet	___	helmet	___
13.	music	___	music	___	music	___	music	___	music	___
14.	horse	___	horse	___	horse	___	horse	___	horse	___
15.	road	___	road	___	road	___	road	___	road	___
TOTAL		_____		_____		_____		_____		_____

Total Score

Form 3 (List F, and Recalls E plus Recognition)

	List F (Interference)		List E (After Interf.)		List E (20-min Del Rec.)	
1.	dish	____	doll	____	doll	____
2.	jester	____	mirror	____	mirror	____
3.	hill	____	nail	____	nail	____
4.	coat	____	sailor	____	sailor	____
5.	tool	____	heart	____	heart	____
6.	forest	____	desert	____	desert	____
7.	perfume	____	face	____	face	____
8.	ladder	____	letter	____	letter	____
9.	girl	____	bed	____	bed	____
10.	foot	____	machine	____	machine	____
11.	shield	____	milk	____	milk	____
12.	pie	____	helmet	____	helmet	____
13.	insect	____	music	____	music	____
14.	ball	____	horse	____	horse	____ Total 5 Trials
15.	car	____	road	____	road	____ Delayed recall
	total	____	**total**	____	**total**	____ Recognition:

RECOGNITION

BUFFERS: telephone _____ zoo _____

nail	____	1.armour	____	1.song	____	**letter**	____
1.stall	____	1.head	____	ball	____	perfume	____
bed	____	hill	____	**helmet**	____	2.plate	____
1.engine	____	forest	____	2.pool	____	coat	____
jester	____	**sailor**	____	foot	____	1.sand	____
milk	____	1.pony	____	1.bread	____	tool	____
2.soot	____	**road**	____	**desert**	____	2.fly	____
heart	____	ladder	____	1.street	____	1.dart	____
1.silk	____	**mirror**	____	**machine**	____	**doll**	____
insect	____	1.envelope	____	1.jail	____	1.captain	____
1.screw	____	**music**	____	girl	____	shield	____
car	____	dish	____	**horse**	____		
face	____	pie	____	2.joker	____	**Total**	____

bold = list E

APPENDIX II

TRAIL MAKING TEST

(RETTAN, 1956)

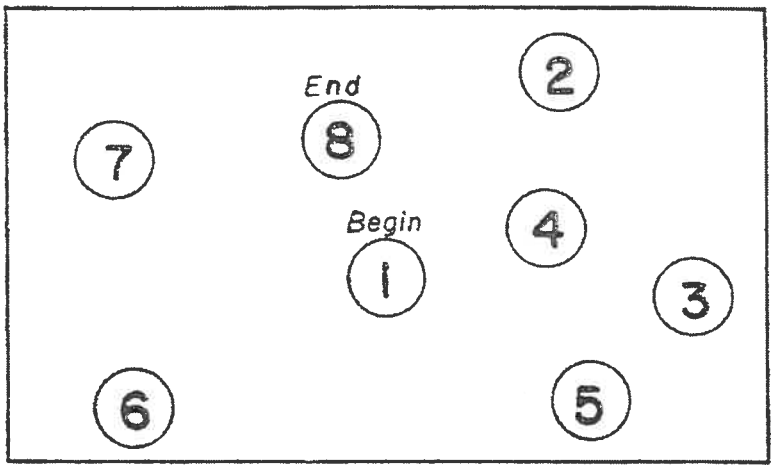
NAME:
DATE:
PRE / POST / FOLLOW-

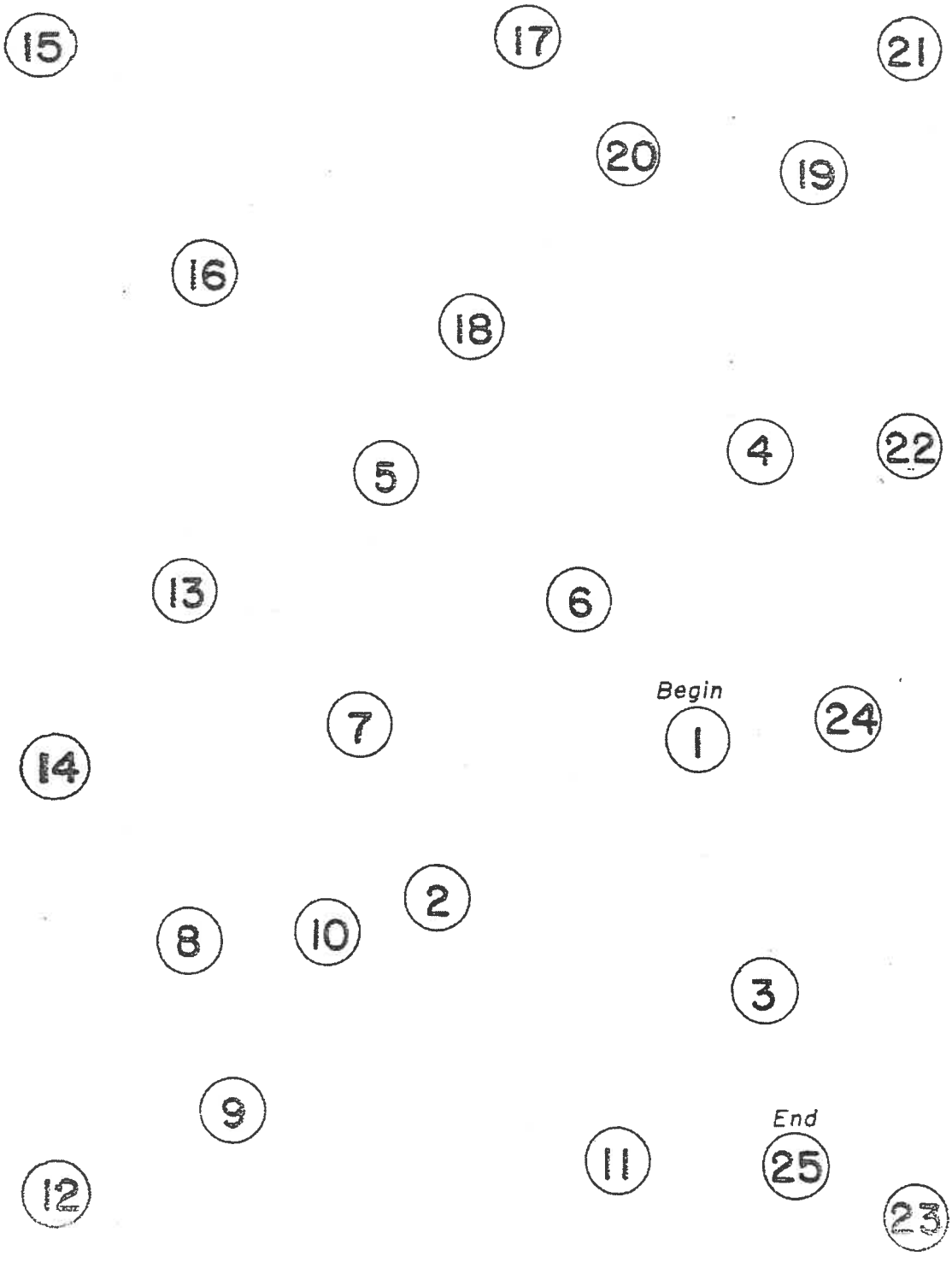
TRAIL MAKING

Part A

TIME:

SAMPLE

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Begin
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End
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23

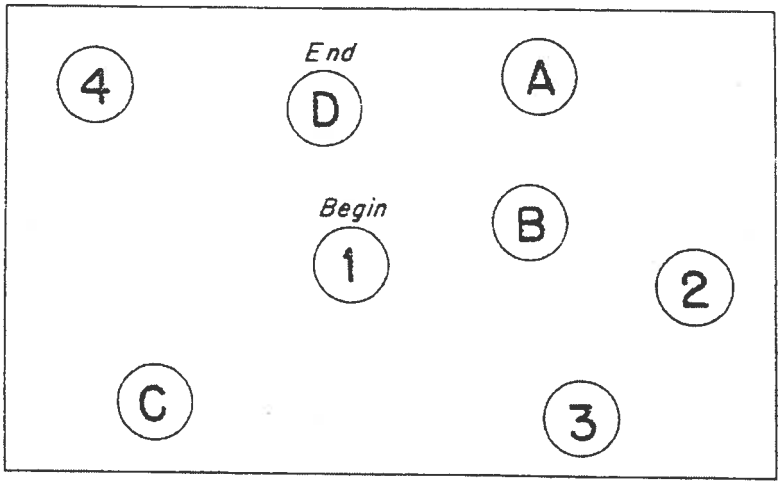
NAME:
DATE:
PRE / POST / FOLL(

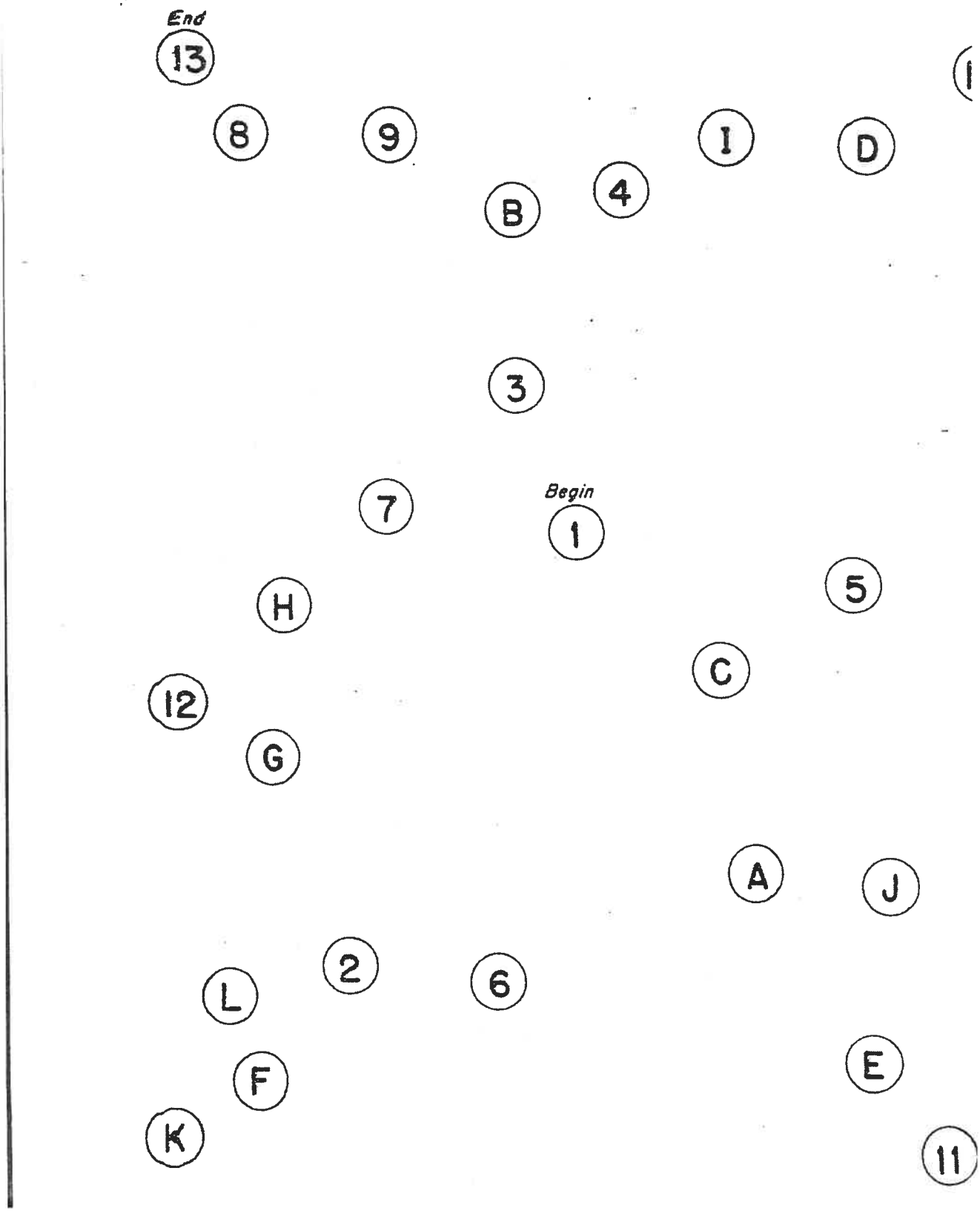
TRAIL MAKING

Part B

TIME:

SAMPLE

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11

APPENDIX III

SYMBOL DIGIT MODALITIES

(SMITH, 1982)

Symbol Digit Modalities Test

Aaron Smith, Ph.D.
University of Michigan

Published by

WESTERN PSYCHOLOGICAL SERVICES
Publishers and Distributors
12031 Wilshire Boulevard
Los Angeles, California 90025

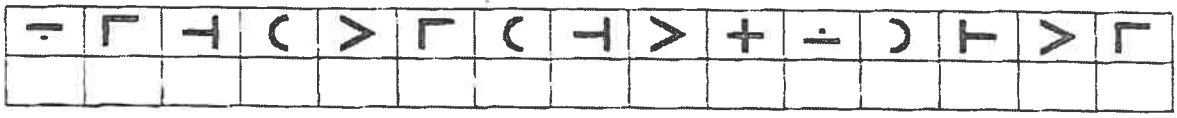
Name	Sex
Age	Birthdate
School	
Grade	
Hand Used (circle one) Left Right	
Date	

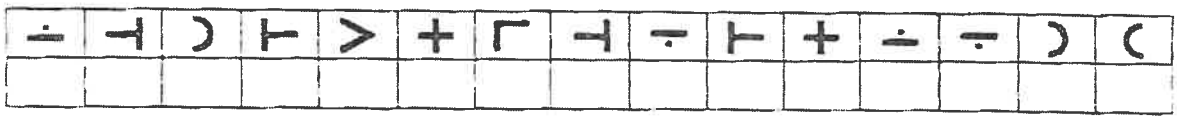
Written Score = ____

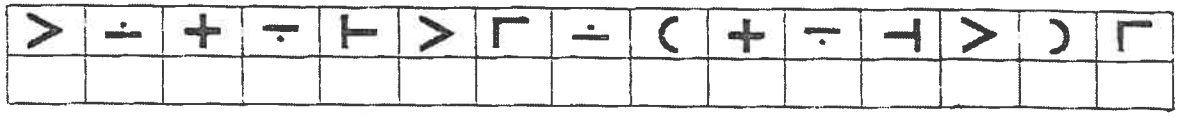
Oral Score = ____

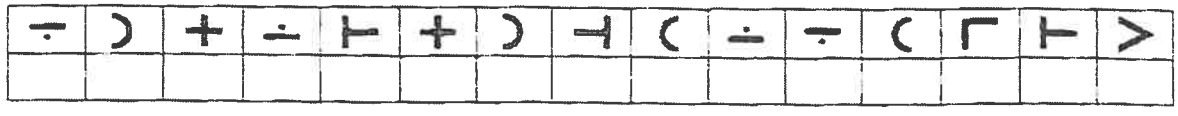
W-123A

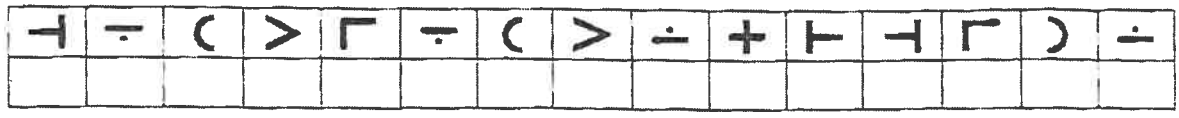
KEY











APPENDIX IV

WESCHLER ADULT INTELLIGENCE SCALE – REVISED

(WESCHLER, 1981)

1. INFORMATION — Discontinue after 5 consecutive failures.	Score 1 or 0
1. Flag	
2. Ball	
3. Months	
4. Thermometer	
START → 5. Sun	
6. Presidents	
7. Weeks	
8. Armstrong	
9. Panama	
10. Labor Day	
11. Brazil	
12. Hamlet	
13. Civil War	
14. Earhart	
15. Clothes	
16. Italy	
17. King	
18. Genesis	
19. Sahara	
20. Relativity	
21. Yeast	
22. Senators	
23. Paris	
24. Blood vessels	
25. Temperature	
26. Curie	
27. Population	
28. Koran	
29. Faust	
Note: Be sure to include scores for items 1-4 in Total.	Max=29
Total	

2. PICTURE COMPLETION — Discontinue after 5 consecutive failures.	Score 1 or 0
1. Door	
2. Tennis	
3. Frog	
4. Playing card	
5. Car	
6. Pitcher	
7. Glasses	
8. Pliers	
9. Boat	
10. Beach	
11. Mirror	
12. Crab	
13. Violin	
14. Sun	
15. Watch	
16. Leaf	
17. Man	
18. Horse	
19. Female profile	
20. Woodpile	
Total	Max=20

3. DIGIT SPAN — Discontinue after failure on BOTH TRIALS of any item. Administer BOTH TRIALS of each item, even if subject passes first trial.

	DIGITS FORWARD	Pass-Fail	Score 2, 1, or 0
1.	5 - 8 - 2		
	6 - 9 - 4		
2.	6 - 4 - 3 - 9		
	7 - 2 - 8 - 6		
3.	4 - 2 - 7 - 3 - 1		
	7 - 5 - 8 - 3 - 6		
4.	6 - 1 - 9 - 4 - 7 - 3		
	3 - 9 - 2 - 4 - 8 - 7		
5.	5 - 9 - 1 - 7 - 4 - 2 - 8		
	4 - 1 - 7 - 9 - 3 - 8 - 6		
6.	5 - 8 - 1 - 9 - 2 - 6 - 4 - 7		
	3 - 8 - 2 - 9 - 5 - 1 - 7 - 4		
7.	2 - 7 - 5 - 8 - 6 - 2 - 5 - 8 - 4		
	7 - 1 - 3 - 9 - 4 - 2 - 5 - 6 - 8		
	Total Forward		Max=14

	DIGITS BACKWARD*	Pass-Fail	Score 2, 1, or 0
1.	2 - 4		
	5 - 8		
2.	6 - 2 - 9		
	4 - 1 - 5		
3.	3 - 2 - 7 - 9		
	4 - 9 - 6 - 8		
4.	1 - 5 - 2 - 8 - 6		
	6 - 1 - 8 - 4 - 3		
5.	5 - 3 - 9 - 4 - 1 - 8		
	7 - 2 - 4 - 8 - 5 - 6		
6.	8 - 1 - 2 - 9 - 3 - 6 - 5		
	4 - 7 - 3 - 9 - 1 - 2 - 8		
7.	9 - 4 - 3 - 7 - 6 - 2 - 5 - 8		
	7 - 2 - 8 - 1 - 9 - 6 - 5 - 3		
	Total Backward		Max=14

*Administer DIGITS BACKWARD even if subject scores 0 on DIGITS FORWARD

[ ] + [ ] = Max=28

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

SAMPLES

10. DIGIT SYMBOL

1	2	3	4	5	6	7	8	9
—	⊥	⊐	⊔	⊔	○	∨	×	=

SCORE

11. SIMILARITIES Discontinue after 4 consecutive failures.	Score 2, 1, or 0
1. Orange—banana	
2. Dog—lion	
3. Coat—suit	
4. Boat—automobile	
5. Eye—ear	
6. Button—zipper	
7. North—west	
8. Egg—seed	
9. Table—chair	
10. Air—water	
11. Poem—statue	
12. Work—play	
13. Fly—tree	
14. Praise—punishment	
Total	Max=28

30 A B C D E

6. BLOCK DESIGN Discontinue after 3 consecutive failures.

Design	Time	Pass-Fail	Score (Circle the appropriate score for each design.)
1. 60"	1		2
	2		0 1
2. 60"	1		2
	2		0 1
3. 60"			0 — 16-60: 4 — 11-15: 5 — 1-10: 6
4. 60"			0 — 16-60: 4 — 11-15: 5 — 1-10: 6
5. 60"			0 — 21-60: 4 — 16-20: 5 — 11-15: 6 — 1-10: 7
6. 120"			0 — 36-120: 4 — 26-35: 5 — 21-25: 6 — 1-20: 7
7. 120"			0 — 61-120: 4 — 46-60: 5 — 31-45: 6 — 1-30: 7
8. 120"			0 — 76-120: 4 — 56-75: 5 — 41-55: 6 — 1-40: 7
9. 120"			0 — 76-120: 4 — 56-75: 5 — 41-55: 6 — 1-40: 7

Max 51

Total

7. ARITHMETIC Discontinue after 4 consecutive failures.

START →

Problem	Response	Score 1 or 0
1. 15"		
2. 15"		
3. 15"		
4. 15"		
5. 30"		
6. 30"		
7. 30"		
8. 30"		
9. 30"		

Problem	Response	Time	Score (Circle)
10. 60"			0 — 11-60: 1 — 1-10: 2
11. 60"			0 — 11-60: 1 — 1-10: 2
12. 60"			0 — 11-60: 1 — 1-10: 2
13. 60"			0 — 16-60: 1 — 1-15: 2
14. 120"			0 — 16-120: 1 — 1-15: 2

Max 19

Total

Note: Be sure to include scores for Items 1-9 in Total.

APPENDIX V

THE COGNITIVE DIFFICULTIES SCALE

(MCNAIR & KAHN, 1983)

Below are statements describing everyday inefficiencies, lapses of attention or memory, and related functions that people often notice about themselves. Please rate the degree to which each statement describes your typical or usual behavior during the past several days. Circle one response for each statement.

	Not at all	Rarely	Sometimes	Often	Very often
1. I have trouble recalling frequently used phone numbers.	0	1	2	3	4
2. I put down things (glasses, keys, wallet, purse, papers) and have trouble finding them.	0	1	2	3	4
3. When interrupted while reading, I have trouble finding my place again.	0	1	2	3	4
4. I need a written list when I do errands to avoid forgetting things.	0	1	2	3	4
5. I forget appointments, dates, or classes.	0	1	2	3	4
6. I forget to return phone calls.	0	1	2	3	4
7. I have trouble getting my keys into a lock.	0	1	2	3	4
8. I forget errands I planned to do on my way home.	0	1	2	3	4
9. I have trouble recalling names of people I know.	0	1	2	3	4
10. I find it hard to keep my mind on a task or job.	0	1	2	3	4

	Not at all	Rarely	Sometimes	Often	Very often
11. I have trouble describing a program I just watched on television.	0	1	2	3	4
12. I don't say quite what I mean to say.	0	1	2	3	4
13. I fail to recognize people I know.	0	1	2	3	4
14. I have trouble getting out information that's at the tip of my tongue.	0	1	2	3	4
15. I have trouble thinking of the names of objects.	0	1	2	3	4
16. I find it hard to understand what I read.	0	1	2	3	4
17. I miss the point of what other people are saying.	0	1	2	3	4
18. I forget names of people soon after being introduced.	0	1	2	3	4
19. I lose my train of thought as I listen to somebody else.	0	1	2	3	4
20. I forget steps in recipes I know well and have to look them up.	0	1	2	3	4
21. I forget what day of the week it is.	0	1	2	3	4
22. I forget to button or zip my clothing.	0	1	2	3	4
23. I need to check or double-check whether I locked the door, turned off the stove, etc.	0	1	2	3	4
24. I make mistakes in writing, typing, or operating a calculator.	0	1	2	3	4
25. I cannot keep my mind on one thing.	0	1	2	3	4

	Not at all	Rarely	Sometimes	Often	Very often
26. I need to have instructions repeated several times.	0	1	2	3	4
27. I leave out ingredients when I cook.	0	1	2	3	4
28. I have trouble manipulating buttons, fasteners, scissors or bottle caps.	0	1	2	3	4
29. I misplace my clothing.	0	1	2	3	4
30. I have trouble sewing or mending.	0	1	2	3	4
31. I find it hard to keep my mind on what I'm reading.	0	1	2	3	4
32. I forget right away what people say to me.	0	1	2	3	4
33. When walking or riding, I forget how I've gotten from one point to another.	0	1	2	3	4
34. I have trouble deciding if I've received the correct change.	0	1	2	3	4
35. I forget to pay bills, record checks, or mail letters.	0	1	2	3	4
36. I have to do things very slowly to be sure I'm doing them right.	0	1	2	3	4
37. My mind just goes blank at times.	0	1	2	3	4
38. I forget the date of the month.	0	1	2	3	4
39. I have trouble using tools (hammer, pliers) for minor household repairs.	0	1	2	3	4

APPENDIX VI

BECK DEPRESSION INVENTORY

(BECK, 1961)

BDI®

Date: _____

Name: _____ Marital Status: _____ Age: _____ Sex: _____

Occupation: _____ Education: _____

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

1	0	I do not feel sad.
	1	I feel sad.
	2	I am sad all the time and I can't snap out of it.
	3	I am so sad or unhappy that I can't stand it.
2	0	I am not particularly discouraged about the future.
	1	I feel discouraged about the future.
	2	I feel I have nothing to look forward to.
	3	I feel that the future is hopeless and that things cannot improve.
3	0	I do not feel like a failure.
	1	I feel I have failed more than the average person.
	2	As I look back on my life, all I can see is a lot of failures.
	3	I feel I am a complete failure as a person.
4	0	I get as much satisfaction out of things as I used to.
	1	I don't enjoy things the way I used to.
	2	I don't get real satisfaction out of anything anymore.
	3	I am dissatisfied or bored with everything.
5	0	I don't feel particularly guilty.
	1	I feel guilty a good part of the time.
	2	I feel quite guilty most of the time.
	3	I feel guilty all of the time.
6	0	I don't feel I am being punished.
	1	I feel I may be punished.
	2	I expect to be punished.
	3	I feel I am being punished.
7	0	I don't feel disappointed in myself.
	1	I am disappointed in myself.
	2	I am disgusted with myself.
	3	I hate myself.
8	0	I don't feel I am any worse than anybody else.
	1	I am critical of myself for my weaknesses or mistakes.
	2	I blame myself all the time for my faults.
	3	I blame myself for everything bad that happens.
9	0	I don't have any thoughts of killing myself.
	1	I have thoughts of killing myself, but I would not carry them out.
	2	I would like to kill myself.
	3	I would kill myself if I had the chance.
10	0	I don't cry any more than usual.
	1	I cry more now than I used to.
	2	I cry all the time now.
	3	I used to be able to cry, but now I can't cry even though I want to.
11	0	I am no more irritated now than I ever am.
	1	I get annoyed or irritated more easily than I used to.
	2	I feel irritated all the time now.
	3	I don't get irritated at all by the things that used to irritate me.
12	0	I have not lost interest in other people.
	1	I am less interested in other people than I used to be.
	2	I have lost most of my interest in other people.
	3	I have lost all of my interest in other people.
13	0	I make decisions about as well as I ever could.
	1	I put off making decisions more than I used to.
	2	I have greater difficulty in making decisions than before.
	3	I can't make decisions at all anymore.

_____ Subtotal Page 1

CONTINUED ON BACK

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14
0 I don't feel I look any worse than I used to.
1 I am worried that I am looking old or unattractive.
2 I feel that there are permanent changes in my appearance that make me look unattractive.
3 I believe that I look ugly.

15
0 I can work about as well as before.
1 It takes an extra effort to get started at doing something.
2 I have to push myself very hard to do anything.
3 I can't do any work at all.

16
0 I can sleep as well as usual.
1 I don't sleep as well as I used to.
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3 I wake up several hours earlier than I used to and cannot get back to sleep.

17
0 I don't get more tired than usual.
1 I get tired more easily than I used to.
2 I get tired from doing almost anything.
3 I am too tired to do anything.

18
0 My appetite is no worse than usual.
1 My appetite is not as good as it used to be.
2 My appetite is much worse now.
3 I have no appetite at all anymore.

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

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

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

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

_____ Subtotal Page 2

_____ Subtotal Page 1

_____ Total Score

APPENDIX VII

CASE REPORT FORMS

SMH BEATING HEART STUDY Patient's Initials: _____ _____ _____

Pt. #: _____ Randomization #_____ Date (d/m/y): ____ / ____ / ____

CONSENT (d/m/y): _____ /_____ /_____ RANDOMIZATION (d/m/y): _____ / _____ / _____

DEMOGRAPHICS

Subject Name: _____ J#: _____ D.O.B. (d/m/y): ____ / ____ /____

Age _____ Gender ❑ M ❑ F Height (cm): _____ Wt (kg): _____

Home Tel#: ( ) _____ Work # ( ) _____ Alt # ( ) _____

Referring Cardiologist _____ Tel # ( ) _____

CARDIAC HISTORY

Condition	NO	YES	DATE	COMMENT
1 Previous MI				
2 Previous Thrombolysis				Agent
3 Previous PTCA				
4 Angiography				Location
5 Other previous cardiac surgery				Type
6 Valvular Disease				Type
7 Arrhythmia				Atrial Ventricular
8 Pacemaker				
9 Other				Specify

PRIOR TO ADMISSION

CLASS	CCS	NYHA
Class I		
Class II		
Class III		
Class IV		

LV GRADE	✓
Grade I (> 50%)	
Grade II (35-50%)	
Grade III (20-35%)	
Grade IV (<20%)	

Carotid Doppler Appointment Booked	
Degree Stenosis	

LV ASSESSMENT	DATE
MUGA	
ECHO	
CATH	

SMH BEATING HEART STUDY **Patient's Initials: _____ _____ _____**

Pt. #: _____ **Randomization #_____** **Date (d/m/y): ____ / ____ / ____**

CARDIAC RISK FACTORS and MEDICAL HISTORY

Condition	NO	YES	IF YES ...	COMMENT
1 Cigarette smoking			Past ❑ Current ❑ Within 6 months ❑	Number of cigarettes per day?
2 HTN			Medication ❑ No ❑ Yes	Agent Dose
3 Family History heart disease			Primary relative < 65 years	
4 Diabetes			Insulin ❑ Oral Agent ❑	Agent Dose
5 Hypercholesterolemia &↑ TG			Medication ❑ No ❑ Yes	Agent Dose
6 PVD				
7 TIA (Transient Ischemic)				
8 Respiratory Disease			Asthma ❑ Emphysema ❑	Other
9 Other:				

INCLUSION and EXCLUSION CRITERIA

	Inclusion Criteria	Yes	No
1.	Age 18-80 years		
2.	Able to give informed consent and comply with the visit schedule		
3.	Accepted for elective CABG surgery		
4.	Complete revascularization can be done either on or off pump		
	Exclusion Criteria	Yes	No
1.	Ejection fraction ≤ 30 % by angiogram or echo (LV Grade III or IV)		
2.	Small vessels (vessels less than 1.5 mm)		
3.	Intramyocardial LAD		
4.	Severely calcified coronary arteries (discretion of surgeon)		
5.	Atherosclerosis of the ascending aorta		
6.	Use of radial artery anticipated		
7.	Redo CABG		
8.	Valve replacement or repair		
9.	Chronic Atrial fibrillation		
10.	3+ mitral valve regurgitation		
11.	> 80% stenosis of the left main coronary artery		
12.	Received aprotinin		
13.	Coagulation disorders (hx or HIT, life threatening reaction to protamin, liver disease with bleeding, or incompatibility to heparin, hemophilia)		
14.	Excessive alcohol use (> 14 drinks / week or documented in referral note)		
15.	History of neurologic disease (ie: previous CVA, psychotic disorders, Parkinson's, brain tumors, epilepsy, head injury with impaired cognition, Alzheimers, essential tremor)		
16.	Pulmonary disease (ie: FeV1 < 1.0 or history of severe COPD)		
17.	Uncontrolled hypertension SBP > 160 DBP > 90 on ≥ 3 anti-hypertensive medications		
18.	On medication that effect CNS or PNS (anti-psychotics or anti- epileptics)		
19	Any change (dose / type) in anti-depressant medication during course of the study.		
20.	Inability to comply with follow-up schedule		
21.	Inability to read and comprehend English.		
22.	Inability to provide informed consent		
23.	Pregnancy, lactation or any child-bearing potential		
24.	Has participated in other research studies in the last 30 days		

SMH BEATING HEART STUDY Patient's Initials: _____ _____ _____

Pt. #: _____ Randomization #_____ Date (d/m/y): ____/____/____

RANDOMIZATION

Patient meets criteria for randomization No ❑ Yes ❑

Date (d/m/y): _____/_____/_____ Time: ____ : ____ hrs

NEUROPSYCHOLOGIC TESTING

Baseline appt booked: _____ Testing Completed: Yes ❑ No ❑

If no, reason _____

3 month appt booked: _____ Testing Completed: Yes ❑ No ❑

If no, reason _____

Rescheduled appt: _____ ❑ Baseline ❑ 3 month Testing Completed ❑ Yes ❑ No

INTRA-OPERATIVE ASSESSMENT

SURGEON:

❑ Dr. Errett

❑ Dr. Bonneau

❑ Dr. Leclerc

❑ Dr. Salasidis

ANAESTHETIST:

❑ Dr. D. Mazer	❑ Dr. Houston	❑ Dr. Braden
❑ Dr. A. Baker	❑ Dr. S. Abrahamson	❑ Dr. Byrick
❑ Dr. H. Samulska	❑ Dr. W. Darrah	❑ Dr. H. Foster
❑ Dr. L. Hutchinson	❑ Dr. S. Lambert	❑ Dr. H. Joo
❑ Dr. P. Leung	❑ Dr. R. Levene	❑ Dr. D. McKee
❑ Dr. D. Mcknight	❑ Dr. J. McLean	❑ Dr. W. Noble
❑ Dr. J. Wassermann	❑ Dr. C. Tousignant	❑ Dr. R. Chen

The surgery was finally done:

❑ Electively = not admitted to hospital, date not changed because of symptoms.

❑ Urgently = surgery required in 24-72 hours

❑ Emergently = surgery required in 24 hours

SMH BEATING HEART STUDY **Patient's Initials:** _____ _____ _____

Pt. #: _____ **Randomization #**_____ **Date (d/m/y):** ____ / ____ / ____

Surgical technique:

On pump procedure: ❑ Pump Time: _____

Off pump procedure: ❑ Total Ischemic Time (off pump): _____

Aortic Cross Clamp: ❑ single ❑ partial occluding clamp (off pump)

Cross-clamp time:_____

Intra-Operative Blood Flow Measurement - Transonic Probe

Graft 1: _____ Flow: _____

Graft 2: _____ Flow: _____

Graft 3: _____ Flow: _____

Graft 4: _____ Flow: _____

Graft 5: _____ Flow: _____

Measure each grafted vessel 15 minutes post removal of cross clamp

INTRA-OPERATIVE COMPLICATIONS

	NO	YES	
Arrest	❑	❑	
Death	❑	❑	
Bleeding:	❑	❑	**Estimated Blood Loss:**_____
Arrhythmia:	❑	❑	**Specify:** Ventricular tachycardia ❑ Ventricular fibrillation ❑ SVT ❑ HB ❑
Hyperglycemia (≥ 14 mmolL/L)	❑	❑	
Significant Hypotension:	❑	❑	*Requiring IABP ❑ *Inotropes ❑

***defined as either IABP and/or inotropes at one of the following doses**

❑ Dobutrex > 5 ug/kg/min
❑ Epinephrine > 0.5ug/kg/min
❑ Dopamine >5ug/kg/min
❑ Levophed > 0.05ug/kg/min)

SMH BEATING HEART STUDY Patient's Initials: _____ _____ _____

Pt. #: _____ Randomization #_____ Date (d/m/y): ____ / ____ / ____

POST-OP LABORATORY RESULTS

INDEXES	NORMAL RANGE	DATE:	DATE:
		8 HOURS	24 HOURS
CK	0-160 UL		
CK-MB rel index	< 0.04		
Troponin I	< 1.1 ug/L		
BUN	3.0 - 7.0 mmol/L		
Creatinine	60 - 120 umol/L		
Hemoglobin	130 – 170 g/L		
WBC (corrected)	4.00 – 11.00 E9/L		

POST-OP INOTROPES REQUIRED NO ❑ YES ❑

If YES, defined as inotropes for > 6 hours at one of the following doses

❑ Dobutrex > 5 ug/kg/min
❑ Epinephrine > 0.5ug/kg/min
❑ Dopamine >5ug/kg/min
❑ Levophed > 0.05ug/kg/min)

POST-OP IABP REQUIRED NO ❑ YES ❑ - Total # hours _____

SMH BEATING HEART STUDY **Patient's Initials: _____ _____ _____**

Pt. #: _____ **Randomization #_____** **Date (d/m/y): ____ / ____ / ____**

FOLLOW-UP RESULTS: POST-OP ASSESSMENT:

Peri-operative morbidity/mortality during hospital admission:

Transfusion Required NO ❑ YES ❑ Total PRBC _____ Autololgous _____ Homologous _____	Platelets _____ Units Whole Blood _____ Units Plasma _____ Units
Chest Tube Losses	Volume ml:
Length of stay in the CVICU	Date (d/m/y) of admission to CVICU:_____ Time: ____ : ____ hrs Date (d/m/y) of discharge to CVICU:_____ Time: ____ : ____ hrs
Death occurs during hospital stay Defined by the death certificate. NO ❑ YES ❑	If yes, date(d/m/y) of death:_____ time: ____ : _____ hrs Cause: Non Cardiac ❑ Cardiac ❑
Atrial Fibrillation requiring a change in Rx: (diagnosed by an ECG or charted as requiring treatment) NO ❑ YES ❑	If yes, Treatment received:
New Stroke Post-op NO ❑ YES ❑	Persistent neurological deficit atE the time of discharge ± CT scan c/w a new stroke.
MI post-op NO ❑ YES ❑	If yes, NQWMI ❑ (CPK-MB > 100 +) QWMI ❑
Infection Post-op Use of antibiotic(s) for a specific clinically diagnosed infection that occurs post-operatively. NO ❑ YES ❑	Pneumonia ❑ UTI ❑ Wound infection ❑ Sepsis ❑ Other: ❑ specify:_____ Antibiotic Start Date (d/m/y) : _____ Stop Date:
Use of pacing post-op YES ❑ NO ❑	If yes, # of hours requiring pacing:
Length of time on mechanical ventilation	# of hours:
Length of stay in hospital	Date (d/m/y) of admission to hospital:_____ Time: _____ : _____ hrs Date (d/m/y) of discharge from hospital:_____ Time: _____ : _____ hrs

SMH BEATING HEART STUDY Patient's Initials: _____ _____ _____

Pt. #: _____ Randomization #_____ Date (d/m/y): ____/____/____

CONCOMITANT MEDICATION PAGE _____ of _____

- ✔ PTR box if medication is prior to randomization
- — (Dash) = Discontinued medication
- ✔ AE box if medication is added for an AE

MEDICATIONS							POST-OP DAY						
MEDICATION	DOSE	RTE	FREQ	INDICATION	START DATE	END DATE	1	2	3	4	5	6	7
				☐ AE	☐ PTR								
				☐ AE	☐ PTR								
				☐ AE	☐ PTR								
				☐ AE	☐ PTR								
				☐ AE	☐ PTR								
				☐ AE	☐ PTR								
				☐ AE	☐ PTR								
				☐ AE	☐ PTR								
				☐ AE	☐ PTR								
				☐ AE	☐ PTR								

HERBAL REMEDIES/VITAMINS							POST-OP DAY						
SUPPLEMENT	DOSE	RTE	FREQ	INDICATION	START DATE	END DATE	1	2	3	4	5	6	7
				☐ AE	☐ PTR								
				☐ AE	☐ PTR								
				☐ AE	☐ PTR								
				☐ AE	☐ PTR								

SMH Beating Heart Study **Patient Initials** ____ ____ _____
Pt# _____ **Randomization #** _____ **Date** ____ / ____ / _____

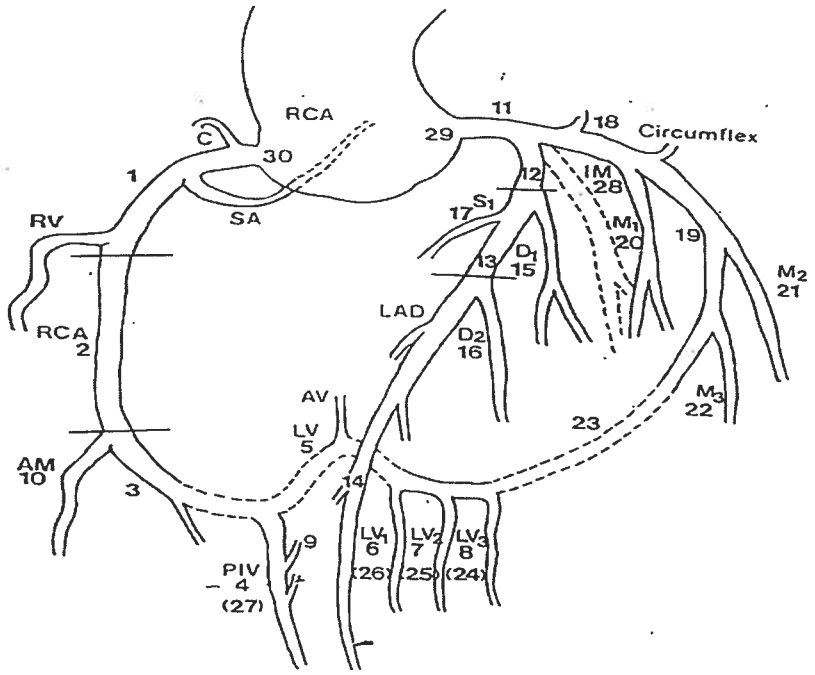
Intra-operative Graft Placement and Flow

1	Proximal RCA	17	1st Septal
2	Mid RCA	18	Proximal Circumflex
3	Distal RCA	19	Mid Circumflex
4	PIV (Right – dominant)	20	1st Obtuse Marginal
5	PL branch	21	2nd Obtuse Marginal
6 – 9	Septals (from RCA)	22	3rd Obtuse Marginal
10	Acute Marginal	23	Distal Circ (Left dominant)
11	Left Main	24-26	Septals (from Circumflex)
12	Proximal LAD	27	PIV (left – dominant)
13	Mid LAD	28	Intermediate
14	Distal LAD	29	Osteal LMC
15	1st Diagonal	30	Osteal RMC
16	2nd Diagonal		

Mark location of distal anastomosis on the diagram below.
Next to the graft symbol, indicate the dopler flow 15 minutes post cross-clamp removal.
For **beating heart**, also indicate the ischemia time for each distal anastomosis.

LEGEND:
○ SVG (Dopler flow) (Ischemia time)
● LIMA / RIMA (Dopler flow) (Ischemia time)
⊗ Free Arterial graft (Free LIMA, Free RIMA or Radial) (Dopler flow) (Ischemia time)

CORONARY SEGMENT ANGIOGRAPHIC DIAGRAM



SMH BEATING HEART STUDY

Patient's Initials: _____ _____ _____

Pt. #: _____ Randomization #_____ Date (d/m/y): ____ / ___ / ____

#	NAME	PRE-OP % Occl	GRAFT		POST – OP ANGIOGRAPHY					
					NATIVE	GRAFT				
			Conduit	Doppler Flow	% Occl	Proximal Anast A - C	Distal Anast A - C	Trunk A - C	Overall A - C	TIMI FLOW 0 - III
1	Proximal RCA									
2	Mid RCA									
3	Distal RCA									
4	PIV (Right - dominant)									
5	PL branch									
6 - 9	Septals (from RCA)									
10	Acute Marginal									
11	Left Main									
12	Proximal LAD									
13	Mid LAD									
14	Distal LAD									
15	1st Diagonal									
16	2nd Diagonal									
17	1st Septal									
18	Proximal Circumflex									
19	Mid Circumflex									
20	1st Obtuse Marginal									
21	2nd Obtuse Marginal									
22	3rd Obtuse Marginal									
23	Distal Circ (Left dominant)									
24 - 26	Septals (from Circumflex)									
27	PIV (left - dominant)									
28	Intermediate									
29	Osteal LMC									
30	Osteal RMC									

LEGEND A = Excellent B = Fair (visual % occluded – two observers) C = 100% occluded

SMH BEATING HEART STUDY **Patient's Initials:** _____ _____ _____

Pt. #: _____ **Randomization #**_____ **Date (d/m/y):** ____ / ____ / ____

3 MONTH FOLLOW-UP

Vital Signs: BP _____ / _____ HR _____ BPM

Angina pattern (CCS Class)

❑ Class I ❑ Class II ❑ Class III ❑ Class IV

CHF (NYHA Class)

❑ Class I ❑ Class II ❑ Class III ❑ Class IV

Any cardiac hospital admissions during study period? ❑ No ❑ Yes

If yes, describe diagnosis:

	NO	YES	
UAP	❑	❑	
MI	❑	❑	
CHF	❑	❑	
Arrhythmia	❑	❑	
Other	❑	❑	Specify: _____

Any death during study period? ❑ NO ❑ YES ❑ Cardiac ❑ Non-cardiac

Date (d/m/y) of death: _____ Time of death: _____ : _____ hrs

CURRENT MEDICATIONS

MEDICATION - DOSE - FREQ	MEDICATION – DOSE - FREQ
1.	7.
2.	8.
3.	9.
4.	10.
5.	11.
6.	12

SMH BEATING HEART STUDY **Patient's Initials:** _____ _____ _____

Pt. #: _____ **Randomization #**_____ **Date (d/m/y):** ____ / ____ / ____

ADVERSE EVENT FORM **PAGE** _____ **of** _____

1) Event: _____

2) Event description: _____

_____

3) Severity: ❑ Mild (easily tolerated) ❑ Moderate (interferes with usual activities)
❑ Severe (incapacitated, unable to work or do usual activities)

4) Duration: Onset (d/m/y): ____ / ____ / ____ Ended (d/m/y): ____ / ____ / ____

❑ Continuing

5) Action: _____

6) Treatment required: ❑ NO ❑ YES, specify _____

7) Clinical Outcome:

❑ Recovered (no residual effects) ❑ Recovered (with residual effects)

❑ Not yet recovered ❑ Died due to this event

❑ Died, other causes ❑ Unknown

8) Comments:

_____

_____

_____

_____

_____

_____ _____

Signature of Coordinator Signature of Investigator

SMH BEATING HEART STUDY **Patient's Initials:** _____ _____ _____

Pt. #: _____ **Randomization #**_____ **Date (d/m/y):** ____ / ____ / ____

STATUS AT STUDY CLOSE OUT

- ❑ completed study protocol
- ❑ prematurely dropped out of trial Date (d/m/y) of drop out _____
- ❑ lost to follow-up Date (d/m/y) last contacted _____
- ❑ deceased Date (d/m/y) patient died _____

Person completing this form: _____

Name of Investigator (print): _____

Investigator's Signature: _____

Date (d/m/y) form signed: _____

Amphetamines

Dextroamphetamine

Benzodiazepines (on initiation or high doses)

Diazepam
Lorazepam
Alprazolam
Oxazepam
Bromazepam
Temazepam
Chlordiazepoxide
Clonazepam
Clorazepate
Flurazepam
Nitrazepam

Antipsychotics

Chlorpromazine
Methotrimeprazine
Mesoridazine
Pericyazine
Pipotiazine
Thioridazine
Fluphenazine
Trifluoperazine
Flupenthixol
Zuclopenthixol
Haloperidol
Pimozide
Loxapine
Clozapine
Risperidone

Anticonvulsants (in toxic doses)

Phenobarbital
Phenytoin
Ethosuximide
Methsuximide
Lomotrigine
Primidone
Valproic Acid
Carbamazepine
Gabapentin

Antiparkinsons

Levodopa
Pergolide
Pramipexole
Ropinirole

APPENDIX VIII

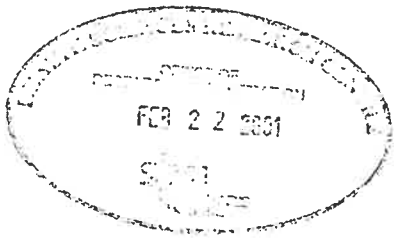
CONSENT FORMS

ST-MICHAEL'S HOSPITAL

ST. MICHAEL'S HOSPITAL

30 Bond Street
Toronto, Ontario
M5B 1W8

A teaching hospital
affiliated with the
University of Toronto



Consent to Participate in a Research Study

Before agreeing to participate in this research study, it is important that you read and understand this research consent form. This form provides all the information we think you will need to know in order to decide whether you wish to participate in the study. If you have any questions after you read this form, ask your doctor. You should not sign this form until you are sure you understand everything on this form. You may also wish to discuss your participation with your family doctor, a family member or a close friend. It is important that you are completely truthful with your study doctor with respect to your health history and any medications you may be taking, in order to prevent any unnecessary harm to you should you decide to participate in this study.

Title of Research Study
A prospective Randomized Outcome Evaluation of Beating Heart versus Cardiopulmonary Bypass - Arrested Heart – Coronary Artery Bypass Grafting

Short Title
Outcome Trial of Beating Heart Bypass Surgery

Investigators:

Lee Errett, MD FRCSC, FRCS
Chief, Division of Cardiovascular and Thoracic Surgery
Tel. (416) 864-5303 Fax (416) 864-5185

ASSOCIATE INVESTIGATORS IN THE DIVISION OF CARDIOVASCULAR AND THORACIC SURGERY, ST MICHAEL'S HOSPITAL

Daniel Bonneau, MD FRCSC	Tel. (416) 864-5706
David Latter, MD FRCSC	Tel. (416) 864-5366
Yves LeClerc, MD FRCSC	Tel. (416) 864-5548
Gary Salasidis, MD FRCSC	Tel. (416) 864-5706
Robert Chisholm, MD FRCPC	Tel. (416) 864-5490
David W. Courtman, Ph.D.	Tel. (416) 864-6060 ext. 2420
Mary Keith, Ph.D.	Tel. (416) 864-6060 ext. 4008
Dalia Slonim, Psy.D.	Tel. (416) 360-4000 ext. 2935
Osman Al-Radi, MD (Resident)	Tel. (416) 334-0516

Study Sponsors

Division of Cardiovascular and Thoracic Surgery, St. Michael's Hospital
Medtronic
700 Central Av. NE, Minneapolis, MN

Purpose of the Research

Your doctors have found that there are blockages in the arteries that supply your heart. They have recommended that you have coronary bypass surgery to bring more blood to your heart. These bypasses are usually constructed from conduit (arteries or veins) removed from other parts of your own body. Your surgeon will randomly perform these bypass procedures by placing you on a heart-lung machine, stopping your heart and restarting it once the operation is complete, alternatively your surgeon may randomly perform this procedure on your heart while it is beating. Both of these techniques are routinely used at St. Michael's Hospital. You are being asked to participate in a study which will compare the outcomes of these two surgical procedures. The primary purpose of this study is to see if bypasses constructed using the two surgical techniques are equally successful. However, other outcomes that will be compared include use of blood and blood products, the costs associated with each procedure well as the time spent in the hospital and the intensive care unit.

Description of the Research

If you agree to participate in this study, you will undergo coronary bypass surgery as has previously been explained to you. On the day of your surgery you will be assigned in a random fashion (flipping a coin) to receive either a beating heart procedure or surgery performed while on a heart –lung machine with the heart stopped. The operation and post-operative care will otherwise be performed in the standard fashion.

Immediately, within 14 days, prior to your surgery you will be asked to undergo a series of 12 neuropsychological examinations performed by a trained psychologist. During this examination you will be asked to respond to a number of questions as well as perform some routine tests designed to evaluate a number of cognitive abilities. You will be asked to undergo this same examination 3 months after your operation. These neuropsychological examinations are not normally performed on patients before or after coronary bypass surgery. In addition, you will be asked to undergo an ultrasound of the vessels in your neck (carotid arteries) in order to determine if there is any blockage of these vessels.

You will be asked to undergo a number of blood tests before and immediately after the operation. These tests will involve the removal of four test tubes of blood (approximately 4 teaspoons) from a vein. These blood tests are routinely performed on patients after coronary artery bypass surgery.

You will also be asked to undergo a diagnostic cardiac angiogram 3 months after your surgery. These angiograms are very similar to the cardiac catheterization that you have had in the past. A cardiologist will insert catheters in your blood vessels and inject dye into your coronary arteries to see if the bypass grafts are still open. Patients who have coronary artery bypass and are free of symptoms do not routinely undergo a follow up angiogram.

The results of your surgery, tests and long-term outcome will be reported to Medtronic, the manufacturer of surgical stabilizer which may have been used during your operation. The results will also be reported in medical journals. Your name and identity will be kept secret in these reports by using a code number.

If you choose not to participate in this study, you will continue to receive the standard care from your doctors. Your operation will be performed using the optimal technique as decided by you and your surgeon. You may withdraw from this study at any time.

Potential Harms (Injury, Discomforts or Inconvenience)

The major risks and discomforts of coronary artery surgery, which your surgeon has already discussed with you, are not greatly affected by the choice of the surgical procedure (beating versus non-beating heart). As with all bypass surgery, the conduit grafts can become clogged and cease to provide blood to the heart. The rate at which this occurs has been reported to be low (less then 10% in the first year after surgery). Preliminary studies have reported similar rates of failure for grafts implanted with beating or non-beating procedures. The purpose of this study is to determine if small differences in failure rates do exist between the two procedures when performed by the same surgeons.

You will be asked to undergo a coronary angiogram 3 months post-operatively. You will have most likely had an angiogram prior to your surgery to determine which arteries of your heart were blocked. In this case, the angiogram will be used to look at how well the dye (injected into a vein above the heart) flows through your new bypassed vessels. The coronary angiogram carries a number of risks. These include a 1% risk of a major dye reaction (allergic type of reaction to the coloring agent used during the angiogram), a 0.005% risk of arterial injury (damage to the artery during the procedure), a 0.1-0.5% of renal failure (problems with your kidneys after injection of the dye), exposure to x-rays as well as a 0.001% chance of stroke or death. The overall risk of an angiogram is estimated to be 1%. While some of these complications may be serious, the majority are minor, such as bruising of the groin (1-2%), and in the instances when they do occur they are easily treated.

The radiation exposure you will receive from participating in this study is equivalent to an exposure of 1.2 rems to your whole body. Naturally occurring radiation

(cosmic radiation, radon, etc.) produces whole body radiation exposures of about 0.3 rems per year. An average chest x-ray will expose you to 14-27 mrem of radiation.

The drawing of blood specimens from a vein usually causes mild discomfort and may cause a small amount of bleeding, bruising or redness. You will be asked to undergo an ultrasound of vessels in your neck (carotid arteries) prior to your surgery. This procedure is not normally performed on all patients prior to coronary artery surgery but will determine if there are any deposits of fat in the arteries in your neck. This is a non-invasive procedure with no increased risk.

Women as Research Subjects

If you are female, you may participate in this study if you are certain you are not pregnant. A pregnancy test will be performed at your request. If you become pregnant (or suspect pregnancy), before this study is completed, you must inform the investigator as it may not be adviseable to conduct an angiogram if you are pregnant.

Potential Benefits

There are no major potential benefits to you for participating in this study. Your participation in this research may allow the medical profession to learn how to design the best surgical procedure to help people with problems similar to yours in the future. One minor benefit to you includes obtaining information regarding the status of your bypassed vessels post-surgery.

Treatment Options

If you decide not to participate in this study, your treatment will continue in the usual manner. In other words, your surgeon will perform the coronary artery bypass surgery using the surgical technique most suitable to your condition. If you sign this form, you are willing to join the research project described to you on this form. Your doctors, or investigators, did explain the other kinds of treatment available to you and to others. You should ask the principal investigator, listed below, any questions which you might have about this research study. You may ask him/her questions in the future if you do not understand something that is being done. The investigators (or doctors) will share with you any new findings which may develop while you are participating in this study.

Confidentiality and Privacy

The records from this research study will be kept confidential and will not be given to anyone who is not helping on this study. Confidentiality will be respected and no information that discloses the identity of the subject will be published without consent unless required by law. The institutional Research Ethics Board (REB) may inspect your medical/research records a part of their monitoring of this study.

Compensation for Injury:

If you suffer a physical injury as a direct result of the administration of study medication, device or procedures, medical care may be obtained by you in the same manner as you would ordinarily obtain any other medical treatment. In no way does signing this form waive your legal rights nor relieve the investigator, sponsors or involved institutions from their legal and professional responsibility.

Participation and Withdrawal:

Your participation in this study is completely voluntary. If you chose not to participate, you will continue to have access to customary care at St. Michael's hospital. If you choose to participate, you can withdraw at any time without any effect on the care you will receive at St. Michael's Hospital.

Contact

If you wish to talk to anyone about this research study because you think you have not been treated fairly, or think you have been hurt by joining this study, or you have any other questions about the study, you should call the principle investigator, Dr. Lee E. Errett, at (416) 864-5303.

If you wish to discuss issues related to your neuropsychological evaluation you can contact Dr. Dalia Slonim at (416) 360-4000 ext. 2935.

Research Ethics Board Contact

If you have any questions as a research subject, you may contact the Chair of the Research Ethics Board (REB) of St. Michael's Hospital, Dr. Julie Spence (416) 360-4000 Ext. 2557.

A prospective Randomized Outcome Evaluation of Beating Heart versus Cardiopulmonary Bypass – Arrested Heart – Coronary Artery Bypass Grafting.

Consent to Participate in a Research Trial

I acknowledge that the research study described above have been explained to me and that any questions that I have asked have been answered to my satisfaction. I have been informed of the alternatives to participation in this study, including the right not to participate and the right to withdraw without compromising the quality of medical care at St. Michael's Hospital for me and for other members of my family. As well, the potential risks, harms and discomforts have been explained to me and I also understand the benefits (if any) of participating in the research study.

I understand that I have not waived my legal rights nor released the investigators, sponsors, or involved institutions from their legal and professional duties. I know that I may ask now, or in the future, any questions I have about the study or the research procedures. I have been assured that records relating to me and my care will be kept confidential and that no information will be released or printed that would disclose personal identity without my permission unless required by law. I have been given sufficient time to read and understand the above information.

I hereby consent to join the Outcome Trial of Beating Heart Surgeries and will be given a copy of this consent form

Subject's Signature	Subject's Name (Printed)
Signature of Parent or Guardian (when applicable)	Printed Name of Parent or Guardian
Witness to Consent Procedure (Signature)	Witness to Consent Procedure (Printed)
Signature of Investigator or Approved Designatee	Investigator Name Printed
Date	

SMH
ST. MICHAEL'S HOSPITAL
Terrence Donnelly Heart Centre

Yves Leclerc
MD FRCSC FACS
Cardiac Surgeon

tel: (416) 864-5548
fax: (416) 864-5187
internet: [redacted]

Division of Cardiovascular and Thoracic Surgery

30 Bond Street
Queen Wing, Suite 3-078
Toronto, Ontario
M5B 1W8

University of Toronto

Consent to Participate in a Research Study II

This form provides additional information that explains what this affiliated study intends to research and comprehend. It is important that you read and understand this consent form. You will then be able to decide if you want to participate in this study.

In many respects the purpose of this study is the same as the one outlined in the previous consent form. Should you choose to participate in this study as well, you will undergo the same Neuropsychological tests as the other study plus one more.

Title of Research Study:

Objective and Subjective Neuropsychological Impairment and the Relationship to Depression, in Randomized CPB and Off-Pump Patients, Following Heart Surgery.

Short Title:

Objective and Subjective Neuropsychological Impairment Following Heart Surgery

Investigators:

Dr Yves Leclerc, MD FRCSC
Division of Cardiovascular and Thoracic Surgery
Contact telephone number: (416) 864 – 5548

Suzanne Geishardt, M.Ps.
University of Montreal
Department of Psychology
Contact telephone number at St-Michael's Hospital: (416) 864 - 5548

Study Sponsors:

Division of Cardiovascular and Thoracic Surgery, St.Michael's Hospital
Medtronic
700 Central Avenue NE. Minneapolis, MN

Purpose of Research:

Your doctors have found that there are blockages in the arteries that supply your heart. They have recommended that you have coronary bypass surgery to bring more blood to your heart. These bypasses are usually constructed from conduit (arteries or veins) removed from other parts of your own body. Your surgeon will randomly perform these bypasses procedures by placing you on a heart-lung machine, stopping your heart and restarting it once the operation is complete, alternatively your surgeon may randomly perform this procedure on your heart while it is beating. Both of these techniques are routinely used at St.Michael's Hospital. You are being asked to participate in a study that will compare the outcomes of these two surgical procedures. The primary purpose of this study is to compare the two types of surgeries in terms of your mood, your neuropsychological function as well as how you perceive and report your neuropsychological abilities.

Description of research:

As in the other study, you will undergo coronary bypass surgery as has been previously explained to you. Before the day of surgery, you will be assigned in a random fashion (flipping a coin) to receive either a beating heart procedure or surgery performed while on a heart–lung machine while the heart is stopped. The operation and post-operative care will otherwise be performed in a standard fashion.

Immediately (within 14 days) prior to surgery you will be asked to undergo a series of NP examinations performed by a trained psychologist. If you choose to participate in this study, one more test will be added to the total amount of tests of the previous study. This additional test assesses perceived neuropsychological function and will be administered at the same time as the other tests (1 – 2 weeks prior to surgery as well as 3 months after surgery). This additional test is self-administered (requires answering questions directly on the form) and takes about 10 minutes to complete. These neuropsychological examinations are not normally performed on patients before and after coronary bypass surgery.

This study will be presented as a Doctoral research project (a graduate study program). As for the other study, these results may also be reported in a research journal. The results of these tests may also be reported to Medtronic, the manufacturer of the surgical stabilizer that may have been used during your operation. Your name and identity will be kept strictly confidential in all of these reports by using a code number.

If you choose not to participate in this study, you will continue to receive the standard care from your doctors. Your operation will be performed using the optimal technique as decided by you and your surgeon. You may withdraw from this study at any time

Potential Harms (injury, discomforts or inconvenience):

If you have consented to participate in the "Outcome Trial of Beating Heart Bypass Surgery" study, you will be subject to the same risks and discomforts in this study. The major risks and discomforts of coronary artery surgery, which your surgeon has already discussed with you, are not greatly affected by the choice of surgical procedure (beating heart versus non-beating heart). As with all bypass surgery, the conduits grafts can become clogged and cease to provide blood to the heart. The rate at which this occurs has been reported to be low (less then 10% in the first year of surgery). Preliminary studies have reported similar rates of failure for grafts implanted with beating or non-beating procedures. One of the purposes of this study is to determine if small differences in failure rates do exist between the two procedures when performed by the same surgeons.

You will be asked to undergo a coronary angiogram 3 months post-operatively. You will have most likely had an angiogram prior to your surgery to determine which arteries of your heart were blocked. In this case, the angiogram will be used to look at how well the dye (injected into a vein above the heart) flows through your new bypassed vessels. The coronary angiogram carries a number of risks. These include a 1% risk of a major dye reaction (allergic type reaction to the coloring agent used during the angiogram), a 0.005% risk of arterial injury (damage to the artery during the procedure), a 0.1 – 0.5% risk of renal failure (problems with your kidneys after injection of the dye), exposure to x-ray as well as 0.001% chance of a stroke or death. The overall risk of an angiogram is estimated to be 1%. While some of these complications may be serious, the majority are minor, such as bruising of the groin (1 – 2%), and the instances when they do occur they are easily treated.

The radiation exposure you will receive from participating in this study is equivalent to an exposure of 1.2 rems of your whole body. Naturally occurring radiation (cosmic radiation, radon, etc.) produces whole body radiation exposures of about 0.3 rems per year. An average chest x-ray will expose you to 14 – 27 mrem of radiation.

The drawing of blood specimens from a vein usually causes mild discomfort and may cause a small amount of bleeding, bruising or redness. You will be asked to undergo an ultrasound of vessels in your neck (carotid arteries) prior to your surgery. This procedure is not normally performed on all patients prior to coronary artery surgery but will determine if there are any deposits of fat in the arteries in your neck. This is a non-invasive procedure with no increased risk.

Woman as Research Participants:

If you are female, you may participate in this study if you are certain you are not pregnant. A pregnancy test will be performed at your request. If you become pregnant (or suspect pregnancy), before this study is completed, you must inform the investigator, as it may not be advisable to conduct an angiogram if you are pregnant.

Potential Benefits:

There are no major potential benefits to you for participating in this study. Your participation in this research may allow the medical profession to learn how to design the best surgical procedure to help people with problems similar to yours in the future. One minor benefit to you includes obtaining information regarding the status of your bypassed vessels post-surgery.

Treatment Options:

If you decide not to participate in this study, your treatment will continue in the usual manner. In other words, your surgeon will perform the coronary artery bypass surgery using the surgical technique most suitable to your condition. If you sign this form, you are willing to join the research project described to you on this form. Your doctors, or investigators, did explain the other kinds of treatment available to you and to others. You should ask the principal investigator, listed below, any questions which you might have about this study. You may ask him/her questions in the future if you do not understand something that is being done. The investigators (or doctors) will share with you any new findings that may develop while you are participating in this study.

Confidentiality and Privacy:

The records from this study will be kept confidential and will not be given to anyone who is not helping on this study. Confidentiality will be respected and no information that discloses your identity will be published without consent unless required by law. The institutional Research Ethics Board (REB) may inspect your medical/research records as a part of their monitoring of this study.

Compensation for Injury:

If you suffer a physical injury as a direct result of the administration of study medication, device or procedures, medical care may be obtained by you in the same manner as you would ordinarily obtain any other medical treatment. In no way does signing this waive your legal rights nor relieve the investigator, sponsors or involved institutions from their legal and professional responsibility.

Participation and Withdrawal:

Your participation in this study is completely voluntary. If you choose not to participate, you will continue to have access to customary care at St.Michael's hospital. If you choose to participate, you can withdraw at any time without any effect on the care you will receive at St.Michael's hospital.

Contact:

If you wish to talk to anyone about this research study because you think you have not been treated fairly, or think you have been hurt by joining this study, or you have any other questions about this study you should call Dr Yves Leclerc at (416) 864 – 5548 or Suzanne Geishardt also at the same telephone number.

Research Ethics Board Contact:

If you have any questions as a research subject, you may contact the Chair of the Research Ethics Board (REB) of St.Michael's hospital, Dr Julie Spence (416) 360 – 4000 Ext. 2557.

Objective and subjective Neuropsychological Impairment and the Relationship to Depression, in Randomized CPB and Off-pump patients, Following Heart Surgery.

Consent to participate in a research trial

I acknowledge that the research study described above has been explained to me and that any questions that I asked has been answered to my satisfaction. I have been informed of the alternatives to participation in this study, including the right not to participate and the right to withdraw without compromising the quality of medical care at St-Michael's Hospital for me and for the other members of my family. As well, the potential risks, harms and discomforts have been explained to me and I also understand the benefits (if any) of participating in the research study.

I understand that I have not waived my legal rights nor released the investigators, sponsors, or involved institutions from their legal and professional duties. I know that I may ask now, or in the future, any questions I have about the study or the research procedures. I have been assured that records relating to me and my care will be kept strictly confidential and that no information will be released or printed that will disclose personal identity without my permission unless required by law. I have been given sufficient time to read and understand the above information.

I hereby consent to join the Objective and Subjective Neuropsychological Impairment Following Heart Surgery study and will be given a copy of this consent form.

Participant's Signature	Participant's Name (Printed) (Printed)	Date
Signature of Parent or Guardian (when applicable)	Name of Parent or Guardian (Printed)	Date
Witness to Consent Procedure (Signature)	Witness to Consent Procedure (Printed)	Date
Signature of Investigator (or Approved Designate)	Investigator Name (Printed)	Date

APPENDIX IX

APPROVAL LETTER

RESEARCH ETHICS BOARD

ST-MICHAEL'S HOSPITAL

Research Ethics Board
Office of Research Administration
Telephone: 416 864-6060 Ext 2557
Facsimile: 416 864-6043
e-mail: [redacted]

Leading with Innovation
Serving with Compassion

ST. MICHAEL'S HOSPITAL
A teaching hospital affiliated with the University of Toronto

November 27 2001

Dr Lee Errett
Division of Cardiovascular and Thoracic Surgery
St Michael's Hospital

Dear Dr Errett:

Re: REB 2K-123: A prospective randomized outcome evaluation of Beating Heart versus Cardiopulmonary Bypass-Arrested Heart: Coronary Artery Bypass Grafting:
Outcome trial of Beating Heart versus Cardiopulmonary Bypass Assisted Surgery
[Amendment: Objective and Subjective Neuropsychological impairment and the relationship to Depression, in randomized CPB and Off-Pump patients, following Heart Surgery]

REB APPROVAL:	**Original Approval Date**	**September 18 2000**
	Annual Review Date	**September 18 2002**

Thank you for your recent communications of November 20 2001 responding to the comments outlined via E-mail dated November 12 2001 regarding Amendment to the above named study. You have adequately addressed all those issues, as well as modified the consent form, with changes highlighted.

I am happy to issue approval for Amendments to the protocol along with the revised consent form dated November 11 2001. In addition, the Cognitive Difficulties Scale and the Perceived Cognitive Function test are appropriate and hereby approved.

During the course of this investigation, any significant deviations from the approved protocol and/or unanticipated developments or significant adverse events should immediately be brought to the attention of the Research Ethics Board.

Good luck with your investigation.

With best wishes

[redacted]

Julie Spence MD
Chair
Research Ethics Board

JS/dp

30 Bond Street
Toronto, Ontario
M5B 1W8
416-360-4000
www.stmichaelshospital.com

APPENDIX X

STATISTICAL ANALYSIS RESULTS

Hypothesis 1 – The beating heart surgery technique will have significantly lower objective NP impairment in comparison with CPB 4 months after surgery

Table XIV – Table of impairment by age by treatment

Age Group	Percent with NP Impairment		Statistical Significance
	Beating Heart	Conventional	
40-49 years	0.0% (0)	0.0% (0)	n/a
50-59 years	22.2% (2)	11.1% (2)	p=0.5815
60-69 years	6.7% (1)	27.3% (3)	p=0.2789
70 + yrs.	37.5% (3)	20.0% (1)	p=1.0000

All significance testing was performed using Fisher's exact test. No evidence of a significant relationship was found.

Hypothesis 2 – There will be no significant relationship between self-reported changes in NP function and objective NP performance, 4 months after surgery, for both groups combined

Table XV: Correlation of changes in subjective and RAVLT test scores;

40-49 years

Objective Measure	**Correlation with Subjective**	**Statistical Significance**
RAVLT	r=-0.82	p=0.1814

Table XVI: Correlation of changes in subjective and RAVLT test scores;

50-59 years

Objective Measure	**Correlation with Subjective**	**Statistical Significance**
RAVLT	r=-0.44	p=0.0614

Table XVII: Correlation of changes in subjective and RAVLT test scores;

60-69 years

Objective Measure	Correlation with Subjective	Statistical Significance
RAVLT	r=-0.51	p=0.1574

Table XVIII: Correlation of changes in subjective and RAVLT test scores;

70 + years

Objective Measure	Correlation with Subjective	Statistical Significance
RAVLT	r=-0.05	p=0.8929

These results should be interpreted with caution since breaking the results out by age group resulted in some extremely small sample sizes. These findings were tested more thoroughly through a series of ANCOVA's and are summarized in the table below:

Table XIX: Linear regression of changes in subjective and objective test scores

Factor	F-Statistic	Degrees of Freedom	Statistical Significance
RAVLT	2.39	1,32	p=0.1322
Age group	1.71	3,32	p=0.1847
RAVLT x age group	0.25	3,32	p=0.8617

No evidence of a significant relationship was found.

Hypothesis 3 – Patients with subjective reports of deterioration after surgery will have higher levels of depression, 4 months after surgery, both groups combined.

Table XX: Correlations of changes in subjective scores and depression – Both groups combined

Age Group	**Correlation with Depression**	**Statistical Significance**
40-49 yrs	R=-0.66	P=0.5453
50-59 yrs	R=-0.42	P=0.0714
60-69 yrs	R=0.17	P=0.6574
70+ yrs	R=0.09	P=0.8223

When broken out by age group, the results of this test found no evidence of a relationship between subjective deterioration and depression levels. A trend was detected in the age group 50 to 59 years of age (p=0.0714) without reaching statistical significance. This finding was tested more thoroughly through an analysis of covariance. The overall model was not significant (F=1.59, df=7,32, p=0.1731) and is further summarized in the following table:

Table XXI: ANCOVA of changes in subjective test scores and depression levels by age group

Explanatory Variable	F-Statistic	Degrees of Freedom	Statistical Significance
Depression at 4 months	0.54	1,32	p=0.4695
Age Group	1.24	3,32	p=0.3103
Depression x Age Group	0.63	3,32	p=0.6000

No evidence of a significant relationship was found.

Hypothesis 4 – The CPB group will have significantly higher subjective NP reports of deterioration than the off-pump group 4 months after surgery.

These tests were performed separately for each age group and are summarized in the following tables:

Table XXII: T-test of changes in subjective test scores vs. treatment – 40-49 yrs

Group	Deterioration % +/- SD	t-statistic	Degrees of Freedom	Statistical Significance
Conventional	-35.7% +/- 8.4%	n/a	n/a	n/a – sample size too small to test
Beating Heart	-58.0% +/- 43.7%			

Table XXIII: T-test of changes in subjective test scores vs. treatment – 50-59 yrs

Group	Deterioration % +/- SD	t-statistic	Degrees of Freedom	Statistical Significance
Conventional	4.6% +/- 32.1%	0.63	17	p=0.5401
Beating Heart	-6.5% +/- 45.4%			

Table XXIV: T-test of changes in subjective test scores vs. treatment – 60-69 yrs

Group	Deterioration % +/- SD	t-statistic	Degrees of Freedom	Statistical Significance
Conventional	34.5% +/- 43.1%	1.47	7	p=0.1861
Beating Heart	6.6% +/- 16.5%			

Table XXV: T-test of changes in subjective test scores vs. treatment – 70+ yrs

Group	Deterioration % +/- SD	t-statistic	Degrees of Freedom	Statistical Significance
Conventional	21.8% +/- 71.5%	0.88	7	p=0.4060
Beating Heart	-8.5% +/- 26.7%			

Based on the results of these tests, there is no evidence to suggest that the degree of reported change in subjective scores differs across the two treatment groups after controlling for age.

Hypothesis 5 – Subjects with the highest self-reported changes in NP scores in the CPB group will be more likely to have NP impairment than the subjects with the highest self-reported changes in NP scores in the off-pump group, 4 months after surgery.

In order to address this hypothesis, the 50% of subjects within each treatment group and age group who reported the greatest extent of NP impairment were identified. All other subjects were not included in this analysis. Fisher's exact test was then performed among these subjects with the highest self-reported degrees of NP impairment, broken out by age group, in order to determine whether the proportion of subjects with objective NP impairment differs across treatment group. (Note: Fisher's exact test was chosen instead of a chi-square test due to the small frequency of subjects with NP impairment in this subset of the data. Chi-square requires a sample size of at least 5 subjects per cell, while Fisher's exact test does not have any minimum sample size requirements).

The results of these analyses are summarized in the following table:

Table XXVI: Fisher's exact test – Impairment vs. self reported changes by age group and treatment

Age Group	Percent Impairment (n)		Fisher's Exact Test Significance
	Beating Heart	Conventional	
40-49 yrs	0.0% (0)	0.0% (0)	n/a
50-59 yrs	0.0% (0)	12.5% (1)	P=1.0000
60-69 yrs	0.0% (0)	0.0% (0)	n/a
70+ yrs	100.0% (1)	50.0% (1)	P=1.0000

Based on the above table we see no evidence of a relationship between objective NP impairment, self-reported changes, age, and treatment group.

Hypothesis 6 – Subjects with the highest self-reported changes in NP scores in the off-pump group will be more likely to be depressed than the subjects with the highest self-reported changes in NP scores in the CPB group, 4 months after surgery.

To test this question, the 50% of subjects within each treatment group and age group combination with the highest self-reported levels of NP impairment were once again used as the study sample. These patients were then classified as depressed or normal based on their 4-month BDI values. Fisher's exact test was performed in order to determine whether any association between treatment and depression exists among this sub-group.

The results of these tests are summarized in the following table:

Table XXVII: Fisher's exact test – Depression vs. self reported changes by age group and treatment

Age Group	Depression		Fisher's Exact Test Significance
	Beating Heart	Conventional	
40-49 yrs	0.0% (0)	0.0% (0)	n/a
50-59 yrs	0.0% (0)	50.0% (4)	p=0.2081
60-69 yrs	0.0% (0)	0.0% (0)	n/a
70+ yrs	0.0% (0)	0.0% (0)	n/a

We can see from the above table that there is no evidence of a relationship between age group, depression, subjective deterioration, and treatment group.