9-1-2013

Predictors of Neuropsychological Status in Cardiac Patients

Joel E. Kamper
Loma Linda University

LOMA LINDA UNIVERSITY
School of Behavioral Health
in conjunction with the
Faculty of Graduate Studies

_____

Predictors of Neuropsychological Status in Cardiac Patients

by

Joel E. Kamper

_____

A Dissertation submitted in partial satisfaction of
the requirements for the degree
Doctor of Philosophy in Clinical Psychology

_____

September 2013

Each person whose signature appears below certifies that this dissertation in his/her opinion is adequate, in scope and quality, as a dissertation for the degree Doctor of Philosophy.

_____, Chairperson
Susan A. Ropacki, Associate Professor of Psychology

_____
Richard E. Hartman, Associate Professor of Psychology

_____
Linda Houston-Feenstra, Director of Cardiovascular health & Wellness, Loma Linda University Medical Center

_____
Holly E. R. Morrell, Assistant Professor of Psychology

ACKNOWLEDGEMENTS

I would like to express my thanks to my committee, Drs. Ropacki, Hartman, Morrell, and Linda Houston-Feenstra, for their guidance through this process. I would also like to thank Angelyna, Audrey, Seda, and the rest of our lab who helped with design and data collection; I could not have done this without you! Finally, I would like to thank my family and, particularly, my wife for their love and support through six years of graduate school.

CONTENT

TABLES

Tables Page

ABBREVIATIONS

CAD	Coronary Artery Disease
CHF	Congestive Heart Failure
MI	Myocardial Infarction
CABG	Coronary Artery Bypass Grafting
CR	Cardiac Rehabilitation
SCD	Sudden Cardiac Death
PCI	Percutaneous Coronary Interventions
NYHA	New York Heart Association
ACE	Angiotensin-Converting Enzyme
CI	Cognitive Impairment
EF	Executive Functioning
PFC	Pre-Frontal Cortex
POCD	Post-Operative Cognitive Decline
SES	Socio-Economic Status
IQ	Intelligence Quotient
AD	Alzheimer's Dementia
TBI	Traumatic Brain Injury
CBT	Cognitive-Behavioral Therapy
PTSD	Post-Traumatic Stress Disorder
LLUMC	Loma Linda University Medical Center
WTAR	Wechsler Test of Adult Reading
FSIQ	Full-Scale IQ

PHQ-9	Patient Health Questionnaire – 9
GAD-7	Generalized Anxiety Disorder – 7
PSS	Perceived Stress Scale
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
WAIS	Wechsler Adult Intelligence Scale
D-KEFS	Delis-Kaplan Executive Function System
CVLT	California Verbal Learning Test
RCFT	Rey-Osterreith Complex Figure Test

ABSTRACT OF THE DISSERTATION

Predictors of Neuropsychological Status in Cardiac Patients
by

Joel E. Kamper

Doctor of Philosophy, Graduate Program in Clinical Psychology
Loma Linda University, September 2013
Dr. Susan A. Ropacki, Chairperson

Heart Disease is one of the leading causes of death and disability in the United States. Disease processes such as Coronary Artery Disease (CAD) and Chronic Heart Failure (CHF) account for the majority of cases, and are responsible for Myocardial Infarctions (MI), Coronary Artery Bypass Grafting (CABG) surgery, and other common disease sequelae and treatment paradigms. While the fact that heart can negatively impact cognitive functioning is well documented, the factors that drive changes in cognition have not been studied in depth. Additionally, while many heart patients choose to enter cardiac rehabilitation (CR) programs designed to decrease morbidly and mortality, most do not. This study used hierarchical regression models to test these two aims. heart patients entering rehabilitation or electing not to participate were assessed using a chart review, standardized neuropsychological measures, and standard questionnaires, with a final sample size of 52 (11 controls, 41 rehabilitation subjects). For Aim 1, health (hypertension, CHF, surgery history), and cognitive reserve (education, premorbid IQ) variables successfully predicted the cognitive status of heart patients across several functional domains, while affective factors (depression, anxiety, stress) were less predictive. For Aim 2, cognitive variables were not significantly associated with whether or not a patient adheres to cardiac rehabilitation. Results indicate that

multiple health and cognitive reserve-related factors impact cognitive functioning. Helping heart patients manage or compensate for identified risk factors could help mediate morbidity and mortality.

CHAPTER ONE

INTRODUCTION

Heart Disease is a major health problem, accounting for 25% of all deaths in the United States (Xu, Kochanek, Murphy, & Tejada-Vera, 2010). This umbrella term contains diagnoses including Coronary Artery Disease (CAD); which includes myocardial infarction (MI), cardiomyopathy, and ischemic heart disease; as well as congestive heart failure (CHF/HF); and hypertensive heart disease. Together, these diseases are responsible for $475.3 billion in direct and indirect costs (*Cardiovascular Disease Costs and Statistics*), making cardiovascular diseases the highest cause of mortality in the United States. Besides the direct health-related factors of heart disease, individuals that live long term with these conditions often experience fatigue, depressive symptoms, and dyspnea which can further contribute to diminished treatment adherence and reduced quality of life (Bennett & Sauve, 2003).

The ability of heart patients to have a positive quality of life, make positive health-related decisions, and perform adequate self-care can be further compromised by cognitive deficits, which have been noted to occur in up to 80% of individuals with diseases such as CHF (Pressler, 2008). A high overlap in the risk factors, signs, and medical procedures associated with heart disease and cognitive dysfunction has been noted (Moser et al., 1999), with MI, CAD-related surgical procedures, and CHF most strongly associated with cerebral insult and neuropsychological dysfunctions (Hammeke & Hastings, 1988; Moser, et al., 1999; Roine, Kajaste, & Kaste, 1993; Savageau, Stanton, Jenkins, & Frater, 1982; Savageau, Stanton, Jenkins, & Klein, 1982; van Swieten et al., 1991). Thus, the disease and treatment processes related to heart disease can directly

impact a patient's affective functioning and cognitive functioning, leading to a diminished ability to participate in self-care (Moser, et al., 1999). Cognitive impairments can also contribute to diminished quality of life and increased mortality (Pressler et al., 2010a, 2010b).

The field of heart disease-associated cognitive dysfunction is relatively new. However, general domains of impairment have been documented, and include attention, learning and memory, psychomotor speed, and executive functioning (Bauer & Pozehl, 2010; Pressler, Subramanian, et al., 2010a, 2010b). While deficits in these areas have been documented, it is unclear exactly how they relate to health markers, premorbid intellectual abilities, and affective factors. This study seeks to fill this gap in the literature by examining the predictive relationship between health markers, intellectual ability, and affective functioning on the overall cognitive abilities and impairments in heart patients by examining the impact of these predictors on cognitive status for a heterogeneous sample of heart patients.

CHAPTER TWO

REVIEW OF THE LITERATURE

Coronary Artery Disease

Coronary Artery Disease is a disease process in which plaque accumulates within the arteries supplying blood to the heart (*Coronary Artery Disease*, 2009). As of 2007, CAD accounted for half of all heart-related deaths, making it the largest cause of mortality for a single disease (*Cardiovascular Disease Costs and Statistics*; Xu, et al., 2010). While most individuals have some arterial plaque buildup, CAD is generally not diagnosed unless a patient manifests clinical symptoms. This lack of parity between disease onset and diagnosis dictates that patients will often need immediate intervention to account for the undetected progression of disease processes (Xu, et al., 2010).

Mechanisms of CAD

At its most basic level, CAD involves atherosclerosis, in which fat, cholesterol, and other substances build up in the arteries perfusing the myocardium (*Coronary Artery Disease*, 2009; Jezierska-Wozniak, Mystkowska, Tutas, & Jurkowski, 2011). This in turn leads to a restriction of functioning, which can lead to angina – chest pain, or a myocardial infarction. If left untreated, CAD will often lead to CHF (*Coronary Artery Disease*, 2009).

The progression from plaque formation to clinical symptoms can take many years, as plaques are generally slow-forming (Libby, 1995). However, well-known risk factors such as hypercholesterolemia, hypertension, diabetes, obesity, and left ventricular hypertrophy can exacerbate plaque formation, acting synergistically and enhancing CAD

risk (Dzau, 1990). In a healthy person, hemodynamic factors such as serum lipids, platelets, and vessel walls maintain a necessary balance. However, chronic conditions such as hypertension and obesity can affect blood flow physics, causing changes in the vascular wall itself that in turn promote aggregation of cholesterol and other substances into plaques (Dzau, 1990; Ross, 1986).

Furthermore, the high cholesterol and oxidative stress present in common chronic diseases such as hypercholesterolemia, hypertension, and diabetes can impact the function of the endothelial cells lining blood vessels (Aronson & Edelman, 2010; Kalay et al., 2010; Kinlay, Libby, & Ganz, 2001). The endothelium is responsible for regulating the vessel and responding to physiological and hemodynamic changes (Kalay, et al., 2010). However, lipids and oxidative stress can reduce the bioavailability of nitric oxide and activate pro-inflammatory signaling pathways (Kalay, et al., 2010). These physiological changes, together with biomechanical changes in the vessel affect endothelial cell functioning, hastening the deposition of plaques and increasing the chance for an acute coronary event (Kinlay, et al., 2001).

While atherosclerosis is defined by the presence of plaque depositions, not all plaques are alike (Libby, 1995). Typical plaques contain a lipid-rich core that is imbibed with macrophage foam cells derived from blood monocytes. The combination of lipids and macrophages causes a large production of tissue factor, a powerful procoagulant that stimulates thrombus or clot formation if it comes in contact with blood (Libby, 1995). Typical plaques also contain a fibrous cap or extracellular matrix that overlays the lipid-rich core. This cap must resist the high stresses in the arterial lumen to prevent the development of an acute coronary event. Thus, it is the integrity of this cap that

determines how stable a plaque will be. Plaques prone to rupturing (thus producing a thrombus) tend to have thin caps, while plaques with thicker caps tend to be much more stable (Libby, 1995). Collagens are mostly responsible for the strength and durability of the fibrous cap. Chronic inflammation and immune stimulation, as well as the inhibition of smooth muscle along the vessel can cause a cascade of physiological changes that inhibits collagen synthesis, leading to a weaker cap (Libby, 1995).

Health Effects

CAD is a condition that includes a series of clinical manifestations. Coronary atherosclerosis itself, which is at the crux of the disease, can be classified into five phases (Doering, 1999). These phases include slow progression, intermediate progression with plaque development, rapid progression with plaque development, development of occlusions, and development of stenotic plaques. The plaques and lesions involved in these phases range from the symptomless, slow-progressing lipid buildups present in people as young as 30 (phase 1) to more rapidly-progressing plaques (phases 3+) that become more complex in their makeup and geometry (Doering, 1999). The more complex and rapid the plaque buildup, the greater chance the plaque may rupture, leading to an acute event such as a myocardial infarction (MI) (Doering, 1999; Gutstein & Fuster, 1999). Each phase thus corresponds to specific symptoms, ranging from mild angina or chest pain to MI or sudden cardiac death (SCD), as well as to more chronic-like disease processes (Doering, 1999; El-Sherif, Khan, Savarese, & Turitto, 2010; Gutstein & Fuster, 1999). While most individuals meet criteria for at least phase 1, the absence of clinical symptoms below phase 3 suggests that by the time an individual is showing early CAD

symptomotology such as angina they already possesses complicated plaques with at least partial occlusion of cardiac arteries (Doering, 1999).

Perhaps the most well-known manifestation of CAD is myocardial infarction (MI). It is defined as the sudden interruption of blood flow in the arteries perfusing the heart, leading to ischemia and subsequent death of heart tissue (the myocardium). This event is often caused by the sudden rupture of unstable atherosclerotic plaques with thin caps, which tend to clot when their lipid-rich core come in contact with blood. This in turn causes a thrombus which cause the actual blockage (Maseri, 2000). While an MI can seem like a sudden event, it is actually affected by at least three major components (Maseri, 1990). These include a patient's chronic atherosclerotic background, the actual ischemia due to thrombosis (arterial clotting), and the heart's reaction in terms of arrhythmias. Thus, individual differences exist in a CAD patient's risk for MI as well as an individual's myocardial response to the infarct (Maseri, 1990). Furthermore, the type and stability of an individual's plaques is integral to the risk of thrombosis, as weaker, less stable plaques are more likely to rupture. Finally, any sudden change in heart function or activity due to excessive exercise or psychosocial stress may exacerbate the immediate risk of an MI (Maseri, 2000).

Treatment

Treatment for CAD can involve several procedures with varying levels of invasiveness. These treatments fall into one of two categories: Pharmacological and surgical methods (Lamy, Natarajan, & Yusuf, 2011). Typically, patients will first undergo an angiogram, which images the heart and surrounding blood vessels (Michaels

& Chatterjee, 2002). This procedure helps the medical team determine the severity of the disease, which will largely dictate the type of procedure performed (Michaels & Chatterjee, 2002). If a patient has arterial narrowing that does not limit coronary blood flow, the disease is most often treated with medications and lifestyle modifications (diet, exercise, etc.). If the atherosclerosis does limit blood flow, surgical procedures are often used (Michaels & Chatterjee, 2002).

Pharmacological and lifestyle treatments are utilized to reduce symptoms of angina and to improve health outcomes in patients with less severe CAD (Michaels & Chatterjee, 2002). Typically, anti-anginal medications such as beta-blockers and calcium channel blockers work to minimize angina through either reducing the heart's oxygen requirements or increasing the amount of arterial blood flow. Medications such as aspirin, cholesterol-lowering drugs and beta-blockers can reduce the risk of death associated with CAD through reducing clotting factors associated with thrombus formation and blocking the harmful effects of hormones that contribute to atherosclerosis (Michaels & Chatterjee, 2002).

Lifestyle changes are also used to help prevent the build-up of lipids and to improve overall health and functioning (Carles et al., 2007; Michaels & Chatterjee, 2002). These changes include smoking cessation, a diet low in cholesterol and fat, regular exercise, weight loss, diabetes management, and blood pressure control. These lifestyle changes are equally as important as medications for patients who undergo surgery, as they help maximize the efficacy of surgical interventions (Michaels & Chatterjee, 2002).

Surgically, several procedures are commonly used to treat CAD (Lamy, et al., 2011). These include percutaneous coronary interventions (PCI), which includes angioplasty and stents, as well as coronary artery bypass grafting (CABG) surgery (Lamy, et al., 2011). If the atherosclerosis is largely contained to one vessel, balloon angioplasty and stents are often utilized (Michaels & Chatterjee, 2002). These procedures, administered in up to 33% of CAD patients, are generally less costly and less invasive than CABG surgery and often as effective in the relief of angina and other symptoms (Stroupe et al., 2006). Angioplasty involves a balloon-tipped catheter being inserted into the problematic artery. The balloon is subsequently inflated to push plaque back against the arterial wall. Additionally, the plaque may be cut away using the catheter itself. After removal or compaction of the plaque, wire-mesh stents are inserted into the artery to support the damaged arterial wall and reduce the chance for recurrence of ischemia (Michaels & Chatterjee, 2002). These stents may be coated with pharmacological agents to assist in keeping the artery functional. While angioplasty and stenting is useful for many patients, a narrow or completely blocked artery is not amenable to these procedures (Michaels & Chatterjee, 2002).

Patients with severe coronary plaques often undergo CABG surgery (Lamy, et al., 2011; Michaels & Chatterjee, 2002; Silbert, Scott, Evered, Lewis, & Maruff, 2007; Stroupe, et al., 2006). Up to 10% of CAD patients will have a CABG procedure performed, which is usually indicated when multiple arteries are blocked or narrowed, or when a main coronary artery becomes blocked. The procedure involves healthy veins or arteries from the leg, chest, or arm being grafted around the blocked portion to restore blood flow (Michaels & Chatterjee, 2002). The number of bypasses refers to the number

of grafts that were utilized, based on how many coronary arteries were blocked. Although angioplasty is less invasive and initially less costly, CABG procedures are often superior in the long-term relief on angina in some patients due to the necessity to periodically repeat a PCI procedure (Lamy, et al., 2011).

Congestive Heart Failure

Congestive heart failure is a disease process characterized by a failure of the myocardium to adequately pump blood, and is defined as the condition in which abnormal heart function causes blood delivery insufficient to satisfy the metabolic requirements of organs and bodily systems (Rengo et al., 1996; "What is Congestive Heart Failure?," 2004). As of 2010, there are 6 million persons with a HF diagnosis in the United States, with both the prevalence and incidence continuing to grow (Lloyd-Jones et al., 2009; Pressler, 2008; Pressler, Subramanian, et al., 2010b).

While HF can affect anyone, it is primarily a disease of aging (Rengo, et al., 1996). Beginning with a 3% incidence rate between ages 45-64, the prevalence roughly doubles with every decade of increased age (Rengo, et al., 1996; Schocken, Arrieta, Leaverton, & Ross, 1992). CHF is often caused by severe CAD, representing a continuous disease process with CHF being generally more chronic and serious than CAD (Bennett & Sauve, 2003; Vogels et al., 2007; Vogels, Scheltens, Schroeder-Tanka, & Weinstein, 2007; "What is Congestive Heart Failure?," 2004). Indeed, CAD and CHF are so closely linked that 75% of patients with CAD or related hypertension with develop CHF (McKee, Castelli, McNamara, & Kannel, 1971; Rengo & Acanfora, 1994). CAD-related causes include severely clogged arteries and past heart damage due to MI.

Other suggested etiologies for CHF include hypertension, myocardial infarction, congenital defects, ischemic heart disease and valvulopathies (McKee, et al., 1971; Rengo & Acanfora, 1994; "What is Congestive Heart Failure?," 2004), with the risk of developing CHF associated with hypertension being much lower than that with a sudden ischemic event (Rengo & Acanfora, 1994). The fact that different studies have found varying etiologies suggests a multifactor risk model, which does not preclude the possibility of other, extra-cardiac factors such as diet and smoking (Rengo & Acanfora, 1994; Rengo, et al., 1996; Rengo, Ferrara, & Leosco, 1991).

Mechanisms of CHF

At an essential level, CHF happens when the inability of the heart to maintain adequate tissue perfusion causes a series of changes which includes the body's attempt to rectify the deficiency, leading to other problems that may further hamper circulation such as hemodynamic changes and complex biochemical modulations (Rengo, et al., 1996). The inability of the heart to maintain adequate perfusion is primarily caused by the loss of myocardial tissue, reduction of contractility, pressure and volume overload, or restrictive myocardial diseases, and is often mediated by CAD (Rengo, et al., 1996).

The loss of myocardial tissue may occur along several pathways. The most dramatic loss of tissue is caused by ischemic events such as a myocardial infarction which can quickly cause the loss of contractile tissue, lessening the heart's ability to maintain adequate tissue perfusion (Rengo, et al., 1996). When coupled with other CHF-related sequelae such as reduced contractility, an ischemic event can have broad consequences (Rengo & Acanfora, 1994). Adding to the loss of myocardial tissue is the

general-age related decline in myocytes, or muscle fibers, noted in the ageing heart (Olivetti, Melissari, Capasso, & Anversa, 1991). While not a causative factor in and of itself, the general decline in myocytes can further hamper an already damaged heart's functional ability.

The reduction of myocardial contractility describes the condition where the heart possesses a decreased ability to contract. This in turn hampers its ability to adequately pump blood and maintain necessary perfusion. The functional loss of optimum contraction is complex and depends on several factors (Rengo, et al., 1996). These include a loss of myocardial tissue and muscular fibers due to a disease like CAD; intrinsic myocardial depression seen with age; circulating catecholamines; autonomic nervous system dysfunction; anoxia; hypercapnia, or excess carbon dioxide in the blood; and acidosis, or excess blood acidity (Rengo, et al., 1996). Because of the multiple factors that can affect contractility, most patients presenting with CHF will possess a large number of the above causative factors. Thee fact that CHF is so closely related to CAD, yet possesses a multi-factor causative model, may explain why some CAD patients develop CHF while others do not.

Pressure and volume overload refer to dysfunction in the amount of blood being pumped. Healthy elderly individuals possess a relatively unchanged ejection fraction, defined as the volumetric fraction of blood pumped with each cycle, compared with their younger counterparts (Rengo, et al., 1996; Rodeheffer et al., 1984), suggesting that blood volume is not problematic for the ageing heart when it is not being stressed. However, the aged myocardium does show a deceased ejection fraction during physical activity when compared with younger hearts (Rodeheffer, et al., 1984). This is due to the fact

that, in the elderly, physical stress induces smaller changes in heart rate than in younger people. Patients who are at risk for CHF generally have lower resting ejection fractions than their same-aged healthy counterparts, and may demonstrate an increase in left ventricular volume as a compensatory measure as the heart tries to adequately perfuse the body with blood (Rengo, et al., 1996; Rodeheffer, et al., 1984). This volumetric increase and reduction in aortic compliance often leads to increased blood pressure. The pressure overload in turn triggers myocardial cells to induce cellular hypertrophy, leading to a further enlarged heart (Olivetti, et al., 1991).

Restrictive myocardial diseases can often occur as a result of cardiac hypertrophy (Hansford & Castro, 1982; Rengo, et al., 1996). This is due to remodeling of the myocardium in response to hypertrophy, leading to diastolic stiffness. Additionally, left ventricular compliance can decrease, leading to further stiffness (Litwin & Grossman, 1993). The pathological restricting of myocardial tissue is compounded in elderly patients, who often show an age-dependent alteration in left ventricle functioning (Nicolino et al., 1993; Rengo, et al., 1996).

Health Effects

CHF causes a large number of non-cognitive health effects. As CHF is often the result of a disease process such as CAD, the clinical manifestations of CHF itself are often overshadowed by other symptoms, especially in elderly patients (Rengo, et al., 1996). Non-specific symptoms such as peripheral edema often occur in CHF, but are not indicative of nor exclusive to this disease process. Other non-specific but common symptoms include severe shortness of breath and fatigue in CHF patients. Progressive

difficulty with physical movement associated with CHF may eventually largely confine a patient to bed (Dolgin, 1994). More specific effects of CHF include increased jugular venous pressure, as well as decreased left ventricle ejection fraction and increased left ventricle volume (Nicolino, et al., 1993; Rengo, et al., 1996), which are related to common but non-specific effects like fatigue.

Although edema is not specific to CHF, it is one of the most often observed clinical effects ("Congestive Heart Failure," 2011; Rengo, et al., 1996). This can be due to several related factors. As blood flow out of the heart slows and the myocardium weakens, venous blood in the extremities backs up due to the myocardium's inability to retrieve it through diastolic contraction. This is especially true in the legs and ankles, where swelling due to edema is common due to their distance from and location below the myocardium. Edema is also common in the lungs, which can interfere with breathing, cause shortness of breath, and interfere with beneficial activities like exercise ("Congestive Heart Failure," 2011). As an additive factor, decreased blood flow to the kidneys interferes with their ability to excrete sodium and maintain adequate homeostasis. This in turn causes more edema. Given enough time, edema will affect most organs in the body.

A common way to classify the extent of CHF and its health effects is using the New York Heart Association (NYHA) Functional Classification Index (Dolgin, 1994). Using this scale, patients are put in one of four categories based on how limited they are in their physical activity, their ability to breathe normally, and their level of pain. Patients in Class I (mild) have no undue fatigue or shortness of breath in ordinary physical activity like walking or climbing stairs. Those in Class II (mild) have fatigue,

palpitations, or shortness of breath during normal physical activity, but are comfortable at rest. Those in Class III (moderate) are also comfortable at rest, but experience symptoms during less-than ordinary physical activity such as walking short distances. Those in Class IV (severe) have symptoms even at rest, and are unable to carry out any physical activity without discomfort (Dolgin, 1994).

Treatment

CHF patients are often treated with a combination of drugs and lifestyle changes (Kostis, Rosen, Cosgrove, Shindler, & Wilson, 1994; Morrissey, Czer, & Shah, 2011). Past treatment modalities were relegated to diuretics and digoxin, with the purpose of reducing edema and controlling the arrhythmias common in CHF patients. While these drugs are useful in decreasing morbidity and reducing hospital admission rates, their use as front-line treatments to improve mortality has waned in favor of newer pharmacologic solutions (Haji & Movahed, 2000). Beta-blockers, once contraindicated for CHF due to their effect on heart rhythm are now being used in combination with other drugs to improve left ventricular function and thereby improve mortality (Morrissey, et al., 2011; Rengo, et al., 1996). Other drugs, such as Angiotensin-Converting Enzyme (ACE) inhibitors are also commonly use to increase cardiac output and volume, and to decrease edema through more efficient sodium excretion (Morrissey, et al., 2011). However, though the number of beneficial pharmacologic therapies for both mortality and morbidity have increased, leading to improved survival, certain cardiomyopathies still remain difficult to treat. Furthermore, hospital admission due to CHF morbidity remains the single most common reason for hospital admission in our aging population

(Morrissey, et al., 2011), suggesting that drugs alone are not sufficient to adequately address CHF symptoms.

Over the past decade or so, non-pharmacologic treatment modalities have been increasingly employed to supplement pharmacotherapy in CHF (Kostis, et al., 1994; Smeulders et al., 2010). Interventions such as exercise training, dietary control of weight, and psychological interventions are often utilized to enhance functional capacity, improve quality of life, and improve survival rates in synergy with medication regimens (Kostis, et al., 1994). Although CHF patients often experience difficulty exercising due to pulmonary edema and other CHF-related factors, combination rehabilitation programs including exercise training, cognitive therapy, and dietary education and management can initiate significant improvements in exercise tolerance, weight loss, and symptoms of depression and anxiety (Kostis, et al., 1994). The inefficacy of these treatments to improve ejection fraction illustrates that combination drug and behavioral regimens lead to the best outcomes. Structured self-management programs can also be effective, especially for patients with better cognitive status and lower education (Smeulders, et al., 2010).

Cardiac Rehabilitation

Cardiac Rehabilitation (CR) programs are coordinated, multifaceted interventions designed to optimize a heart patient's functioning while stabilizing, slowing, or reversing the underlying physiological disease processes (Leon et al., 2005). While once of a singular focus, they now involve a patient's physical, psychological, and social functioning which, when combined with disease process management, can best reduce

morbidity and mortality (Lavie & Milani, 2011; Leon, et al., 2005). Because they are no longer limited to exercise training, CR programs are now used as both treatment programs for those with CHF or symptomatic CAD as well as prevention programs to reduce modifiable heart disease risk factors (Gunstad et al., 2005; Leon, et al., 2005). This broadening in scope also means that CR programs include patients with diverse sequelae such as heart transplant candidates/recipients, CHF patients, CAD patients with or at risk for MI, CAD patients who have undergone surgical procedures, those with valvular disease, and patients with pulmonary disease (Leon, et al., 2005). CR programs are typically offered to all cardiac patients as a recommended option for treatment.

Rehabilitation programs are multidisciplinary and designed to benefit patients' overall health. Thus, programs are often individualized and involve exercise training, dietary therapy, risk factor modification including medications, psychoeducation sessions, psychological interventions including depression and anger management, and cardioprotective therapies to reduce weight and increase metabolism (Lavie & Milani, 2011; Leon, et al., 2005; Luszczynska & Cieslak, 2009). CR has proven very beneficial, with decreased morbidity, lower mortality and lowered risk of secondary disease process development seen in patients who attend these programs (Lavie & Milani, 2011; Leon, et al., 2005). Younger patients (<65) are especially able to benefit from these multidisciplinary programs, with older patients (>65) deriving most of their benefit from exercise alone (Ferrara et al., 2006) However, because CR attendance is often not well enforced or advertised, only about 10-20% of eligible patients actually attend (Leon, et al., 2005).

Compared with healthy control subjects, heart patients entering CR tended to have impaired attention, learning and memory, psychomotor speed, and executive functioning (Moser, et al., 1999). While this is no different from the general heart disease population, it does indicate that cognitive impairment may impact CR patients' ability to benefit from the program (Kakos et al., 2010; Moser, et al., 1999). However CR programs themselves, through their multidisciplinary designs, can improve patients' cognitive abilities (Gunstad, et al., 2005). This is especially true in the domains of attention, memory, and psychomotor speed, which both improved after CR (Carles, et al., 2007; Gunstad, et al., 2005; Stanek et al., 2011). While patients may show executive gains, improved executive functioning is not as likely and represents a moderator for the health benefits an impaired patient can receive from CR programs (Kakos, et al., 2010; Stanek, et al., 2011).

Cognitive Impairments

Cognitive impairment (CI) is common in heart patients (Bennett & Sauve, 2003; Roine, et al., 1993; Savageau, Stanton, Jenkins, & Frater, 1982; Savageau, Stanton, Jenkins, & Klein, 1982; Vogels, Scheltens, et al., 2007), with some cognitive dysfunction occurring in up to 80% of hospitalized and chronic CHF patients, and up to 35% in less severe CAD patients who undergo surgical procedures (Kneebone, Andrew, Baker, & Knight, 1998; Pressler, Kim, Riley, Ronis, & Gradus-Pizlo, 2010). The presence of CI in heart patients represents a major cause of morbidity, leading to worse overall outcomes as well as an increased risk of mortality (Hogue et al., 2006; Zuccala et al., 2003). Among those who have significant cognitive impairments, current performance on

neuropsychological tests is equivalent with healthy individuals five years older (Elwood, Pickering, Bayer, & Gallacher, 2002). Cognitive deficits have been indicated in all groups of heart patients, including those who have CAD and CHF (Silbert, et al., 2007; Vogels, Oosterman, et al., 2007). Impairment in CAD patients includes those who have had an MI (Roine, et al., 1993) and those that have undergone cardiac surgery such as CABG (Savageau, Stanton, Jenkins, & Frater, 1982; Savageau, Stanton, Jenkins, & Klein, 1982). There is even evidence of pre-surgical cognitive impairment in CAD patients (Hogue, et al., 2006), suggesting that both surgical intervention and the actual heart disease processes contribute to cognitive dysfunction. The role of heart disease in CI is so central that CHF is indicated as one of the major risk factors for dementia in elderly patients (Acanfora et al., 1996).

Causative Hypotheses

Heart disease can impact CI through primary and secondary methods. Primary methods include direct effects that heart disease can have on cognition (Bennett & Sauve, 2003). These direct effects include atherosclerosis, experiencing an MI, undergoing corrective surgery, and having congestive heart failure. Secondary sources of impairment can arise from treatment regimens themselves, such as the drugs used to treat heart patients (Nykamp, Morgan, & Roland, 2009).

Several primary hypotheses have been proposed as to the causes of CI in heart patients (Bennett & Sauve, 2003). These hypotheses include cerebral infarction due to cardiac mural emboli and cerebral ischemia due to chronic or intermittent cerebral hypoperfusion (Bennett & Sauve, 2003; Gruhn et al., 2001; Pullicino & Hart, 2001;

Taylor & Stott, 2002), and both label ischemia as the main culprit. Non-ischemic hypotheses include the effects of drugs used to treat heart patients (Nykamp, et al., 2009).

The cardiac mural emboli hypothesis, which is most applicable in patients with heart failure, suggests that plaques from cardiac arteries may break off and become lodged in the cerebrum, causing stroke or acute ischemia (Bennett & Sauve, 2003; Pullicino & Hart, 2001). Any stroke that occurs in heart patients of any type is likely cardioembolic due to left ventricle systolic dysfunction, which encourages thrombus formation (Pullicino & Hart, 2001). CHF patients with impaired ejection fractions (often described as below 40-50%) are most likely to form thrombi and have a subsequent cerebral infarction (Beer et al., 2009; de Jonge et al., 2006; Moser, et al., 1999; Pullicino & Hart, 2001).

The second hypothesis labels cerebral hypoperfusion as the main cause of ischemia. In CAD patients, this can manifest from surgical blood loss and hypoperfusion, ischemia due to an MI, or a combination of other health factors pre-surgery (Hogue, et al., 2006; Lal, 2007; Roine, et al., 1993). In CHF patients, a chronic systolic dysfunction of the left ventricle reduces ejection fraction and heart efficiency, causing a long-term reduction in cerebral blood flow (Gruhn, et al., 2001; Pullicino & Hart, 2001). Though the length of time ischemia is present can vary between heart patients, the cognitive deficits observed are similar in type and quality, with their duration and severity correlated with the degree of hypoperfusion, as well as the presence of CHF (Bennett & Sauve, 2003; Hogue, et al., 2006; Roine, et al., 1993).

A third hypothesis relating CI to heart patients focuses on the secondary effects of pharmacological treatment. While the ischemic effects associated with heart disease and

its various surgical interventions have been discussed, secondary effects from the medications used to improve health outcomes may adversely affect a patient's cognitive abilities as well (Nykamp, et al., 2009). Because the cognitive effects seen from cardiac drug use mimic those seen from ischemic factors, care must be taken to identify and manage pharmacological factors in order to decrease patient morbidity (Bennett & Sauve, 2003; Nykamp, et al., 2009).

Affected Domains

Since both CAD and CHF are part of the larger umbrella of heart disease, they can both affect cognition in similar ways (Roine, et al., 1993; Vogels, Scheltens, et al., 2007). Because CHF can be thought of, in part, to be one end of a continuum that begins with angina and other less severe CAD symptoms, the cognitive deficits observed in CHF patients mimic those seen in CAD patients, but are both more pervasive and severe (Bennett & Sauve, 2003; Vogels, Oosterman, et al., 2007; Vogels, Scheltens, et al., 2007). While half of patients who experience an MI, CABG surgery, or other acute event had no cognitive sequelae after one year, patients with CHF had more persistent and chronic cognitive problems (Bennett & Sauve, 2003; Roine, et al., 1993; Savageau, Stanton, Jenkins, & Frater, 1982), suggesting that chronic heart disease has a large influence over a patient's cognitive abilities. Cognitive deficits observed in heart patients fall into several neuropsychological categories, including attention, verbal memory, working memory, executive function, and psychomotor speed (Bauer & Pozehl, 2010; Bennett & Sauve, 2003; Bennett, Sauve, & Shaw, 2005; Murkin, Newman, Stump, & Blumenthal, 1995; Sauve, Lewis, Blankenbiller, Rickabaugh, & Pressler, 2009).

Attention

Attention is defined as a concentration of mental activity (Matlin, 2002). It generally relates to an organism's ability to selectively focus its mental activity on a specific stimulus (Matlin, 2002). Attention to a stimulus is critical for other functions such as memory and language, mediates one's ability to encode a memory or carry on a conversation with a friend, and can be unconscious/reactive (bottom-up) or conscious (top-down) (Leon-Carrion, 1997; Matlin, 2002). Anatomically, attention is not related to any one specific cerebral structure, but depends on a complex network of systems to operate (Leon-Carrion, 1997). This includes both posterior systems, which orient an individual to external stimuli, and anterior systems, which orient an individual to perceptions and meanings to guide action (Leon-Carrion, 1997).

Impaired attention is well-documented in heart patients (Bennett & Sauve, 2003; Hammeke & Hastings, 1988; Rengo et al., 1995). Attention problems can be due to both the direct effects of heart disease and other, related conditions such as hypertension (Cherubini et al., 2007). Impairments have been noted for both simple (single stimulus) and complex (several competing stimuli) tasks (Bennett & Sauve, 2003), although simple attention is most related to cardiac predictors such as fibrillations and reductions in ejection fraction. While multiple studies have found impaired attention for all heart patients, there is some evidence that attention problems are more pronounced in patients with CHF (Vogels, Oosterman, et al., 2007). This suggests that longer-term heart disease, such as exhibited by CHF patients, is related to more significant deficits in attention.

Because attention modulates other cognitive functions, it has profound implications for a patient's general cognitive status and overall quality of life (Bennett, et al., 2005). A patient who cannot attend to valuable health information will be unable to later recall or implement this information. Because attention is closely related with and modulates other cognitive functions such as memory, a patient with poor attention may present with poor memory recall as a result of impaired attention processes (Vogels, Oosterman, et al., 2007). In a disease like CAD or CHF, impaired attention can additionally lead to higher morbidity (Stanek, et al., 2011).

Memory and Working Memory

Memory is defined as an organism's ability to recall previous learned information, and is intimately tied to learning (Eichenbaum, 2002). Memory can refer to declarative or procedural types, which refer to whether something is explicit (such as a learned fact) or implicit (such as a behavior or action). Neuropsychologically, memory is generally associated with the semantic and episodic types, which are both components of declarative memory and refer to memories of learned facts and past events, respectively (Feinberg & Farah, 2003). The brain structure most often associated with learning and recall is the hippocampus, a bi-lateral mesial temporal lobe structure that associates and synthesizes current stimuli with previously learned information (Eichenbaum, 2002). In this way, it associates and compares stimuli with cognitive maps or memories to integrate new information into the memory system (Eichenbaum, 2002). The recall of this information is also facilitated by the hippocampus, although old memories are able to be recalled without its aid (Eichenbaum, 2002). Traditionally, the left hippocampus is most

often associated with learning and memory for verbal information and the right for non-verbal or visuospatial information (Bennett & Sauve, 2003; Eichenbaum, 2002; Feinberg & Farah, 2003).

Working memory is another type of memory that is generally associated with the prefrontal cortex (Eichenbaum, 2002). In contrast to traditional, "long-term" memory, working memory refers to the ability to temporarily hold information online while it is manipulated or processed. After processing, it can be stored through the hippocampus and other medial temporal structures, or outputted (Eichenbaum, 2002).

Learning and memory deficits are common in heart patients (Bennett, et al., 2005). Deficits include the sub-domains of learning, working memory, verbal memory, and visuospatial memory (Antonelli Incalzi et al., 2003; Beer, et al., 2009; Bennett, et al., 2005; Hammeke & Hastings, 1988; Lim, Alexander, LaFleche, Schnyer, & Verfaellie, 2004). While both CAD and CHF patients often present with memory impairments, CHF patients are more likely to have pervasive deficits that persist over time (Bennett & Sauve, 2003; Lim, et al., 2004). CAD patients, conversely, are likely to experience a recovery of memory abilities, although functional recovery is limited to the first three months after an MI or surgery (Lim, et al., 2004). Among CHF patients, those with more severe symptoms (NYHA class IV) do not demonstrate more pervasive deficits than patients with less severe CHF (NYHA class II) (Antonelli Incalzi, et al., 2003).

CHF patients with memory impairments often possess bilateral mesial temporal lobe atrophy on MRI, with more pronounced right-sided volume loss (Beer, et al., 2009). The affected area includes the hippocampus, which is particularly sensitive to the hypoxia seen in heart patients (Bennett & Sauve, 2003; Eichenbaum, 2002). This may

help explain why CHF patients present with more pervasive and long-lasting learning and memory impairments compared to their CAD counterparts.

Functionally, heart patients with memory impairments may experience an interference with rehabilitation and treatment regimens (Moser, et al., 1999; Vogels, Oosterman, et al., 2007). However, given the transient nature of memory impairments in recovered CAD and less-impaired CHF patients (NYHA class I), memory deficits may not be significant enough to appreciably affect CR or other treatment programs (Grubb, Simpson, & Fox, 2000). Rehabilitation programs that focus on repetition and memory aids are more likely to overcome these obstacles, further making memory impairment less of an issue (Grubb, et al., 2000). However, memory deficits, especially due to mesial temporal lobe atrophy, remain serious problems for heart patients (Beer, et al., 2009; Vogels, Oosterman, et al., 2007; Vogels, Scheltens, et al., 2007).

Executive Functioning

Executive functioning (EF) refers to the top-down processes that organize and mediate other neuropsychological constructs, such as attention and memory (Feinberg & Farah, 2003). Specifically, EF involves mental strategy, organization, cognitive flexibility, response inhibition, the shifting of attention and mental set, and the ability to abstract (Feinberg & Farah, 2003). A key component in EF is top-down processing, or the ability of a neural network to guide behavior through internal states or intentions (Miller & Cohen, 2001). Top-down processing incorporates internal representations or goals in modulating behavior, and serves as a mechanism of cognitive control. EF is mediated primarily by the fronto-striatial networks in the brain, which are responsible for

the top-down control that influences and coordinates other neural networks, such as memory (Feinberg & Farah, 2003).

Anatomically, there are several areas generally associated with executive functioning. The pre-frontal cortex (PFC), part of the fronto-striatal network, plays a primary role in executive functioning and cognitive control (Miller & Cohen, 2001). The PFC's ability to experientially modify its anatomy, as well as its numerous and diverse inputs and projection pathways make it an ideal area to organize and synthesize information, organize complex tasks, and shift mental set (Feinberg & Farah, 2003; Miller & Cohen, 2001). Representations in this area have been noted to exert top-down influence over other brain systems, so as to best delineate a pathway needed to perform a specific task. Besides the PFC, the striatum and other basal ganglia structures are also responsible for executive functioning and control (Kalat, 2004; Kropotov & Etlinger, 1999; Miller & Cohen, 2001). These structures are intimately connected with the PFC through afferent and efferent connections, and mirror the functions of the PFC (Kalat, 2004). Specifically, basal ganglia structures are involved in planning, rule learning, and organizing sequences of movements (Kalat, 2004). They also play a major role in response inhibition and being able to actively decide which response is the most appropriate for a given stimulus (Kropotov & Etlinger, 1999).

Executive deficits are commonly observed in heart patients (Kakos, et al., 2010; Petrucci et al., 2009; Pressler, Kim, et al., 2010). Similar to other functional areas, EF deficits are seen in both CAD and CHF patients (Lim, et al., 2004; Vogels, Oosterman, et al., 2007). Patients with CAD appear to have variable EF deficits, with no persistent or pervasive pattern of impairment (Lim, et al., 2004). In CHF patients, executive functions

are more often impaired, with impairments evident in both CHF patients living independently and those being seen for more severe physiological symptoms (Bauer & Pozehl, 2010; Bennett, et al., 2005; Vogels, Oosterman, et al., 2007). This suggests that EF, like memory, is impaired across the NYHA severity spectrum in CHF patients.

Heart patients with the neuroanatomical atrophy more often seen in CHF are more likely to have EF impairments (Beer, et al., 2009). The most commonly observed areas of anatomical volume loss include the medial temporal lobes bilaterally, which directly affects memory (through hippocampal atrophy) but less directly influences EF. However, imaging has also revealed periventricular and deep white matter hyperintensities, which includes white matter pathways integral in the fronto-striatal networks observed in EF (Beer, et al., 2009). The loss of afferent and efferent connections, as well as general cerebral volume loss may help explain the executive deficits commonly observed in heart patients.

Like other functional domains, impaired executive functioning has major implications for health and disease morbidity (Kakos, et al., 2010). Because of the inability to focus, plan, and mentally organize information, patients with EF impairments are less likely to adhere to treatment regimens and display limited gains in cardiovascular fitness and quality of life (Kakos, et al., 2010). This, in turn, leads to lower health outcomes and little benefit from CR and other commonly used comprehensive treatment programs. Thus, EF dysfunction reveals a serious and potentially less changeable set of impairments that can directly impact health recovery.

Psychomotor Speed

Psychomotor speed refers to the ability to rapidly and fluently perform physical body motor movements with precision (McGrew, 2009). These movements, often involving the fingers and hands, is largely independent of direct cognitive control (McGrew, 2009). Domains including Speed of Limb Movement, or the ability to make rapid discrete limb movements; Writing Speed Fluency, or the ability to correctly copy or write words quickly; Speed of Articulation, or the ability to rapidly perform speech articulations; and Movement Time, or the time taken to physically move a body part to make a required movement all fall under the heading of psychomotor speed (McGrew, 2009). This ability is important for the quick and accurate automated abilities that are important for numerous daily activities, such as typing, writing, and speaking.

Anatomically, psychomotor slowing (dysfunction) is associated with periventricular white matter lesions immediately proximal to the lateral ventricles (Hannesdottir et al., 2009; Tiemann, Penner, Haupts, Schlegel, & Calabrese, 2009). Of particular association with psychomotor speed are the tracts that connect the frontal lobes to other cortical and subcortical structures (Hannesdottir, et al., 2009), similar to those used in the EF system. Lesions in other white matter tracts are less associated with psychomotor dysfunction, suggesting that the performance of frontal periventricular tracts are of specific importance (Hannesdottir, et al., 2009; Tiemann, Penner, et al., 2009). Since demyelination or lesions in white matter affect its ability to quickly and reliably carry action potentials, the association of psychomotor slowing with white matter health is not surprising. Additionally, small lesions that are neurologically classified as

"clinically silent" may result in selective neuropsychological deficits in domains like psychomotor speed (Tiemann et al., 2009).

Like the other domains discussed, psychomotor slowing is common in heart patients (Hoth, Poppas, Moser, Paul, & Cohen, 2008; Tiemann, Reidt, et al., 2009; Vogels, Scheltens, et al., 2007). Psychomotor impairments are most common in CAD patients that have had an MI or corrective surgery, as well as in CHF patients (Bauer et al., 2011; Tiemann, Reidt, et al., 2009). Similar to other cognitive domains, CHF patients tend to have a greater incidence of psychomotor impairment than their CAD counterparts, with some studies suggesting a significant difference between CAD and CHF patients (Hoth, et al., 2008). However, CAD patients that have more severe symptoms, including MI, or those that have had surgical intervention – even less invasive interventions like angioplasty – do have a higher rate of psychomotor impairment (Stanek, et al., 2011; Tiemann, Reidt, et al., 2009), with deficits resolving in most patients by 6 months post-surgery (Hammeke & Hastings, 1988). The psychomotor improvement of heart patients who underwent CR or a similar intervention did differ, however, with CAD patients much more likely to demonstrate improvements in psychomotor functioning than their CHF counterparts when encountering treatment (Bennett, et al., 2005; Stanek, et al., 2011; Vogels, Scheltens, et al., 2007). Patients who have hypertension, which is often associated with heart disease, tend to have greater psychomotor impairments, as hypertension alone is often associated with psychomotor dysfunction and its addition to heart disease pathology causes compiled impairment (Hannesdottir, et al., 2009).

Psychomotor impairment has major implications for morbidity and mortality in heart patients (Pressler, Kim, et al., 2010). Although psychomotor speed is not directly

associated with specific functional deficits, e.g. poor memory encoding with attention impairments, it is related to a patient's morbidity and mortality, as well as their quality of life (Pressler, Kim, et al., 2010). The detrimental association between psychomotor speed and health is particularly evident in CHF patients with low ejection fractions (<40%). In this population, representative of the more severe end of the heart disease spectrum, patients who died within twelve months had worse psychomotor abilities compared with those who did not (Pressler, Kim, et al., 2010). This suggests that psychomotor abilities tend to decrease significantly as one's disease process becomes more severe. Thus, psychomotor impairment serves as in indirect marker of disease severity; although it may be relatively unchanged in less severe heart patients, those with more critical symptoms demonstrate psychomotor impairments that are correlated with their morbidity and mortality.

Predictors of Cognitive Status

The relationship of cognitive impairment to disease processes in heart patients can be complex, with several domains related to cognitive status in heart patients. The domains include variables associated with a patient's health, cognitive reserve, and affective functioning, and suggest a more complex causative model of cognitive impairment than simple disease severity measures.

Health Predictors

Blood Pressure

Chronic high blood pressure, or hypertension, is a medical condition

independently associated with impaired cognitive abilities (Cherubini, et al., 2007). It is defined as having chronic high blood pressure above 140 systolic or 90 diastolic, and affects more than half of those over 60 years of age (Chobanian et al., 2003). While many persons with hypertension may live relatively symptom-free, those who poorly manage their disease put themselves at risk for developing cognitive impairments (Cherubini, et al., 2007). In non-heart patients, hypertension often affects cognition through an increased risk of vascular dementia, characterized by small cerebral micro-bleeds that can affect one's cognition (including memory), motor abilities, and personality (Acanfora, et al., 1996; Cherubini, et al., 2007; Feinberg & Farah, 2003; van Swieten, et al., 1991).

Hypertension is a major risk factor for the development of CAD and CHF (Croft et al., 1999; Wynands, Sheridan, Batra, Palmer, & Shanks, 1970). Not only is hypertension a risk factor for developing CHF, but it can put asymptomatic persons at a greater risk for increased arterial atherosclerosis and future heart disease-related insults and disease processes as well (Dzau, 1990; Kalay, et al., 2010). In CHF, hypertension (along with CAD) is seen as a direct precursor, and can facilitate acceleration of disease processes in non-CAD individuals (Bennett, et al., 2005). Because of its independent association with cognitive deficits, as well as its intimate association with CHF, the presence and degree of hypertension in heart patients can be seen as a predictive measure of cognitive status and impairment.

Surgery History

Post-operative cognitive dysfunction (POCD) is known to result as a complication

of major surgery (Ropacki, Bert, Ropacki, Rogers, & Stern, 2007). Cognitive dysfunction can be particularly evident for those undergoing CABG and other heart-related procedures (Ropacki, et al., 2007; Royter, N, & Russell, 2005; van Dijk et al., 2000). Previous research has estimated that between 33 and 83% of patients undergoing CABG and other heart procedures have cognitive dysfunction post-operatively, with between 4 and 47% exhibiting neuropsychological deficits two months out, and up to 25% exhibiting deficits 6 months out (Newman et al., 2001; Ropacki, et al., 2007; Royter, et al., 2005; Selnes, Goldsborough, Borowicz, & McKhann, 1999; Sun, Lindsay, Monsein, Hill, & Corso, 2012; van Dijk, et al., 2000). These deficits may occur with or without focal neurologic deficits (Sun, et al., 2012)

The etiology of such impairments is somewhat unclear, but are likely due to both general surgical effects such as anesthesia and specific effects of cardiac surgery such as the potential for cerebral embolisms, hypoperfusion, and the effects of perioperative drugs (Newman, et al., 2001; Ropacki, et al., 2007; Royter, et al., 2005; Selnes, et al., 1999; Sun, et al., 2012). Thus, while POCD can occur after any surgery, it is particularly likely after cardiac surgery (Newman, et al., 2001). For these reasons, a patient's surgery history can affect his or her cognitive abilities. While recent surgeries are more likely to produce POCD, there is some evidence that longer-term cognitive dysfunction can occur post-surgery, particularly in patients more prone to stroke, dementia, or low cognitive reserve (Ropacki, et al., 2007; Sun, et al., 2012).

Presence of CHF

While cognitive dysfunction is common to all types of heart patients, numerous

studies have cited CHF patients as having the most severe cognitive symptoms (Beer, et al., 2009; Bennett & Sauve, 2003; Hoth, et al., 2008; Lim, et al., 2004; Pullicino et al., 2008; Rengo, et al., 1995; Vogels, Scheltens, et al., 2007). CHF often represents the endpoint of CAD patients (Rengo, et al., 1996), and its presence thus represents a person who has experienced heart disease processes for a long period of time. Additionally, CHF is a disease characterized by chronic symptoms and disease processes, rather than the more acute clinical manifestations seen in CAD patients. For these reasons, the presence of CHF in CR patients can be seen as a predictor of worse cognitive abilities compared to those not diagnosed with congestive heart failure.

Cognitive Predictors

The concept of cognitive reserve is used to explain the dissociation between an individual's pathology and their cognitive impairment (Stern, 2009; Vemuri et al., 2011). That is, patients with higher levels of cognitive reserve have a greater capacity to cope with neurological insults than those with lower levels of cognitive reserve, explaining why cognitive decline is initiated at different times in relation to the onset of pathology (Vemuri, et al., 2011). While all patients with a chronic disease process such as CHF or dementia will eventually end up at the same level of impairment, those with higher cognitive reserve have a later point of cognitive decline, displaying a later onset of cognitive symptoms than those with low cognitive reserve (Stern, 2009). The nature of this relationship does, however, specify that those with high cognitive reserve will display a steeper rate of decline once cognitive symptoms are evident (Ropacki, et al., 2007; Stern, 2002, 2009).

Cognitive reserve is an active model, suggesting that the brain actively copes with pathology using pre-existing cognitive processes or enlisting compensatory strategies (Stern, 2002, 2009). An individual's neural reserve is thought to be mediated by differences in neural efficiency as well as flexibility and greater capacity, as measured by epidemiological research and imagining studies examining cerebral blood flow (Stern, 2009). An individual's neural compensation refers to the ability to compensate for pathological disruption by employing brain structures or networks not normally used for those functions, helping to sustain or even boost cognitive performance (Stern, 2009). Thus, cognitive reserve is not a fixed cutoff, but focuses on processes that allow a patient to sustain brain damage yet maintain function. Anatomically, cognitive reserve is mediated less by specific brain structures, and more by higher-level neural networks in a top-down approach that tend to be faster and more flexible in certain individuals (Stern, 2009)

The measures that are typically associated with cognitive reserve are variables of lifetime experience and socioeconomic status (SES), such as educational attainment, income, or an individual's Intelligence Quotient (IQ) (Manly, Touradji, Tang, & Stern, 2003; Ropacki, et al., 2007; Stern, 2002, 2009). These variables have been found to be highly correlated with an individual's level of cognitive reserve; higher IQ and greater educational attainment are generally associated with a later point of cognitive decline (Stern, 2009). With regards to IQ, an individual's premorbid IQ, the term given to more stable abilities such as vocabulary and word reading which are less likely to be impacted by neurological insults or pathology, is often utilized as a predictor of cognitive reserve (Albert & Teresi, 1999; Green et al., 2008; Stern, 2009).

There are relatively little data on cognitive reserve in heart patients, with most research examining Alzheimer's Dementia (AD) and traumatic brain injury (TBI) patients (Stern, 2002, 2009; Ylioja, Hanks, Baird, & Millis, 2010). The few studies that do relate heart disease and cognitive reserve have suggested that, similar to AD and TBI patients, heart patients with higher levels of reserve show less cognitive impairment when controlling for the severity of disease process (Singh-Manoux et al., 2008). Specifically, there is little association between CAD inflammatory processes and cognition in high SES patients compared with their low SES counterparts, suggesting cognitive reserve processes help high-SES CAD patients stave off cognitive impairment (Singh-Manoux, et al., 2008; Singh-Manoux et al., 2009). CAD patients with high cognitive reserve do, however, show a sharp decline in functioning after CABG surgery relative to their low-reserve counterparts, suggesting a possible "threshold effect," where high-reserve individuals surpass their ability to cognitively cope and decline at a relatively steep rate to eventually match the abilities of low-reserve patients (Ropacki, et al., 2007; Stern, 2009). These findings, and the fact that an association between heart disease and cognition is dependent on reserve correlates such as SES (Singh-Manoux, et al., 2009) suggest that the mechanisms of cognitive reserve are as important in heart patients as they are in their AD and TBI counterparts.

Affective Predictors

Affective variables refer to psychological, psychosocial, and mood-related factors that can impact one's health. While traditionally not part of the medical treatment model, variables like depression, anxiety, and stress/distress are increasingly being studied in

conjunction with heart failure (Rengo, et al., 1995). These factors can have major implications for health, relating to both morbidity and mortality.

Depression

Depression is common in medically ill patients, and has major ramifications for disease morbidity and mortality (Carney & Freedland, 2009; Krishnan, 2005; Naqvi, Naqvi, & Merz, 2005). The presence of major depression concurrent with a medical illness is more likely to lead to reduced quality of life and can increase the risk of mortality (Krishnan, 2005). While this depression is often treatable, its incidence is commonly overlooked in favor of a more singular focus on a patient's physical symptoms (Krishnan, 2005; Thombs et al., 2008). The lack of screening for depression in medically ill patients suggests that screening for and treating this debilitating disease could improve health outcomes and quality of life (Krishnan, 2005; Thombs, et al., 2008). A combination of therapy and medication, similar to the suggested treatment regimen in non-ill individuals, has been found to be useful in treating patients with medical conditions (Krishnan, 2005; Thombs, et al., 2008).

Because depression is common in older individuals, a disease process like heart disease that often strikes older individuals is characterized by a high incidence of depression (Freedland et al., 2009; Kent & Shapiro, 2009; Thombs, et al., 2008). In patients with acute CAD, such as those who have recently experienced an MI, a diagnosis of major depression is related with double the risk of cardiac death, especially in patients who have depression that is difficult to treat (Carney & Freedland, 2009; Kent & Shapiro, 2009; Naqvi, et al., 2005; van den Brink et al., 2002). Similarly, in patients with more

chronic heart disease processes like CHF, the presence of depression can have a major impact on quality of life, leading to a greater incidence of disability and death, possibly incurring a similar double risk of death as seen in CAD patients (Bennett & Sauve, 2003; Kent & Shapiro, 2009). While a combination therapy of cognitive behavioral therapy (CBT) and medication does little to affect primary cardiac measures, these treatment modalities are extremely useful in improving a patient's quality of life, which has secondary benefits for a reduced risk of mortality (Freedland, et al., 2009; Naqvi, et al., 2005). Thus, depression mediates the relationship between a patient's level of illness and their morbidity and mortality.

In contrast to depression's clear effects on health and mortality, its relationship to neuropsychological functioning in heart patients is less clear (Bennett & Sauve, 2003; Sauve, et al., 2009). While depression is commonly associated with cognitive difficulties such as attention deficits, verbal and visual learning and memory impairments, slowed processing speed, and executive dysfunction, there is conflicting evidence for cognitive impairment in heart patients due to depression (Baune et al., 2010; Beer, et al., 2009; Delgado & Schillerstrom, 2009; Vogels, Scheltens, et al., 2007). While some studies have found no cognitive differences due to depression, others have reported negative effects on a patient's cognitive functioning due to depression (Bennett & Sauve, 2003; Vogels, Scheltens, et al., 2007). Because the relationship of depression to a heart patient's overall health is more complex than a simple causal relationship, it perhaps also serves as a mediator of cognitive status in medical patients with impaired cognitive status.

Anxiety

Like depression, heart patients often have a higher incidence of anxiety than healthy controls, with some studies suggesting double the incidence rate over population means (Kent & Shapiro, 2009; D. K. Moser et al., 2007). The presence of anxiety is similarly associated with higher disease morbidity and mortality (Bennett & Sauve, 2003; Bennett, et al., 2005; Kent & Shapiro, 2009). While depression is seen in heart patients mostly as a result of the disease pathology, anxiety is often additionally observed as a risk factor for the initial development of heart disease, with more anxious individuals being at a higher risk of cardiac-related death (Kent & Shapiro, 2009). Anxiety as a predisposing factor is most often associated with sudden cardiac death, rather than non-fatal MI. Post-event anxiety can also impact health, with anxious heart patients undergoing treatment being more at risk for serious in-hospital complications and worse long-term disease morbidity than those that do not have anxiety (Kent & Shapiro, 2009; D. K. Moser, et al., 2007). However, the presence of both depression and anxiety do not confer added risk over the presence of one of these affective symptoms (Kent & Shapiro, 2009).

While anxiety is not as classically associated with cognitive impairment as depression, there is some evidence that anxiety is related to impaired cognition in heart patients, conferring a risk independent of depression (Vogels, Scheltens, et al., 2007). However, other studies have found no significant differences in cognitive outcomes due to anxiety, even in samples with a higher rate of anxiety than controls (Bennett & Sauve, 2003; Grubb, et al., 2000; Sauve, et al., 2009). Because of anxiety's complex relationship with heart disease, serving as both a risk factor for initial symptom

development and a mediator of morbidity and quality of life, its status as an established risk factor for cognitive impairment in this population is not clear.

Psychosocial Stress

Stress has long been studied in conjunction with heart disease. The classic "type A" personality, characterized by individuals that are aggressive, high-strung, hurried, and competitive, has classically been viewed as a risk factor for developing heart disease (Kent & Shapiro, 2009), although the data are somewhat controversial. While the presence or absence of a "type A" personality risk factor may be debated, CAD patients who have experienced an MI have significantly higher work, home, financial and general stress, as well as a greater number of stressful life events (Kent & Shapiro, 2009). Similarly, stress has a negative impact on overall quality of life and mortality in heart patients, similar to the impacts of depression and anxiety (Kent & Shapiro, 2009; Vogels, Scheltens, et al., 2007). Some patients with impaired ejection fraction or a history of MI who undergo surgery even develop Posttraumatic Stress Disorder (PTSD) symptoms, leading to a two- to four-fold increase in the risk of mortality (Kent & Shapiro, 2009). While psychosocial stress can be a primary contributor in the development and maintenance of heart disease processes, it is also related to the formation of depression, especially when medical illnesses are interpreted as stressful (Freedland, et al., 2009). Thus, stress can influence health in a number of ways and represents both a cause and effect of heart disease processes.

The data on psychosocial stress and cognitive functioning in heart patients are quite limited (Pressler, 2008). While the impact of stress on health is clear, its impact on

cognitive abilities is less well known. Because stress is related to depression and anxiety, it may affect cognition in a mediation model with depression and anxiety serving as mediating variables (Alagiakrishnan, McCracken, & Feldman, 2006; Kent & Shapiro, 2009; Vogels, Scheltens, et al., 2007). Alternatively, the relationship between stress and cognitive ability in heart patients may mirror that seen between stress and AD patients, who experience exacerbated cognitive decline as a result of vascular disease processes (Alagiakrishnan, et al., 2006; Cherubini, et al., 2007). Whatever the relationship, it is clear that stress can impact health directly, and may be a factor in cognitive impairment as well.

CHAPTER THREE

OBJECTIVES AND HYPOTHESES

While the presence of cognitive impairments in heart patients is well known, the degree to which health, cognitive, and affective factors influence these impairments and heart patients' cognitive abilities is relatively unknown (Bennett & Sauve, 2003; Vogels, Scheltens, et al., 2007). While individual factors (such as IQ or depression) have been shown to affect patients' cognitive abilities, the presence of different types of predictors in a hierarchical model provides the ability to discern which elements provide the most benefit or harm to heart patients' cognitive functioning. This study examines these relationships through two separate, but related, aims.

The first aim of this study is to characterize which factors best predict the cognitive functioning of heart patients. This aim was addressed through hierarchical linear regression models, more fully described in the methods section.

Aim 1 consists of 6 hypotheses, one for each domain identified as affected in heart patients (attention, immediate memory, delayed memory, working memory, executive functioning, and psychomotor speed) (Bauer & Pozehl, 2010; Bennett & Sauve, 2003; Bennett, et al., 2005; Vogels, Scheltens, et al., 2007). For each hypothesis it is hypothesized that both medical and affective predictors as a group will negatively affect cognitive functioning, and that variables associated with higher cognitive reserve will predict better cognitive functioning for those without CHF. Furthermore, it is hypothesized that the presence of CHF and hypertension, as well as more numerous surgeries, higher depression, higher anxiety, and greater stress will negatively impact cognitive functioning, while higher levels of education and premorbid IQ will positively

impact cognitive functioning. Finally, it is hypothesized that generally non-impaired cognitive abilities, such as visuospatial ability, will not be predicted by the hierarchical model. This hypothesis will be tested using a 7th regression analysis.

The second aim of this study is to determine which cognitive factors predict a patient's enrollment in a cardiac rehabilitation program. Specifically, this aim examined potential neuropsychological explanations for the choice to enroll or not enroll in a rehabilitation program. This aim was addressed through a hierarchical logistic regression model.

Aim 2 consists of a single hypothesis. It is hypothesized that both cognitive reserve (education, IQ) and current cognitive ability (overall cognitive ability, working memory, executive functioning, and psychomotor speed) will impact a person's likelihood of choosing to enroll in cardiac rehabilitation. Furthermore, it is hypothesized that both variables related to cognitive reserve variables and all four current cognitive status variables will serve as individual predictors, which higher levels of reserve and cognitive ability predicting higher involvement in cardiac rehabilitation programs.

CHAPTER FOUR

METHODS

Participants

The participants that were used for this study are two groups of patients. The first sample (N=60) contains patients who attend the cardiac rehabilitation program at Loma Linda University Medical Center (LLUMC). These individuals ranged in age from 23-93 years (Mean=61.38, SD=12.82, 65% male), and all were referred by their physician for rehabilitation with the goal of improving their cardiac health through the comprehensive program provided by CR. All patients have some degree of heart disease, hence their referral to CR, although their exact diagnoses differ (e.g., CHF, MI, CABG surgery, etc.). All participant data were gleaned from baseline neuropsychological assessments that are done clinically to inform patient care as part of the CR intake examination process. Thus, this study looked not at the treatment effects of CR, but simply used this population because of its heterogeneous heart disease population. Obtaining participant data when patients first come to CR (before any treatment) served to ameliorate any potential treatment effects.

The second sample (N=14) consists of control patients who did not elect to participate in cardiac rehabilitation. These individuals ranged in age from 39-87 years (Mean=66.82, SD=15.03, 64% male). These patients had similar demographics to the CR sample, with the exception of a higher rate of CHF, and attend the LLUMC Heart Center for outpatient care. Control patients were tested on a voluntary basis in conjunction with a visit to their care provider.

Materials

Independent Variables/Predictors

Materials for this study included a demographic questionnaire, a standard cognitive measure, and a medical chart review to glean information related to potential predictors of cognitive status. These items served as the independent variables and predictors of cognitive status. The specific predictors used included: presence of hypertension, presence of CHF, and surgery history (medical predictors); education and premorbid intelligence (cognitive reserve); and level of depression, anxiety, and psychosocial stress (affective predictors).

Medical Predictors

Predictors in the medical domain included the presence of hypertension, the presence of CHF, and surgery history. These variables were gleaned using a demographic questionnaire. The presence of hypertension and CHF were obtained through interview questions using the demographics questionnaire, and corroborated with a medical chart review. Surgery history was gleaned through a medical chart review, and was defined as the total number of past surgeries. Due to record keeping practices, it was not possible to examine or delineate surgery type.

Cognitive Reserve

Predictors related to cognitive reserve included education and premorbid intelligence. Education was measured using the demographic questionnaire self-report, and was expressed in level of education achieved via a seven-point likert scale.

Educational categories included less than high school, high school/GED, some college, associates degree/technical school, bachelor's degree, master's degree, and doctoral degree. Patients' premorbid intelligence, which represents their intellectual ability apart from and before the onset of any pathology that could affect their functioning, was measured using the Wechsler Test of Adult Reading (WTAR) (Wechsler, 2001). This measure is designed to provide an intelligence estimate for a patient's level of functioning before any disease pathology, including heart disease and related medical diseases. It provides a standard score estimate of a patient's full-scale IQ (FSIQ), which is indicative of their overall cognitive abilities (Wechsler, 2001).

Affective Predictors

Affective predictors included depression, anxiety, and psychosocial stress measures which were all administered in a short self-report battery. Depression was measured using the Patient Health Questionnaire 9 (PHQ-9) (Kroenke, Spitzer, & Williams, 2001). This measure consists of nine items on a four-point likert scale, with a tenth item measuring symptom impact on daily functioning. Unlike other depression measures, the PHQ-9 is designed for medical patients in primary care settings and is useful for patients of all ages and medical diagnoses, including heart disease (Kroenke, et al., 2001). Although it is half the length of other depression screeners, it possesses sufficient sensitivity and specificity for identifying and diagnosing depression, particularly in the medical population that will be examined in this study (Kroenke, et al., 2001). Inter-rate reliability of the normative sample was 0.84; internal consistency (Cronbach's α) for the present study was 0.90.

Anxiety was measured using the Generalized Anxiety Disorder 7 (GAD-7) questionnaire (Spitzer, Kroenke, Williams, & Lowe, 2006). This measure consists of seven items on a four-point likert scale, with an eighth item measuring symptom impact on daily functioning. The GAD-7, like the PHQ-9, was designed for and validated with medical patients in primary care settings. Although it focuses primarily on symptoms of Generalized Anxiety Disorder (GAD), it possesses sufficient sensitivity (89%) and specificity (82%), and was validated in a diverse range of medical settings with a wide age range (Spitzer, et al., 2006). Internal consistency, measured using Cronbach's α, was 0.92 for the normative sample and 0.91 for the present study.

Psychosocial stress was measured using the Perceived Stress Scale (PSS), which measures patients' perceived levels of stress (Cohen, Kamarck, & Mermelstein, 1983). This scale directly measures how stressful an individual perceives his or her life to be, and is highly correlated with stressful life events, depression, physical symptoms, anxiety, and use of primary care services (Cohen, et al., 1983). The original scale consisted of fourteen items on a four-point likert scale; the present study used an empirically-validated truncated version consisting of four items, also on a four-point likert scale. Like the other affective measures, this scale was developed and validated with a wide group of individuals, including patients receiving medical treatment. It is useful for a wide range of ages and is valid for use will all individuals, including heart patients (Cohen, et al., 1983). Internal consistency, measured using Cronbach's α, was 0.85 for the normative sample and 0.10 for the present study.

Dependent Variables

Patients' cognitive abilities served as the dependent variables and were tested primarily using a full administration of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) cognitive battery (Randolph, 1998), which serves as a general purpose cognitive screener (Silverberg, Wertheimer, & Fichtenberg, 2007). This battery has two alternate forms (A and B), which can aid in tracking changes over time, although only one timepoint will be used for this study. To best capture the hypothesized cognitive domains, several supplementary tests were used in addition to the RBANS. These include digits backward from the Wechsler Adult Intelligence Scale (WAIS) III and IV (Wechsler, 1997, 2008), FAS and CFL verbal fluency measures (Bechtoldt, Benton, & Fogel, 1962; Benton, 1969; Fogel, 1962), and Trail Making from the Delis-Kaplan Executive Function System (D-KEFS) (Delis, Kaplan, & Kramer, 2001). The use of both RBANS forms, as well as two digits backwards tasks (WAIS III and IV) and two fluency measures allows for future research to track changes over time, and will pair with other studies that will use the alternate forms to assess change at a later timepoint.

The RBANS battery was chosen for its utility as a cognitive screener, providing a reasonably complete neuropsychological profile in a brief amount of time (Bauer & Pozehl, 2010; Randolph, 1998). It provides normative data for individuals ages 20-89 years of age with regards to their total cognitive abilities, as well as across 5 sub-domains: Immediate memory, delayed memory, attention, language, and visuospatial abilities (Randolph, 1998). Three out of these five domains relate to areas of impairment seen in heart patients (excepting language and visuospatial abilities), but a full protocol is

necessary to get a measure of overall functioning, as well as to adhere to standardized protocol for valid administration (Randolph, 1998; Randolph, Tierney, Mohr, & Chase, 1998). A "Total Index Score" is tabulated that will serve as a predictor for Aim 2.

Since heart disease is most common in individuals older than 55, particular care was taken to ensure the RBANS' utility with this age group before including it in the present study. The RBANS manual provides normative, standardized data in decade-increments up to age 89. Subsequent studies examining the battery's utility with older adults have found it to be of clinical use with this age group, and it is sensitive enough to detect pathological changes in cognitive functioning (Duff et al., 2005; Randolph, et al., 1998). Additional validity testing has suggested that refined age and education-corrected base rates could enhance the test's sensitivity for older adults, especially when examining individual subtests (Duff et al., 2003; Patton et al., 2006). However, while these corrections are of definite utility for individuals greater than 80 years of age, corrections for younger individuals may be of less clinical utility (Gontkovsky, Mold, & Beatty, 2002). Because of conflicting evidence regarding corrected norms and the utility of norms corrections being most evident when examining individual subtests, the standard, normative data from the RBANS manual was used for this study.

Of equal importance to the RBANS utility with adults older than 55 is its use for patients with heart disease. While the RBANS manual details its use in medical settings, there are few published studies which describe using it with heart patients in a medical setting specifically (Randolph, 1998). Research that does exist suggests that the RBANS is useful with heart patients, and is sensitive enough to detect impairments with this population (Bauer & Pozehl, 2010; Moser et al., 2004; D. J. Moser et al., 2007). This

includes individuals with a history of CHF, as well as those with CAD, and suggests that the RBANS is useful even for detecting cognitive changes correlated with pre-CAD vascular changes (Moser, et al., 2004; D. J. Moser, et al., 2007).

Attention

One cognitive domain that was examined is attention. Attention was measured using the "attention" index on the RBANS (Randolph, 1998). This index contains two subtests, a digit span forward test and a digit symbol test, both similar to those used on the WAIS intelligence measures (Randolph, et al., 1998; Smith, 1973; Wechsler, 1987). On the digit span test, patients were asked to repeat a series of numbers of increasing length, and are required to sustain attention in order to track the strings of digits. The digit symbol test consists of arbitrary symbols associated with numbers in a key. Below the key are numerous symbols with no numbers; patients were asked to match the correct numbers with their appropriate symbols as quickly as possible, with a test length of 90 seconds.

These subtests are classically associated with, and valid for, measuring attention (Putzke, Williams, Rayburn, Kirklin, & Boll, 1998; Smith, 1973; Turner & Gilliland, 1977), and have long been used as attention correlates. Patients who are administered the RBANS had their attention index score calculated using normative data from the RBANS manual. This data provided a patient's normalized standard score (Mean=100, Std. Dev.=15).

Memory

Another cognitive domain that was examined is memory. Memory was measured using several measures and indices, divided by its relevant domains. These domains were chosen because of identified areas of impairment in heart patients (Bauer & Pozehl, 2010; Bennett & Sauve, 2003; Vogels, Scheltens, et al., 2007).

Immediate Memory

The sub-domain of immediate memory was measured using the "immediate memory" index from the RBANS (Randolph, 1998). This index contains two subtests, a list learning task and a story memory task, both of which test immediate verbal memory (Randolph, 1998; Randolph, et al., 1998). Visuospatial/non-verbal memory, classically seen as the complement to verbal memory, will also be gleaned through the full RBANS administration. Given the lack of non-verbal deficits in heart patients, visuospatial ability is not a theoretical focus of this study (Bauer & Pozehl, 2010; Bennett, et al., 2005). However, by briefly analyzing and showing no differences in this domain, the results of this study can be further validated.

On the list learning test, patients were presented with 10 unrelated words at a pace of 1 every 1.5 seconds. They were then asked to repeat as many of these words as possible. There are four learning trials for this test, which are summed to provide an additive score of a patient's ability to recall unrelated words with no time delay. For the story memory test, patients were read a brief story at a pace slower than normal. They were then be asked to recall as much of this story as possible. Each patient had two attempts at hearing and recalling the story, with an additive score from both trials

representative of a patient's ability to recall semantically-related verbal information with no delay.

Tests such as list and story memory tasks are often used as correlates of immediate memory (Randolph, 1998). Measures such as the California Verbal Learning Test (CVLT) and the logical memory subtest from the Wechsler Memory System (WMS) are commonly used to test immediate verbal memory for unrelated and semantically-related verbal information, respectively, and are very similar to their RBANS counterparts (Delis, Kramer, Kaplan, & Ober, 2000; Randolph, 1998; Randolph, et al., 1998; Wechsler, 2009). As with other domains, each patient's immediate memory index score was calculated using normative data from the RBANS manual. A normative comparison of the two subtests yielded an immediate memory standard score, which will allow for calculation of the changeability of memory compared with independent predictors, as well as whether or not a patient is impaired in this area.

Delayed Memory

The sub-domain of delayed memory was measured using the "delayed memory" index from the RBANS. This index was calculated using the same list learning and story memory tasks from the immediate memory index, the difference being that delayed memory looks at retention of this previously learned content after about a 15-20 minute delay (Randolph, 1998). For the list learning task, patients were asked to recall words learned during the four acquisition/immediate memory trials. They were also asked to recognize which words were on the list in a forced-choice modality, which can assist in the recall of learned information that cannot be spontaneously remembered (Delis, et al.,

2000; Randolph, 1998). For the story memory component, patients were asked to simply recall as much of the semantically-related story information as is possible.

The delayed memory index also includes a task of non-verbal/visuospatial information, where a patient was asked to draw a complex figure that was previously administered. Although immediate visuospatial ability was used as a null hypothesis for this study, given the lack of evidence of involvement of these abilities in heart patients (Bauer & Pozehl, 2010), the delayed memory index as a whole was used. A heart patient's score on the entire delayed memory index has shown to be impaired, although this could be driven primarily by the verbal component (Bauer & Pozehl, 2010). Regardless, the delayed memory index computes delayed memory as a composite of verbal/non-verbal memory, and was used in its entirety to best mirror previous findings.

Delayed memory tasks similar to those utilized by the RBANS are often used as correlates of memory retention and delayed memory, and reflect the delayed memory portions of the CVLT and Logical Memory, both classically used to test memory (Delis, et al., 2000; Randolph, 1998; Wechsler, 2009). Delayed memory tasks serve as complements to the immediate memory portions, and provide information about a patient's ability to retain information over a period of time (Randolph, 1998). The non-verbal/visuospatial retention portion of the RBANS delayed memory index is similar to a classically used test of non-verbal retention, the Rey-Osterreith Complex Figure Test (RCFT) (Meyers & Meyers, 1995; Osterrieth, 1944; Rey, 1941). As with other domains, the non-contextual list, semantically-related story, forced choice list recognition, and figure recall subtests were used to calculate the delayed memory index, which yielded a standard score useful for testing patient's abilities and the presence of impairment.

Working Memory

Working memory was measured using the digit span backwards test from the WAIS-III and –IV (Wechsler, 1997, 2008). This test, which involves asking patients to listen to a digit string of increasing length and repeat it backwards, has long been associated with working memory due to the necessity to mentally retain, briefly hold, and manipulate the digits before repeating them backwards (Reynolds, 1997; Wechsler, 2008). The differences in utilized mental processes between the forward (attention) and backwards (working memory) digit span tasks are so great that they possess adequate clinical utility when used on their own, rather than combining them into one overall "digit span" measure (Reynolds, 1997). Like the digits forward task, digits backward is useful for patients of all ages and diagnoses as a working memory correlate (Wechsler, 1997, 2008).

Patients administered digit span backwards were asked to repeat backwards a digit string of increasing length. They received one point for every span repeated correctly, which is summated to give a total score. The task was discontinued when patients get both strings of the same length incorrect. The total score was then normalized into a scaled score (Mean=10, SD=3), which can be directly compared with other normalized scores to test the relationship of predictors to working memory.

Executive Functioning

The domain of executive functioning was assessed using several different measures. These measures include the verbal fluency measures CFL/FAS as well as the Trail Making test from the D-KEFS (Bechtoldt, et al., 1962; Benton, 1969; Delis, et al.,

2001; Ruff, Light, Parker, & Levin, 1996). On the verbal fluency task, patients were asked to think of as many words that start with a specific letter as possible within 60 seconds. These letters will either be C, F, and L; or F, A, and S. A patient's summed number of responses for all three letters was then compared with normative data to yield a z-score that enabled comparisons similar to other cognitive domains (Mitrushina, Boone, Razani, & D'Elia, 2005; Ruff, et al., 1996; Strauss, Sherman, & Spreen, 2006). On the Trail Making test, patients were administered five conditions, although only the fourth is pertinent to executive functioning. The first three conditions, which acclimate the patient to the test, included a visual cancellation task marking all of the "3's" on a page, a number sequencing task connecting sequential numbers with a line, and a letter sequencing task connecting sequential letters with a line. The primary task of interest is the fourth condition, which had subjects switch back and forth between connecting numbers and letters in sequence (Delis, et al., 2001). The time it took to complete this sequencing task was recorded as the dependent variable, and converted to a scaled score for analysis. The fifth condition was a motor speed task relevant to psychomotor speed.

Verbal fluency tasks, similar to the FAS and CFL tasks used for this study, were originally developed as brief measures to help diagnose aphasia (Bechtoldt, et al., 1962; Benton, 1969; Fogel, 1962; Ruff, et al., 1996). Regardless of the letters used (FAS, CFL, etc.), verbal fluency instruments have classically been viewed and used as measures of executive functioning, specifically relating to the organization and top-down processing mediated by the prefrontal cortex (Mitrushina, et al., 2005). Similar to other tests in this study, verbal fluency measures are useful with patients of all ages, including those with medical diagnoses (Mitrushina, et al., 2005). There is also considerable evidence of their

utility with patients of varying educational, SES, and intellectual backgrounds, making these tests and their corresponding normative data valid for all patients who speak English (Mitrushina, et al., 2005; Ruff, et al., 1996).

The fourth condition of the D-KEFS Trail Making test, used as one of two executive function measures for this study, is very similar to the classic Trail Making Test part B, which was originally developed by the Army in World War II and later incorporated in standard neuropsychological batteries (*Army Individual Test Battery Manual of Directions and Scoring*, 1944; Brown & Partington, 1942; Delis, et al., 2001; Partington & Leiter, 1949; Reitan, 1955). This condition is firstly a test of cognitive flexibility, which is a classical component of executive functioning as it is required for higher-level skills such as divided attention and multitasking (Delis, et al., 2001). Furthermore, this condition is useful for testing individuals of all ages and diagnoses, and is highly sensitive to cognitive impairment. Finally, Trail Making tests such as that found on the D-KEFS are often used with older adults, including those with medical conditions (Mitrushina, et al., 2005).

For the purpose of analysis, both executive measures were collapsed into an executive composite score. This was done by converting each subject's score on both measures to a z-score using normative data for each measure. The z-scores were then averaged to obtain a composite score.

Psychomotor Speed

The domain of psychomotor speed was measured using condition five (motor speed) of the D-KEFS Trail Making test (Delis, et al., 2001). For the motor speed

subtest, patients were asked to connect empty circles following a dotted line as quickly as possible. Although the accuracy of movements is important, the overall speed at which a patient can connect the circles is the primary variable (Delis, et al., 2001).

Trail-making tests, such as the trails test from the D-KEFS battery, are often associated with psychomotor speed (Bauer & Pozehl, 2010; Mitrushina, et al., 2005). This is because the ability to quickly and skillfully complete the test has a strong motor component that works synergistically with executive and other abilities (Delis, et al., 2001; Mitrushina, et al., 2005). Although relatively new, the D-KEFS trails test incorporates a pure "motor speed" condition (condition 5) which will be used for this study, designed to get an essential measurement of a patient's psychomotor abilities without the added cognitive components present in other trails modalities (Delis, et al., 2001). Similar to other measures, a patient's total time spent completing the motor speed condition was converted into a standardized scale score for comparison and analysis.

Design

Aim 1 of this study examined the effects that independent predictors across three domains (medical, cognitive reserve, affective) have on heart patients' cognitive functioning. A hierarchical linear regression was used for each cognitive domain, with predictors grouped into three levels based on their type. Medical predictors populated level one, cognitive predictors level two, and affective predictors level three. Only CR patients were used for this aim. This was due to the fact that the majority of control patients had a CHF diagnosis, which would have biased the results of the regression analyses for Aim 1.

Aim 2 of this study examines the effects that cognitive variables have on a person's decision to voluntarily enroll in a cardiac rehabilitation program. Both the rehabilitation and control samples were used for this aim. A single hierarchical logistic regression was used, with the first level containing cognitive reserve variables and the second including current cognitive ability variables.

Procedure

Participants for this study were recruited from cardiac patients attending CR or patients who had chosen to not attend a rehabilitation program. All patients attending CR programs receive a brief neuropsychological evaluation to aid in treatment and planning, and participants were gleaned from this group. Patients entering CR sign a waiver upon beginning CR that allows their de-identified data to be used for research purposes, so no formal informed consent process was needed.

Patients were tested clinically as part of the standard intake procedure during their first week attending CR, before the bulk of interventions have started. This minimized any benefits patients may receive from CR treatments. Patients were given a clinical evaluation, consisting of a demographic questionnaire, a full RBANS battery (A or B), CFL/FAS verbal fluency, digits backwards from the WAIS III or IV, and trails from the D-KEFS. The use of both RBANS batteries, as well as two verbal fluency and digit span backwards tasks is for clinical purposes, with the aim to track patients' cognitive progress following CR using comparable measures. Only one timepoint (initial intake) was utilized for this study, with patients randomly assigned to CFL or FAS, WAIS III or IV digits backwards, and RBANS A or B. Following the neuropsychological measures, a

self-report battery was administered that captures data relating to patients' depression, anxiety, stress, and other affective variables. All data for this study were gleaned from these clinical evaluations.

Non-rehabilitation control patients were recruited from a list of patients attending the outpatient heart failure clinic at the Loma Linda University Medical Center Heart Center. These patients were contacted regarding their interest in participating in an optional research study. They were met after appointments with their cardiac health providers, and administered a testing battery identical to that used with the CR patients. Additionally, control patients were consented using documentation approved through the Loma Linda University IRB board (Appendix 1). Each patient was given a copy of the research agreement, with a signed copy kept by the investigators.

Analyses

To test the aims and hypotheses, hierarchical linear and logistic regression models were employed, as discussed above. These models were tested using SPSS 17, and included appropriate assumptions testing for each analysis. Because no pilot data exist, an a priori power analysis was not possible.

Pre-Analysis Data Cleaning and Assumption Checking

Pre-analysis statistical procedures and assumption checking were completed to clean the data and ensure adherence to regression-specific assumptions (Tables 1, 2, & 3). The effects of gender were first examined by correlating gender with dependent variables. No significant correlations were observed, thus gender was not included in the

final model. This finding supports normative data used in interpretation of the RBANS and other employed measures, which do not find it necessary to control for gender (Bechtoldt, et al., 1962; Delis, et al., 2001; Randolph, 1998; Randolph, et al., 1998; Ruff, et al., 1996; Wechsler, 2001, 2008).

Data cleaning focused on removing subjects with missing data or those with primarily non-cardiac diagnoses. At the start of this procedure, there were a total of 73 subjects in the analysis (60 rehabilitation subjects and 13 controls). Subjects were included only if they possessed a primary cardiac diagnosis and had fully complete data (listwise deletion). The final sample size was 52 subjects (41 rehabilitation and 11 controls).

Table 1

Descriptive Data for Aim 1.

			95% CI			
	Mean	SD	Lower	Upper	Min	Max
Heart Failure	0.32	0.47	0.17	0.47	0	1
Hypertension	0.63	0.49	0.48	0.79	0	1
Surgeries	2.88	1.68	2.35	3.41	0	7
Education	4.24	1.77	3.68	4.80	1	7
Premorbid IQ	104.85	12.58	100.88	108.82	72	125
Depression	1.10	1.20	0.72	1.48	0	4
Anxiety	1.22	1.19	0.84	1.60	0	4
Stress	5.12	3.60	3.99	6.26	0	15
RBANS Attention Index	94.39	19.88	88.12	100.67	53	138
RBANS Immed. Mem. Index	87.88	17.46	82.37	93.39	41	117
RBANS Del. Mem. Index	92.68	16.67	87.42	97.94	43	124
Digit Span Bck (Wk. Mem.)	9.29	3.04	8.33	10.25	4	17
Executive Composite Index	-0.22	1.05	-0.55	0.11	-2.75	2.61
D-KEFS Trails 5 (Psy. Sp.)	10.71	2.32	9.98	11.44	4	14
RBANS VisuoSpatial Index	87.71	16.11	82.62	92.80	36	116

Table 2

Descriptive Data for Aim 2.

	Control				Rehabilitation			
			95% CI				95% CI	
	Mean	SD	Lower	Upper	Mean	SD	Lower	Upper
Education	4.55	1.51	3.53	5.56	4.24	1.77	3.68	4.80
Premorbid IQ	107.45	9.61	101.00	113.91	104.85	12.58	100.88	108.82
RBANS Attn.	102.00	20.05	88.53	115.47	94.39	19.88	88.12	100.67
RBANS IM	95.27	14.02	85.85	104.69	87.88	17.46	82.37	93.39
RBANS DM	98.18	13.29	89.26	107.11	92.68	16.67	87.42	97.94
DS Bck	9.64	4.03	6.93	12.34	9.29	3.04	8.33	10.25
Exec Fnct.	0.01	0.81	-0.54	0.55	-0.22	1.05	-0.55	0.11
Trails	12.18	1.17	11.40	12.97	10.71	2.32	9.98	11.44

Table 3

Zero-order correlations.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Heart Failure	1.00														
Hypertension	-.14	1.00													
Surgeries	.43**	.07	1.00												
Education	.06	.25	.09	1.00											
Premorbid IQ	.07	.20	.29	.71**	1.00										
Depression	.08	.15	-.03	-.06	-.11	1.00									
Anxiety	.18	.10	-.19	-.10	-.19	.84**	1.00								
Stress	.17	.21	.02	-.14	-.15	.77**	.74**	1.00							
RBANS Attn.	-.18	.29	.18	.36*	.40**	-.13	-.08	-.05	1.00						
RBANS IM	.18	.38*	.27	.30	.41**	-.10	.01	.01	.51**	1.00					

RBANS DM	.16	.41**	.14	.26	.24	.04	.14	.07	.40**	.68**	1.00				
DS Bck	-.17	.31*	.16	.44**	.45**	-.02	-.07	-.07	.55**	.49**	.29	1.00			
Exec Fnct.	-.09	.31*	.27	.47**	.64**	-.06	-.14	-.05	.62**	.54**	.50**	.52**	1.00		
Trails	-.21	.04	.09	.22	.33*	-.23	-.15	-.12	.51**	.31*	.20	.19	.49**	1.00	
RBANS VS	.28	.06	.31*	.29	.33*	-.11	-.06	-.02	.41**	.45**	.63**	.17	.37*	.24	1.00

*$p < .05$ **$p < .01$

Aim 1

Assumption checking was completed for the hierarchical linear regression models for Aim 1. The form of relationship (linearity) assumption was tested by examining scatterplots of independent variables on each dependent variable. Loess fit lines were computed for each relationship. The relationship between each predictor and its dependent variable were generally linear in appearance, and thus no significant deviations from this assumption were noted.

The correct specification of independent variables assumption was tested by conceptually examining the inclusion of each variable. Since all variables in this study were chosen based on background research, no variables were excluded. Based on theory and previous research, each variable should contribute to the regression models.

The assumption of no measurement error was examined conceptually and through reliability analyses. Although formal reliability data were not reported in the literature, measures were chosen for this study based on their applicability to the chosen patient population. Formal reliability analyses were also computed using Cronbach's α for both multi-item predictors and functional domains, as well as the seven regression models. Reliability data for predictors and functional domains were generally acceptable (Table 4). Values of α for most of the seven regression models (nine variables in total for each model) demonstrated poor reliability, which likely resulted in attenuated relationships with the variables of interest. These values are somewhat lower than the value of .7 generally needed for conducting group research (Furr & Bacharach, 2007). No action was taken due to each variable being specifically selected for this study based on conceptual backing in the literature.

Table 4

Reliability Data for Regression Models and Independent Predictors.

	Reliability (Cronbach's α)
Predictors Only	.21
Attention Model	.36
Immediate Memory Model	.39
Delayed Memory Model	.33
Working Memory Model	.33
Executive Functioning Model	.28
Psychomotor Speed Model	.27
Visuospatial Model	.36
PHQ-9	.90
GAD-7	.91
PSS-4	.10
RBANS Attention Index	.42
RBANS Immediate Memory Index	.64
RBANS Delayed Memory Index	.63
Executive Composite	.69
RBANS Visuospatial Index	.14

The assumption of homoscedasticity was tested by examining the spread of standardized residuals from each model across independent variables values. The assumption seemed to generally be met. Although some variables, such as depression and stress, displayed mild cases of heteroscedasticity for the immediate memory model, the overall trend for all variables was towards homoscedasticity.

The assumption of normal distribution of residuals was examined using a series of Q-Q plots. While some models, such as working memory and psychomotor speed, had several residuals that were not quite as normally distributed as other models, no significant violations occurred.

Multivariate outliers were assessed by examining measures of influence, which take into account both leverage and discrepancy data. DFFITS and Cook's D metrics were obtained for all Aim 1 analyses, and visualized using index plots. Several cases exhibited marginally high amounts of influence on one or two analyses, but none exhibited undue leverage to the degree that warranted removing them from the analyses.

Multicollinearity was assessed by examining tolerance and VIF statistics for all analyses. No multicollinearity, defined as Tolerance < .10 or VIF > 10, was detected. The lowest level of tolerance observed was .21 for anxiety in the model analyzing visuospatial functioning; this variable also exhibited the highest VIF, a value of 4.9, in the same analysis.

Aim 2

Assumption checking was also completed on the logistic regression for Aim 2. Expected frequencies were not computed due to the lack of categorical independent

variables.

Linearity in the logit was computed using the Box-Tidwell approach (Tabachnick & Fidell, 2006). No interaction terms were significant, suggesting appropriate linearity between continuous independent variables and the logit of the dependent variable.

Multicollinearity was assessed for continuous predictors by examining the standard errors of predictors (Tabachnick & Fidell, 2006). Multicollinearity was further assessed by examining tolerance and VIF statistics, using the same cutoffs as described above. No multicollinearity was found.

Outliers were examined using standardized residuals. While overall residual values were quite low ($M = 0.02$, $SD = 0.93$), control patients tended to have larger residual values than rehabilitation patients; the highest residual value was -3.04. No control patients were eliminated from the analysis, however, given the small final sample size (n = 11).

CHAPTER FIVE

RESULTS

Aim 1

Attention

The hypothesis that having fewer medical problems, higher cognitive reserve, and fewer affective symptoms are associated with better attention was partially confirmed (Table 5). The first step of the hierarchical regression analysis, which included CHF status, hypertension status, and surgery history, did not account for a significant proportion of the variance in attention, $F(3, 37) = 2.47$, $p > .07$. The regression model at step 1 accounted for 17% of the variance in attention. None of the included variables were significant individual predictors.

The second step of the model added in education and premorbid IQ. The optimal linear combination of education and premorbid IQ accounted for a significant proportion of the variance in attention above and beyond all previously entered predictor variables, $\Delta F(2, 35) = 2.69$, $\Delta R^2 = .11$. The total regression model at step 2 accounted for 28% of the variance in attention. No single variables were significant predictors in this model.

The third step of the model added depression, anxiety, and stress. The optimal linear combination of depression, anxiety, and stress did not account for a significant proportion of the variance in attention above and beyond all previously entered predictor variables, $\Delta F(3, 32) = 1.42$, $\Delta R^2 = .09$. The final regression model at step 3 accounted for 36% of the variance in attention. Of the individual variables, heart failure served as a significant individual predictor of attention, $t(39) = -2.29$, $p < .03$. The unstandardized regression coefficient for this variable was -17.16, suggesting that, while controlling for

other independent variables in the model, patients with CHF scored 17.16 points less on the attention index than patients without CHF. Depression served as a marginally significant predictor, $t(39) = -2.00$, $p < .053$. The unstandardized regression coefficient for this variable was -9.98, suggesting that, while controlling for other independent variables in the model, as depression increased by one point, attention decreased by 9.98 points.

Table 5

Attention as a Function of Health, Cognitive, and Affective Predictors.

	Model 1			Model 2			Model 3			
	B	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*	sr^2
HF	-11.35	7.13	-.27	-11.57	6.88	-.27	-17.16	7.51	-.41*	.10
Hyp.	9.51	6.24	.23	6.22	6.17	.15	5.30	6.37	.13	.01
Surg.	3.35	1.99	.28	2.56	2.02	.22	4.11	2.20	.35	.07
Edu.				1.99	2.38	.18	2.32	2.36	.21	.02
Pr. IQ				0.32	0.34	.20	0.33	0.34	.21	.02
Dep.							-9.98	4.98	-.60	.08
Anx.							8.82	5.18	.53	.06
Stress							0.64	1.34	.12	.00
R^2		.17			.28			.36		
F		2.47			2.69*			2.28*		
ΔF		2.47			2.69			1.42		

*$p < .05$ **$p < .01$

Immediate Memory

The hypothesis that having fewer medical problems, higher cognitive reserve, and fewer affective symptoms are associated with better immediate memory was confirmed (Table 6). The first step, which included CHF status, hypertension status, and surgery

history, accounted for a significant proportion of the variance in immediate memory, $F(3, 37) = 3.51$, $p < .03$. The regression model at step 1 accounted for 22% of the total variance in immediate memory. Of the individual variables, only hypertension was a significant predictor, $t(39) = -2.62$, $p < .02$. The unstandardized regression coefficient for this variable was 13.89, suggesting that, while controlling for the other independent variables in the model, individuals with hypertension scored 13.89 points higher on the immediate memory index than those without.

The second step of the model added in education and premorbid IQ. The optimal linear combination of education and premorbid IQ did not account for a significant proportion of the variance in immediate memory above and beyond all previously entered predictor variables, $\Delta F(2, 35) = 2.12$, $\Delta R^2 = .08$. The total regression model at step 2 accounted for 31% of the variance in immediate memory. Hypertension remained a significant predictor of attention, $t(39) = -2.30$, $p < .03$. Individuals with hypertension scored 12.19 points higher on the immediate memory index than individuals without hypertension.

The third step of the model added depression, anxiety, and stress. The optimal linear combination of depression, anxiety, and stress did not account for a significant proportion of the variance in immediate memory above and beyond all previously entered predictor variables, $\Delta F(3, 32) = 1.44$, $\Delta R^2 = .08$. The final regression model at step 3 accounted for 39% of the total variance in immediate memory. Hypertension remained a significant predictor of attention, $t(39) = -2.26$, $p < .04$. Individuals with hypertension scored 12.38 points higher on the immediate memory index than those without hypertension.

Table 6

Immediate Memory as a Function of Health, Cognitive, and Affective Predictors.

	Model 1			Model 2			Model 3			
	B	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*	sr^2
HF	5.60	6.10	.15	6.16	5.93	.17	1.97	6.46	.05	.00
Hyp.	13.89	5.29	.39*	12.19	5.31	.34*	12.38	5.48	.35*	.10
Surg.	1.85	1.69	.18	0.84	1.74	.08	2.22	1.89	.21	.03
Edu.				-0.48	2.05	-.05	-0.38	2.03	-.04	.00
Pr. IQ				0.48	0.30	.34	0.48	0.29	.34	.05
Dep.							-8.18	4.29	-.56	.07
Anx.							8.06	4.46	.55	.06
Stress							-0.07	1.15	-.06	.00
R^2		.22			.31			.39		
F		3.51*			3.08*			2.54*		
ΔF		3.51*			2.12			1.44		

*$p < .05$ **$p < .01$

Delayed Memory

The hypothesis that having fewer medical problems, higher cognitive reserve, and fewer affective symptoms are associated with better delayed memory was partially

confirmed (Table 7). The first step, which included CHF status, hypertension status, and surgery history, accounted for a significant proportion of the variance in delayed memory, $F(3, 37) = 3.36$, $p < .03$. The regression model at step 1 accounted for 21% of the total variance in delayed memory. Of the individual variables, only hypertension was a significant predictor, $t(39) = -2.94$, $p < .01$. The unstandardized regression coefficient for this variable was 14.93, suggesting that, while controlling for the other independent variables in the model, individuals with hypertension scored 14.93 points higher on the delayed memory index than those without.

The second step of the model added in education and premorbid IQ. The optimal linear combination of education and premorbid IQ did not account for a significant proportion of the variance in delayed memory above and beyond all previously entered predictor variables, $\Delta F(2, 35) = 0.55$, $\Delta R^2 = .02$. The total regression model at step 2 accounted for 24% of the variance in delayed memory. Hypertension remained a significant predictor of attention, $t(39) = -2.56$, $p < .02$. Individuals with hypertension scored 13.62 points higher on the delayed memory index than those without.

The third step of the model added depression, anxiety, and stress. The optimal linear combination of depression, anxiety, and stress did not account for a significant proportion of the variance in attention above and beyond all previously entered predictor variables, $\Delta F(3, 32) = 0.06$, $\Delta R^2 = .06$. The final regression model at step 3 accounted for 29% of the total variance in delayed memory. Hypertension remained a significant predictor of attention, $t(39) = -2.46$, $p < .02$. Individuals with hypertension scored 13.80 points higher on the delayed memory index than those without.

Table 7

Delayed Memory as a Function of Health, Cognitive, and Affective Predictors.

	Model 1			Model 2			Model 3			
	B	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*	sr^2
HF	7.37	5.81	.21	7.24	5.93	.21	3.65	6.63	.10	.01
Hyp.	14.93	5.08	.44*	13.62	5.31	.40*	13.80	5.62	.40*	.14
Surg.	0.17	1.62	.02	-0.11	1.74	-.01	1.17	1.94	.12	.01
Edu.				0.88	2.05	.09	0.82	2.09	.09	.00
Pr. IQ				0.11	0.30	.08	0.13	0.30	.09	.00
Dep.							-4.70	4.40	-.34	.03
Anx.							7.23	4.57	.52	.06
Stress							-0.64	1.18	-.14	.01
R^2		.21			.24			.29		
F		3.36*			2.18			1.66		
ΔF		3.36*			0.55			0.85		

*$p < .05$ **$p < .01$

Working Memory

The hypothesis that having fewer medical problems, higher cognitive reserve, and fewer affective symptoms are associated with better working memory was partially

confirmed (Table 8). The first step, which included CHF status, hypertension status, and surgery history, did not account for a significant proportion of the variance in working memory, $F(3, 37) = 2.38$, $p > .08$. The regression model at step 1 accounted for 16% of the total variance in working memory. None of the included variables served as significant individual predictors in this model.

The second step of the model added in education and premorbid IQ. The optimal linear combination of education and premorbid IQ accounted for a significant proportion of the variance in working memory above and beyond all previously entered predictor variables, $\Delta F(2, 35) = 4.24$, $\Delta R^2 = .16$. The total regression model at step 2 accounted for 33% of the variance in working memory. No included variables served as individual predictors.

The third step of the model added depression, anxiety, and stress. The optimal linear combination of depression, anxiety, and stress did not account for a significant proportion of the variance in attention above and beyond all previously entered predictor variables, $\Delta F(3, 32) = 0.16$, $\Delta R^2 = .01$. The final regression model at step 3 accounted for 34% of the total variance in working memory. There were no significant individual predictors.

Table 8

Working Memory as a Function of Health, Cognitive, and Affective Predictors.

	Model 1			Model 2			Model 3			
	B	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*	sr^2
HF	-1.56	1.09	-.24	-1.63	1.02	-.25	-1.91	1.17	-.30	.06
Hyp.	1.63	0.96	.26	1.00	0.91	.16	0.99	0.99	.16	.02
Surg.	0.45	0.31	.25	0.32	0.30	.18	0.42	0.34	.23	.03
Edu.				0.43	0.35	.25	0.53	0.37	.25	.03
Pr. IQ				0.05	0.05	.21	0.05	0.05	.21	.02
Dep.							-0.23	0.78	-.09	.00
Anx.							0.53	0.81	.21	.01
Stress							-0.06	0.21	-.07	.00
R^2		.16			.33			.34		
F		2.38			3.38*			2.02		
ΔF		2.38			4.24*			0.16		

*$p < .05$ **$p < .01$

Executive Functioning

The hypothesis that having fewer medical problems, higher cognitive reserve, and fewer affective symptoms are associated with better executive functioning was confirmed

(Table 9). The first step, which included CHF status, hypertension status, and surgery history, accounted for a significant proportion of the variance in executive functioning, $F(3, 37) = 2.90$, $p < .05$. The regression model at step 1 accounted for 19% of the total variance in executive functioning. Of the included variables, surgery history served as an individual predictor. After controlling for other variables in the model, there was a 0.21-point increase in executive functioning for each additional surgery a patient had undergone

The second step of the model added in education and premorbid IQ. The optimal linear combination of education and premorbid IQ accounted for a significant proportion of the variance in executive functioning above and beyond all previously entered predictor variables, $\Delta F(2, 35) = 9.54$, $\Delta R^2 = .29$. The total regression model at step 2 accounted for 48% of the variance in executive functioning. Of the individual variables, only premorbid IQ served as a significant predictor, $t(39) = 2.87$, $p < .01$. After controlling for other variables in the model, every one-point increase in premorbid IQ was accompanied by a .04 point increase in executive functioning.

The third step of the model added depression, anxiety, and stress. The optimal linear combination of depression, anxiety, and stress did not account for a significant proportion of the variance in attention above and beyond all previously entered predictor variables, $\Delta F(3, 32) = 0.06$, $\Delta R^2 = .01$. The final regression model at step 3 accounted for 48% of the total variance in executive functioning. Premorbid IQ remained a significant predictor of executive functioning, $t(39) = 2.75$, $p < .01$. After controlling for other variables in the model, every one-point increase in premorbid IQ was accompanied by a .04-point increase in executive functioning.

Table 9

Executive Functioning as a Function of Health, Cognitive, and Affective Predictors.

	Model 1			Model 2			Model 3			
	B	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*	sr^2
HF	-0.44	0.37	-.20	-0.41	.037	-.18	-0.45	0.36	-.20	.03
Hyp.	0.56	0.32	.26	0.33	0.28	.15	0.30	0.30	.14	.02
Surg.	0.21	0.10	.34*	0.12	0.09	.18	0.12	0.10	.19	.02
Edu.				0.03	0.11	.05	0.03	0.11	.06	.00
Pr. IQ				0.04	0.12	.53**	0.04	0.02	.53**	.12
Dep.							-0.07	0.24	-.08	.00
Anx.							0.02	0.25	.03	.00
Stress							0.02	0.06	.08	.00
R^2		.19			.48			.48		
F		2.90*			6.36**			3.68**		
ΔF		2.90*			9.54**			0.06		

*$p < .05$ **$p < .01$

Psychomotor Speed

The hypothesis that having fewer medical problems, higher cognitive reserve, and fewer affective symptoms are associated with better psychomotor speed was not

confirmed (Table 10). The first step, which included CHF status, hypertension status, and surgery history, did not account for a significant proportion of the variance in psychomotor speed, $F(3, 37) = 1.17$, $p < .34$. The regression model at step 1 accounted for 9% of the total variance in psychomotor speed. No included variables served as significant individual predictors.

The second step of the model added in education and premorbid IQ. The optimal linear combination of education and premorbid IQ did not account for a significant proportion of the variance in psychomotor speed above and beyond all previously entered predictor variables, $\Delta F(2, 35) = 2.04$, $\Delta R^2 = .10$. The total regression model at step 2 accounted for 18% of the variance in psychomotor speed. No included variables served as significant individual predictors.

The third step of the model added depression, anxiety, and stress. The optimal linear combination of depression, anxiety, and stress did not account for a significant proportion of the variance in attention above and beyond all previously entered predictor variables, $\Delta F(3, 32) = .1.73$, $\Delta R^2 = .11$. The final regression model at step 3 accounted for 30% of the total variance in psychomotor speed. Of the included variables, both heart failure status, $t(39) = -2.31$, $p < .03$, and depression, $t(39) = -2.28$, $p < .03$, served as individual predictors. After controlling for other variables in the model, individuals with heart failure scored 2.13 points less on the measure of psychomotor speed than those without. Depressed patients experienced a 1.39 drop in psychomotor speed for every one-point increase in their depressive symptoms, after controlling for other variables.

Table 10

Psychomotor Speed as a Function of Health, Cognitive, and Affective Predictors.

	Model 1			Model 2			Model 3			
	B	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*	sr^2
HF	-1.54	0.87	-.31	-1.49	0.85	-.30	-2.13	0.92	-.43*	.12
Hyp.	-0.10	0.76	-.02	-0.39	0.77	-.08	-0.49	0.78	-.10	.01
Surg.	0.32	0.24	.23	0.19	0.25	.14	0.36	0.27	.26	.04
Edu.				0.03	0.29	.02	0.08	0.29	.06	.00
Pr. IQ				0.06	0.04	.31	0.06	0.04	.31	.04
Dep.							-1.39	0.61	-.72*	.12
Anx.							0.99	0.63	.51	.05
Stress							0.13	0.16	.20	.01
R^2		.09			.18			.30		
F		1.17			1.56			1.68		
ΔF		1.17			2.04			1.73		

*$p < .05$ **$p < .01$

Visuospatial Functioning

The hypothesis that having fewer medical problems, higher cognitive reserve, and fewer affective symptoms are not associated with better visuospatial functioning (null

hypothesis) was confirmed (Table 11). The first step, which included CHF status, hypertension status, and surgery history, did not account for a significant proportion of the variance in visuospatial functioning, $F(3, 37) = 1.80$, $p < .17$. The regression model at step 1 accounted for 13% of the total variance in visuospatial functioning. No included variables served as significant individual predictors.

The second step of the model added in education and premorbid IQ. The optimal linear combination of education and premorbid IQ did not account for a significant proportion of the variance in visuospatial functioning above and beyond all previously entered predictor variables, $\Delta F(2, 35) = 1.62$, $\Delta R^2 = .07$. The total regression model at step 2 accounted for 20% of the variance in visuospatial functioning. No included variables served as significant individual predictors.

The third step of the model added depression, anxiety, and stress. The optimal linear combination of depression, anxiety, and stress did not account for a significant proportion of the variance in attention above and beyond all previously entered predictor variables, $\Delta F(3, 32) = 0.43$, $\Delta R^2 = .03$. The final regression model at step 3 accounted for 23% of the total variance in visuospatial functioning. No included variables served as significant individual predictors.

Table 11

Visuospatial Functioning as a Function of Health, Cognitive, and Affective Predictors.

	Model 1			Model 2			Model 3			
	B	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*	sr^2
HF	6.76	5.92	.20	6.58	5.87	.19	4.58	6.68	.13	.01
Hyp.	2.25	5.18	.07	0.05	5.26	.00	-0.23	5.66	-.01	.00
Surg.	2.11	1.65	.22	1.60	1.72	.17	2.11	1.95	..22	.03
Edu.				1.39	2.02	.15	1.58	2.10	.17	.01
Pr. IQ				0.20	0.29	.16	0.19	0.30	.15	.01
Dep.							-5.01	4.43	-.37	.03
Anx.							3.08	4.61	.23	.01
Stress							0.54	1.19	.12	.00
R^2		.13			.20			.23		
F		1.80			1.77			1.21		
ΔF		1.80			1.62			0.43		

*$p < .05$ **$p < .01$

Aim 2

The hypothesis that having higher cognitive reserve and better cognitive functioning are associated with a greater likelihood to attend cardiac rehabilitation was

not confirmed (Table 12). The Hosmer-Lemeshow goodness of fit statistic for the first step, which included education and premorbid IQ, was not significant, $\chi^2(8) = 5.85$, $p < .7$, suggesting good discrimination and fit of the model for the data. However, no individual predictor significantly predicted cardiac rehabilitation status.

The second step of the model added in attention, immediate memory, delayed memory, working memory, executive functioning, and psychomotor speed. The Hosmer-Lemeshow goodness of fit statistic was not significant, $\chi^2(8) = 8.06$, $p < .5$, suggesting good discrimination and fit of the model. As in step one, no individual predictor significantly predicted cardiac rehabilitation status.

Table 12

Cognitive Rehabilitation Enrollment as a Function of Cognitive Reserve and Neuropsychological Predictors.

	Model 1				Model 2			
	B	Wald χ^2	OR	95% CI	B	Wald χ^2	OR	95% CI
Education	-.10	0.12	0.91	0.53, 1.57	-.23	0.55	0.79	0.43, 1.46
Premorbid IQ	-.01	0.12	0.99	0.91, 1.07	.03	0.21	1.03	0.92, 1.14
RBANS Attn.					.00	0.00	1.00	0.95, 1.05
RBANS IM					-.03	0.62	0.97	0.89, 1.05
RBANS DM					-.01	0.04	0.99	0.93, 1.06
DS Bck					.07	0.23	1.07	0.80, 1.44
Exec Fnct.					.23	0.18	1.26	0.43, 3.68
Trails					-.43	2.58	0.65	0.38, 1.10
R^2	.01				.10			
χ^2	0.83				6.42			
$\Delta\chi^2$	0.83				5.59			

*p < .05 **p < .01

CHAPTER SIX

DISCUSSION

The overall results from this experiment show that health, cognitive reserve, and affective variables do predict cognitive functioning in heart patients across several functional domains (Table 13). One or several of these variables were effective in predicting attention, immediate memory, delayed memory, executive functioning, and psychomotor speed. Cognitive ability predictors did not successfully predict participation in cardiac rehabilitation programs.

Table 13

Table of Significant Individual Predictors for Aim 1.

	Attn.	Imm. Mem.	Del. Mem.	Wor. Mem.	Ex. Func.	Psy. Speed	VisSpa.
Heart Failure	√					√	
Hypertension		√	√				
Surgeries					√		
Education							
Premorbid IQ					√		
Depression	~√					√	
Anxiety							
Stress							

Aim 1 Conclusions

Health, cognitive reserve, and affective variables partially predicted attention in a mixed diagnosis sample of heart patients. While health variables were marginally predictive of attention, the addition of both variables related to cognitive reserve and affective variables greatly improved the model, leading from an initial R^2 of .17 to a final value of .36. While the initial model was marginally significant ($p > .07$), it is likely that the model would be statistically significant with a larger sample size. In the final model, only heart failure served as a significant individual predictor of attention. Specifically, patients with CHF demonstrated significantly worse attention. This finding is congruent with previous research, which suggests that patients with CHF experience the largest impact on cognitive functioning (Beer, et al., 2009; Bennett & Sauve, 2003; Rengo, et al., 1995; Vogels, Oosterman, et al., 2007). Additionally, depression served as a marginally significant predictor of attention. While there is some contention over depression's effects on overall cognition in heart patients, no studies have examined the specific relationship between depression and attention in this population, although it is associated with decreased attention in the general population (Baune, et al., 2010; Beer, et al., 2009; Bennett & Sauve, 2003; Bennett, et al., 2005; Delgado & Schillerstrom, 2009; Vogels, Oosterman, et al., 2007). Given the marginally significant finding in this study, as well as the moderate effect size ($sr^2 = .28$), it is possible that depression may have some influence on attention in heart patients. Since attention mediates other cognitive domains, like memory, any impact on attention can have wider functional consequences (Mitrushina, et al., 2005; Strauss, et al., 2006). It is likely that the effect of this variable would have been statistically significant with a larger sample size.

Predictor variables successfully delineated immediate memory. While the final model was significant, the initial step containing health variables, particularly hypertension, accounted for the most variance in immediate memory, as evidenced by the largest sr^2 values. Hypertension exhibited a significant positive relationship with immediate memory, suggesting better memory among those diagnosed with hypertension. There are several plausible explanations for this relationship. First, although hypertension is known to adversely affect memory in the general population (Cherubini, et al., 2007; Feinberg & Farah, 2003; van Swieten, et al., 1991), it generally affects cognition in heart patients indirectly as a precursor to the development of CAD or CHF (Bennett & Sauve, 2003; Bennett, et al., 2005; Vogels, Oosterman, et al., 2007; Wynands, et al., 1970). Thus, the relationship between hypertension and memory is potentially not direct, and may be mediated by heart-related factors, which could explain its seemingly beneficial relationship with memory. The more likely explanation relates to treatment. While hypertension is a risk factor for cognitive dysfunction, this relationship is contingent on the long-term poor management of blood pressure (Cherubini, et al., 2007). Because of the fact that the sample for this study contained patients undergoing medical treatment for heart problems, it is likely that all individuals with a diagnosis of hypertension were also being treated for their symptoms. Such treatment may explain why an opposite relationship between hypertension and memory was observed; isolating those treated only for hypertension could help clarify this discrepancy. Multicollinearity effects were not observed for this model, and thus are likely not responsible for the aberrant finding regarding hypertension and immediate memory.

Predictor variables were moderately successful in predicting delayed memory. The first step of the model, consisting only of medical variables, successfully predicted delayed memory functioning. This relationship was again contingent on a positive relationship between hypertension and memory, likely due to either mediation by heart-related factors or the fact that all persons diagnosed with hypertension in a medical setting likely had their symptoms controlled through treatment paradigms. However, neither the cognitive reserve nor affective variables contributed overall to the model, likely due to decreasing power with the addition of more predictors. While anxiety explained a moderate amount of unique variance in delayed memory (sr^2 = .24), this individual relationship was not significant, possibly due to poor reliability or low power.

Predictor variables were moderately successful in predicting working memory. While medical variables, particularly hypertension, were associated with the working memory, they did not add enough unique variance as a group for a significant first step. The second step, however, was associated with a significant increase in R^2, leading to overall significance for the model. Semi-partial correlations revealed that education and premorbid IQ exhibited roughly equal contributions to the final model (.03 and .02, respectively). The addition of the third step rendered the final model non-significant, likely due to reduced power subsequent to the additional predictors.

Predictor variables successfully predicted executive functioning. Medical variables added significantly to the model, driven primarily by surgery history. Similar to hypertension in previous models, surgery history was positively associated with executive functioning, rather than being negatively associated as expected. Statistically, this relationship could be due to the relationship between number of surgeries and

hypertension. These two variables were significantly related according to their zero-order correlations; given the fact that they both have exhibited counterintuitive relationships with dependent variables in this study, the observed effects could be due to multicollinearity. However, further analysis revealed that tolerance and VIF statistics for this model did not suggest the presence of multicollinearity. Methodological explanations include the possibility that patients with more numerous surgeries have had their cardiac problems mostly corrected, thus explaining the positive relationship. A more plausible explanation, however, involves the timeline of POCD after major surgery. While up to 25% of patients can exhibit deficits up to 6 months out, POCD is known to eventually resolve for the vast majority of patients, given enough time (Newman, et al., 2001; Ropacki, et al., 2007; Royter, et al., 2005; Selnes, et al., 1999; Sun, et al., 2012; van Dijk, et al., 2000). The surgery history variable for this study examined the total number of surgeries, not contingent on time. Thus, any POCD symptoms may have resolved by the time of the neuropsychological evaluation. The second step of the model explained a significant amount of additional variance in executive functioning, primarily due to the effects of premorbid IQ. Affective variables added very little to the final model, as evidenced by their small semipartial correlations.

Predictor variables were somewhat successful in predicting psychomotor speed. While heart failure status was marginally significantly associated with psychomotor speed, this relationship was not strong enough for the first step of the model to be significant. Additionally, while both education and premorbid IQ were marginally associated with psychomotor speed, neither predictor contributed significantly to the model. Depression and heart failure were significantly associated with psychomotor

speed in the final model; however this relationship was not statistically powerful enough to render the step or overall model significant. Because of the final R^2 of .30, it is likely that this final step would have been significant given a larger sample size. While depression generally leads to psychomotor slowing (Baune, et al., 2010; Delgado & Schillerstrom, 2009), it is possible that this effect is somehow mediated or attenuated in heart patients. Interestingly, although psychomotor speed is often impaired in heart patients (Hoth, et al., 2008; Tiemann, Penner, et al., 2009; Vogels, Scheltens, et al., 2007), the mean for patients in the present study was close to the 50^{th} percentile, suggesting this sample of heart patients did not experience a decline in this area. Thus, the relative sparing of psychomotor abilities in the present study, illustrated by the fact that patients scored no different from the normal range for healthy participants, may help to explain possible mediation between depression and psychomotor speed. Although it is unknown why psychomotor speed was spared in this sample, it could be due to the normative data used to score the D-KEFS Trails paradigm. The inclusion of other psychomotor tests, such as the grooved pegboard or finger tapping test, could provide some perspective on this finding.

As hypothesized, predictor variables were not successful in predicting visuospatial functioning. While it is possible that health variables would have led to a significant initial step given a larger sample size, the present study found no association. While some evidence exists of visuospatial memory deficits in the heart population, visuospatial ability as a whole is generally unaffected (Bauer & Pozehl, 2010; Bennett & Sauve, 2003; Bennett, et al., 2005; Sauve, et al., 2009).

It should be noted that many analyses in Aim 1 would benefit from additional participants, ideally approaching the suggested 10 subjects per predictor (Tabachnick & Fidell, 2006). As mentioned in the results and discussion sections, there were several instances where one step of a model would be significant, only to be rendered non-significant by the addition of additional predictors at a later step. Because of the fact that once any model reaches overall significance it should retain it, this phenomenon is best understood to result from low statistical power due to a restricted sample size. Thus, although Aim 1 overall exhibited good confirmation of hypotheses, the results would likely be strengthened with the inclusion of additional subjects.

Aim 2 Conclusions

Predictor variables were not successful in predicting participation in cardiac rehabilitation based on cognitive factors. There are several reasons that may explain this finding. Statistically, the low number of control subjects (n = 11), relative to rehabilitation subjects (n = 41) may have resulted in low statistical power or heterogeneity of variance. Based on the suggested sample size of 10 subjects per predictor (Tabachnick & Fidell, 2006), the final sample size of 52 subjects was below the 70-80 suggested. To examine the effects that a low N may have had, exploratory analyses were conducted by collapsing all cognitive variables into a single predictor by converting each variable to a z-score and combining into a composite measure. This model, like the full-scale model, was not statistically significant, suggesting that the failure of the full model to predict admittance to rehabilitation may be a true finding. Final Cox and Snell R^2 for the full model was .036, suggesting that only 3.6% of the

decision on whether to attend rehabilitation or not was contingent on cognitive factors. Of the individual predictors, processing speed was the closest to significance.

The lack of cognitive explanations for the decision to attend rehabilitation suggests other factors are at work. Possible explanations include that not all heart patients were actually offered or referred to rehabilitation as was assumed. If this were the case, it could introduce random error into the analysis. It is also possible that other factors such as limited availability, satisfaction with current treatment options, or other factors affected this analysis. That is, patients who are currently being treated in the heart clinic may have rejected participation in cardiac rehabilitation not because of a cognitive factor, but due to the fact that they were satisfied with their current treatment options or lacked the time to commit to attending rehabilitation several times per week. Finally, it is possible that the final model lacked the necessary sample size, resulting in a Type II error. Data will continue to be collected prior to publication, ensuring a sufficient sample size to reduce the likelihood of such an error.

Summary

In summary, several health and cognitive factors affect neuropsychological functioning in heart patients across many of the domains identified. Health-related factors appear to have an impact on cognitive functioning in this population. This set of variables significantly predicted immediate memory, delayed memory and executive functioning, suggesting that the combination of hypertension, heart failure status, and surgery history influences cognitive functioning on its own, without the addition of other factors. Both heart failure status and hypertension served as individual predictors in

several models although, paradoxically, hypertension was often positively associated with cognitive functioning. This relationship, as discussed above, may be due to the fact that patients with a diagnosis of hypertension in a medical setting are likely being treated for their symptoms.

Cognitive reserve-related factors also had predictive power in heart patients, after controlling for health-related factors. The effects of variables associated with cognitive reserve were particularly notable in the domains of attention, working memory, and executive functioning, where they worked in concert to predict performance. Individually, the only significant predictor was premorbid IQ in the model predicting executive functioning. The lack of individual predictive power observed with the education variable is likely methodological; although multicollinearity was not observed, WTAR scores correct for education, and thus may restrict any individual influence that education may provide. Based on the small but relevant effect sizes uniquely attributable to premorbid IQ for a variety of non-significant domains, including immediate memory (sr^2 = .05) and psychomotor speed (sr^2= .04), it is likely that additional significant relationships would have appeared given better model reliability or additional power (Ferguson, 2009).

Affective predictors did not predict cognitive functioning as well as initially hypothesized. Of the regression models, the only marginally significant finding was a tenuous association between depression and both attention and psychomotor speed. While the effects of depression, anxiety, and stress are clearly linked with cognitive difficulties, including reduced attention (Alagiakrishnan, et al., 2006; Baune, et al., 2010; Cherubini, et al., 2007; Delgado & Schillerstrom, 2009; Freedland, et al., 2009; Kent &

Shapiro, 2009; Vogels, Oosterman, et al., 2007; Vogels, Scheltens, et al., 2007), their relationships with cognitive functioning in heart patients is less clear (Bennett & Sauve, 2003; Grubb, et al., 2000; Pressler, 2008; Sauve, et al., 2009). While these affective variables were significantly associated with many dependent variables on zero-order correlations, they conferred little additional variance after controlling for health and cognitive-related factors. Given the medium observed effect sizes uniquely attributable to affective variables for domains including attention, immediate memory, and psychomotor speed, it is likely that the lack of significance for these variables is due to either poor reliability or low power.

Implications

Cognitive dysfunction in cardiac patients is well documented, and may affect treatment adherence (Bauer, et al., 2011; Bennett & Sauve, 2003; Bennett, et al., 2005; Sauve, et al., 2009; Vogels, Oosterman, et al., 2007; Vogels, Scheltens, et al., 2007). Findings from the present study suggest that patients with health comorbidities common in heart patients likely experience more cognitive dysfunction, which could affect treatment. As a result, properly managing hypertension and CHF, as well as limiting the number of surgeries, could lead to better cognitive outcomes, improving treatment adherence. For patients with any of the abovementioned conditions, efforts to encourage treatment adherence such as psychoeducation; utilization of pill boxes, notebooks, and other compensatory strategies to track medications; as well as follow-up care to ensure treatment adherence may lead to decreased morbidity and better health outcomes.

Cognitive reserve findings suggest that, similar to the Alzheimer's Dementia literature (Ropacki, et al., 2007; Stern, 2002, 2009; Vemuri, et al., 2011), cardiac patients with better reserve-related abilities likely experience better neuropsychological abilities than those who scored lower on reserve-related measures, even after controlling for health-related factors. Thus, cardiac patients with higher levels of reserve-related factors, including premorbid IQ, have better executive functioning, which may additionally lead to better health outcomes and reduced morbidity. To help correct for this factor, cardiac patients with low education or premorbid IQ could be engaged in additional methods to encourage treatment adherence, similar to those described above to correct for health-related factors.

Affective findings suggest that addressing health and cognitive factors, rather than affective difficulties, may be most helpful to heart patients, given the former's stronger relationship with cognitive ability. However, given the high levels of subjective distress, morbidity, and even mortality associated with affective factors, adding or continuing treatment for these conditions, especially depression, may lead to better health outcomes (Bennett & Sauve, 2003; Carney & Freedland, 2009; Cherubini, et al., 2007; Kent & Shapiro, 2009; Moser, et al., 1999; Naqvi, et al., 2005). Thus, while treating depression and other affective factors may have limited effects on cognitive ability in heart patients, the literature supports the positive effects that treatment of these conditions has for overall health.

Future Directions

Findings from this study suggest several future directions. Primarily, given the

low sample size for control patients, revisiting Aim 2 after more subjects are recruited could alter the findings observed in the present study. This aim will only be considered for publication if and when the recommended control patient sample size of 35 is achieved.

Also related to Aim 2, actual adherence and completion of CR could be investigated. While the present study sought to differentiate between those who chose to attend CR or not, no attention was given to success once enrolled in a treatment paradigm. This direction could include tracking who actually completed rehabilitation to examine whether success or failure in CR is predicted by any cognitive factors.

Another possible future direction relates to health outcomes. This study shows that a constellation of health, cognitive reserve, and affective factors impact cognitive functioning in heart patients. Since impaired cognitive functioning is often associated with poorer health outcomes (Kakos, et al., 2010; Moser, et al., 1999; Vogels, Oosterman, et al., 2007; Vogels, Scheltens, et al., 2007), it is likely that addressing the influencing factors described in this study can reduce patient morbidity and mortality. To formally test this hypothesis, it will be important to formulate and test models that describe the impact health, cognitive reserve, and affective predictors have on health outcomes when mediated by cognitive factors. Such studies are likely to help us better interpret and understand the clinical applicability of the current study.

A future direction could also include examining the effects that a treatment paradigm has on heart patients' cognitive abilities. This could include testing patients directly after a heart diagnosis is made and at post-treatment. While some treatments, such as POCD, are well-documented (Ropacki, et al., 2007), particularly after CABG and

other procedures, it would be useful to examine the effects of less invasive procedures, such as laparoscopic surgeries, pharmacotherapies, and other modalities.

Finally, a future direction could include stratifying patients based on their presenting problem (e.g., CHF, MI, etc.), to further study the effects that disparate heart diagnoses have on cognitive ability. In addition, researchers may consider studying the potential interaction between diagnosis and treatment modality.

REFERENCES

Acanfora, D., Trojano, L., Iannuzzi, G. L., Furgi, G., Picone, C., Rengo, C., et al. (1996). The brain in congestive heart failure. *Arch Gerontol Geriatr, 23*(3), 247-256.

Alagiakrishnan, K., McCracken, P., & Feldman, H. (2006). Treating vascular risk factors and maintaining vascular health: is this the way towards successful cognitive ageing and preventing cognitive decline? *Postgrad Med J, 82*(964), 101-105.

Albert, S. M., & Teresi, J. A. (1999). Reading ability, education, and cognitive status assessment among older adults in Harlem, New York City. *Am J Public Health, 89*(1), 95-97.

Antonelli Incalzi, R., Trojano, L., Acanfora, D., Crisci, C., Tarantino, F., Abete, P., et al. (2003). Verbal memory impairment in congestive heart failure. *J Clin Exp Neuropsychol, 25*(1), 14-23.

Army Individual Test Battery Manual of Directions and Scoring. (1944). Washington, D.C.: U.S. War Department, Adjutant General's Office.

Aronson, D., & Edelman, E. R. (2010). Revascularization for coronary artery disease in diabetes mellitus: angioplasty, stents and coronary artery bypass grafting. *Rev Endocr Metab Disord, 11*(1), 75-86.

Bauer, L., & Pozehl, B. (2010). Measurement of cognitive function in chronic heart failure: a feasibility study. *Appl Nurs Res*.

Bauer, L., Pozehl, B., Hertzog, M., Johnson, J., Zimmerman, L., & Filipi, M. (2011). A brief neuropsychological battery for use in the chronic heart failure population. *Eur J Cardiovasc Nurs*.

Baune, B. T., Miller, R., McAfoose, J., Johnson, M., Quirk, F., & Mitchell, D. (2010). The role of cognitive impairment in general functioning in major depression. *Psychiatry Res, 176*(2-3), 183-189.

Bechtoldt, H. P., Benton, A. L., & Fogel, M. L. (1962). An application of factor analysis in neuropsychology. *Psychological Record, 12*, 147-156.

Beer, C., Ebenezer, E., Fenner, S., Lautenschlager, N. T., Arnolda, L., Flicker, L., et al. (2009). Contributors to cognitive impairment in congestive heart failure: a pilot case-control study. *Intern Med J, 39*(9), 600-605.

Bennett, S. J., & Sauve, M. J. (2003). Cognitive deficits in patients with heart failure: a review of the literature. *J Cardiovasc Nurs, 18*(3), 219-242.

Bennett, S. J., Sauve, M. J., & Shaw, R. M. (2005). A conceptual model of cognitive deficits in chronic heart failure. *J Nurs Scholarsh, 37*(3), 222-228.

Benton, A. L. (1969). Development of a multilingual aphasia battery: Progress and problems. *Journal of the Neurological Sciences, 9*, 39-48.

Brown, R. R., & Partington, J. E. (1942). The intelligence of the narcotic drug addict. *Journal of General Psychology, 26*, 175-179.

Cardiovascular Disease Costs and Statistics. American Heart Association.

Carles, S., Jr., Curnier, D., Pathak, A., Roncalli, J., Bousquet, M., Garcia, J. L., et al. (2007). Effects of short-term exercise and exercise training on cognitive function among patients with cardiac disease. *J Cardiopulm Rehabil Prev, 27*(6), 395-399.

Carney, R. M., & Freedland, K. E. (2009). Treatment-resistant depression and mortality after acute coronary syndrome. *Am J Psychiatry, 166*(4), 410-417.

Cherubini, A., Lowenthal, D. T., Paran, E., Mecocci, P., Williams, L. S., & Senin, U. (2007). Hypertension and cognitive function in the elderly. *Am J Ther, 14*(6), 533-554.

Chobanian, A. V., Bakris, G. L., Black, H. R., Cushman, W. C., Green, L. A., Izzo, J. L., Jr., et al. (2003). Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension, 42*(6), 1206-1252.

Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A global measure of perceived stress. *J Health Soc Behav, 24*(4), 385-396.

Congestive Heart Failure. (2011). (Vol. 2011): American Heart Association.

Coronary Artery Disease. (2009). National Heart, Lung, and Blood Institue.

Croft, J. B., Giles, W. H., Pollard, R. A., Keenan, N. L., Casper, M. L., & Anda, R. F. (1999). Heart failure survival among older adults in the United States: a poor prognosis for an emerging epidemic in the Medicare population. *Arch Intern Med, 159*(5), 505-510.

de Jonge, P., Ormel, J., van den Brink, R. H., van Melle, J. P., Spijkerman, T. A., Kuijper, A., et al. (2006). Symptom dimensions of depression following myocardial infarction and their relationship with somatic health status and cardiovascular prognosis. *Am J Psychiatry, 163*(1), 138-144.

Delgado, P. L., & Schillerstrom, J. (2009). Cognitive difficulties associated with depression: What are the implications for treatment? *Psychiatric Times, 26*(3).

Delis, D., Kaplan, E., & Kramer, J. (2001). *Delis-Kaplan Executive Function System*. San Antonio, Tx: The Psychological Corporation.

Delis, D., Kramer, J., Kaplan, E., & Ober, B. A. (2000). *California Verbal Learning Test - Second Edition*. San Antonio, TX: Pearson.

Doering, L. V. (1999). Pathophysiology of acute coronary syndromes leading to acute myocardial infarction. *J Cardiovasc Nurs, 13*(3), 1-20; quiz 119.

Dolgin, M. (1994). *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels*. Boston: Little Brown and Company.

Duff, K., Patton, D., Schoenberg, M. R., Mold, J., Scott, J. G., & Adams, R. L. (2003). Age- and education-corrected independent normative data for the RBANS in a community dwelling elderly sample. *Clin Neuropsychol, 17*(3), 351-366.

Duff, K., Schoenberg, M. R., Patton, D., Paulsen, J. S., Bayless, J. D., Mold, J., et al. (2005). Regression-based formulas for predicting change in RBANS subtests with older adults. *Arch Clin Neuropsychol, 20*(3), 281-290.

Dzau, V. J. (1990). Atherosclerosis and hypertension: mechanisms and interrelationships. *J Cardiovasc Pharmacol, 15 Suppl 5*, S59-64.

Eichenbaum, H. (2002). *The Cognitive Neuroscience of Memory*: Oxford University Press.

El-Sherif, N., Khan, A., Savarese, J., & Turitto, G. (2010). Pathophysiology, risk stratification, and management of sudden cardiac death in coronary artery disease. *Cardiol J, 17*(1), 4-10.

Elwood, P. C., Pickering, J., Bayer, A., & Gallacher, J. E. (2002). Vascular disease and cognitive function in older men in the Caerphilly cohort. *Age Ageing, 31*(1), 43-48.

Feinberg, T. E., & Farah, M. J. (2003). *Behavioral Neurology and Neuropsychology* (Second ed.): McGraw-Hill.

Ferguson, C. J. (2009). An Effect Size Primer: A Guide for Clinicians and Researchers. *Professional Psychology: Research and Practice, 40*(5), 532-538.

Ferrara, N., Corbi, G., Bosimini, E., Cobelli, F., Furgi, G., Giannuzzi, P., et al. (2006). Cardiac rehabilitation in the elderly: patient selection and outcomes. *Am J Geriatr Cardiol, 15*(1), 22-27.

Fogel, M. L. (1962). The Gerstmann syndrome and the parietal symptom-complex. *Psychological Record, 12*, 85-90.

Freedland, K. E., Skala, J. A., Carney, R. M., Rubin, E. H., Lustman, P. J., Davila-Roman, V. G., et al. (2009). Treatment of depression after coronary artery bypass surgery: a randomized controlled trial. *Arch Gen Psychiatry, 66*(4), 387-396.

Furr, R. M., & Bacharach, V. R. (2007). *Psychometrics: An Introduction* (1 ed.): Sage Publications.

Gontkovsky, S. T., Mold, J. W., & Beatty, W. W. (2002). Age and educational influences on RBANS index scores in a nondemented geriatric sample. *Clin Neuropsychol, 16*(3), 258-263.

Green, R. E., Melo, B., Christensen, B., Ngo, L. A., Monette, G., & Bradbury, C. (2008). Measuring premorbid IQ in traumatic brain injury: an examination of the validity of the Wechsler Test of Adult Reading (WTAR). *J Clin Exp Neuropsychol, 30*(2), 163-172.

Grubb, N. R., Simpson, C., & Fox, K. A. (2000). Memory function in patients with stable, moderate to severe cardiac failure. *Am Heart J, 140*(1), E1-5.

Gruhn, N., Larsen, F. S., Boesgaard, S., Knudsen, G. M., Mortensen, S. A., Thomsen, G., et al. (2001). Cerebral blood flow in patients with chronic heart failure before and after heart transplantation. *Stroke, 32*(11), 2530-2533.

Gunstad, J., Macgregor, K. L., Paul, R. H., Poppas, A., Jefferson, A. L., Todaro, J. F., et al. (2005). Cardiac rehabilitation improves cognitive performance in older adults with cardiovascular disease. *J Cardiopulm Rehabil, 25*(3), 173-176.

Gutstein, D. E., & Fuster, V. (1999). Pathophysiology and clinical significance of atherosclerotic plaque rupture. *Cardiovasc Res, 41*(2), 323-333.

Haji, S. A., & Movahed, A. (2000). Update on digoxin therapy in congestive heart failure. *Am Fam Physician, 62*(2), 409-416.

Hammeke, T. A., & Hastings, J. E. (1988). Neuropsychologic alterations after cardiac operation. *J Thorac Cardiovasc Surg, 96*(2), 326-331.

Hannesdottir, K., Nitkunan, A., Charlton, R. A., Barrick, T. R., MacGregor, G. A., & Markus, H. S. (2009). Cognitive impairment and white matter damage in hypertension: a pilot study. *Acta Neurol Scand, 119*(4), 261-268.

Hansford, R. G., & Castro, F. (1982). Effect of senescence on Ca2+-ion transport by heart mitochondria. *Mech Ageing Dev, 19*(1), 5-13.

Hogue, C. W., Jr., Hershey, T., Dixon, D., Fucetola, R., Nassief, A., Freedland, K. E., et al. (2006). Preexisting cognitive impairment in women before cardiac surgery and its relationship with C-reactive protein concentrations. *Anesth Analg, 102*(6), 1602-1608; table of contents.

Hoth, K. F., Poppas, A., Moser, D. J., Paul, R. H., & Cohen, R. A. (2008). Cardiac dysfunction and cognition in older adults with heart failure. *Cogn Behav Neurol, 21*(2), 65-72.

Jezierska-Wozniak, K., Mystkowska, D., Tutas, A., & Jurkowski, M. K. (2011). Stem cells as therapy for cardiac disease - a review. *Folia Histochem Cytobiol, 49*(1), 13-25.

Kakos, L. S., Szabo, A. J., Gunstad, J., Stanek, K. M., Waechter, D., Hughes, J., et al. (2010). Reduced executive functioning is associated with poorer outcome in cardiac rehabilitation. *Prev Cardiol, 13*(3), 100-103.

Kalat, J. W. (2004). *Biological Psychology* (Eighth Edition ed.). Canada: Wadsworth.

Kalay, N., Yarlioglues, M., Ardic, I., Duran, M., Kaya, M. G., Inanc, T., et al. (2010). The assessment of atherosclerosis on vascular structures in patients with acute coronary syndrome. *Clin Invest Med, 33*(1), E36-43.

Kent, L. K., & Shapiro, P. A. (2009). Depression and related psychological factors in heart disease. *Harv Rev Psychiatry, 17*(6), 377-388.

Kinlay, S., Libby, P., & Ganz, P. (2001). Endothelial function and coronary artery disease. *Curr Opin Lipidol, 12*(4), 383-389.

Kneebone, A. C., Andrew, M. J., Baker, R. A., & Knight, J. L. (1998). Neuropsychologic changes after coronary artery bypass grafting: use of reliable change indices. *Ann Thorac Surg, 65*(5), 1320-1325.

Kostis, J. B., Rosen, R. C., Cosgrove, N. M., Shindler, D. M., & Wilson, A. C. (1994). Nonpharmacologic therapy improves functional and emotional status in congestive heart failure. *Chest, 106*(4), 996-1001.

Krishnan, K. R. (2005). Treatment of depression in the medically ill. *J Clin Psychopharmacol, 25*(4 Suppl 1), S14-18.

Kroenke, K., Spitzer, R. L., & Williams, J. B. (2001). The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med, 16*(9), 606-613.

Kropotov, J. D., & Etlinger, S. C. (1999). Selection of actions in the basal ganglia-thalamocortical circuits: review and model. *Int J Psychophysiol, 31*(3), 197-217.

Lal, B. K. (2007). Cognitive function after carotid artery revascularization. *Vasc Endovascular Surg, 41*(1), 5-13.

Lamy, A., Natarajan, M., & Yusuf, S. (2011). Medical treatment, PCI, or CABG for coronary artery disease? *BMJ, 342*, d966.

Lavie, C. J., & Milani, R. V. (2011). Cardiac rehabilitation and exercise training in secondary coronary heart disease prevention. *Prog Cardiovasc Dis, 53*(6), 397-403.

Leon-Carrion, J. (1997). *Neuropsychological Rehabilitation: Fundamentals, Innovations, and Directions*: St. Lucie Press.

Leon, A. S., Franklin, B. A., Costa, F., Balady, G. J., Berra, K. A., Stewart, K. J., et al. (2005). Cardiac rehabilitation and secondary prevention of coronary heart disease: an American Heart Association scientific statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity), in collaboration with the American association of Cardiovascular and Pulmonary Rehabilitation. *Circulation, 111*(3), 369-376.

Libby, P. (1995). Molecular bases of the acute coronary syndromes. *Circulation, 91*(11), 2844-2850.

Lim, C., Alexander, M. P., LaFleche, G., Schnyer, D. M., & Verfaellie, M. (2004). The neurological and cognitive sequelae of cardiac arrest. *Neurology, 63*(10), 1774-1778.

Litwin, S. E., & Grossman, W. (1993). Diastolic dysfunction as a cause of heart failure. *J Am Coll Cardiol, 22*(4 Suppl A), 49A-55A.

Lloyd-Jones, D., Adams, R., Carnethon, M., De Simone, G., Ferguson, T. B., Flegal, K., et al. (2009). Heart disease and stroke statistics--2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation, 119*(3), e21-181.

Luszczynska, A., & Cieslak, R. (2009). Mediated effects of social support for healthy nutrition: fruit and vegetable intake across 8 months after myocardial infarction. *Behav Med, 35*(1), 30-38.

Manly, J. J., Touradji, P., Tang, M. X., & Stern, Y. (2003). Literacy and memory decline among ethnically diverse elders. *J Clin Exp Neuropsychol, 25*(5), 680-690.

Maseri, A. (1990). Mechanisms of myocardial ischemia. *Cardiovasc Drugs Ther, 4 Suppl 4*, 827-831.

Maseri, A. (2000). From syndromes to specific disease mechanisms. The search for the causes of myocardial infarction. *Ital Heart J, 1*(4), 253-257.

Matlin, M. W. (2002). *Cognition* (Fifth ed.): Harcourt.

McGrew, K. S. (2009). CHC theory and the human cognitive abilities project: Standing on the shoulders of the giants of psychometric intelligence research. *Intelligence, 37*, 1-10.

McKee, P. A., Castelli, W. P., McNamara, P. M., & Kannel, W. B. (1971). The natural history of congestive heart failure: the Framingham study. *N Engl J Med, 285*(26), 1441-1446.

Meyers, J. E., & Meyers, K. R. (1995). *Rey Complex Figure Test and Recognition Trial*. Lutz, FL: Psychological Assessment Resources.

Michaels, A. D., & Chatterjee, K. (2002). Cardiology patient pages. Angioplasty versus bypass surgery for coronary artery disease. *Circulation, 106*(23), e187-190.

Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annu Rev Neurosci, 24*, 167-202.

Mitrushina, M., Boone, K. B., Razani, J., & D'Elia, L. F. (2005). *Handbook of Normative Data for Neuropsychological Assessment* (Second ed.). New York, NY: Oxford University Press.

Morrissey, R. P., Czer, L., & Shah, P. K. (2011). Chronic heart failure: current evidence, challenges to therapy, and future directions. *Am J Cardiovasc Drugs, 11*(3), 153-171.

Moser, D. J., Cohen, R. A., Clark, M. M., Aloia, M. S., Tate, B. A., Stefanik, S., et al. (1999). Neuropsychological functioning among cardiac rehabilitation patients. *J Cardiopulm Rehabil, 19*(2), 91-97.

Moser, D. J., Hoth, K. F., Robinson, R. G., Paulsen, J. S., Sinkey, C. A., Benjamin, M. L., et al. (2004). Blood vessel function and cognition in elderly patients with atherosclerosis. *Stroke, 35*(11), e369-372.

Moser, D. J., Robinson, R. G., Hynes, S. M., Reese, R. L., Arndt, S., Paulsen, J. S., et al. (2007). Neuropsychological performance is associated with vascular function in patients with atherosclerotic vascular disease. *Arterioscler Thromb Vasc Biol, 27*(1), 141-146.

Moser, D. K., Riegel, B., McKinley, S., Doering, L. V., An, K., & Sheahan, S. (2007). Impact of anxiety and perceived control on in-hospital complications after acute myocardial infarction. *Psychosom Med, 69*(1), 10-16.

Murkin, J. M., Newman, S. P., Stump, D. A., & Blumenthal, J. A. (1995). Statement of consensus on assessment of neurobehavioral outcomes after cardiac surgery. *Ann Thorac Surg, 59*(5), 1289-1295.

Naqvi, T. Z., Naqvi, S. S., & Merz, C. N. (2005). Gender differences in the link between depression and cardiovascular disease. *Psychosom Med, 67 Suppl 1*, S15-18.

Newman, M. F., Kirchner, J. L., Phillips-Bute, B., Gaver, V., Grocott, H., Jones, R. H., et al. (2001). Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. *N Engl J Med, 344*(6), 395-402.

Nicolino, A., Ferrara, N., Longobardi, G., Acanfora, D., Rengo, C., & Rengo, F. (1993). Left ventricular diastolic filling in elderly hypertensive patients. *J Am Geriatr Soc, 41*(3), 217-222.

Nykamp, D., Morgan, J., & Roland, A. (2009). Cognitive decline after invasive intervention in cardiovascular disease: is it drug related? *Consult Pharm, 24*(9), 681-685.

Olivetti, G., Melissari, M., Capasso, J. M., & Anversa, P. (1991). Cardiomyopathy of the aging human heart. Myocyte loss and reactive cellular hypertrophy. *Circ Res, 68*(6), 1560-1568.

Osterrieth, P. A. (1944). Le test de copie d'une figure complex: Contribution a l'etude de la perception et de la memoire. *Archives de Psychologie, 30*, 286-356.

Partington, J. E., & Leiter, R. G. (1949). Partington Pathways Test. *Psychological Services Center Bulletin, 1*, 9-20.

Patton, D. E., Duff, K., Schoenberg, M. R., Mold, J., Scott, J. G., & Adams, R. L. (2006). RBANS index discrepancies: base rates for older adults. *Arch Clin Neuropsychol, 21*(2), 151-160.

Petrucci, R. J., Wright, S., Naka, Y., Idrissi, K. A., Russell, S. D., Dordunoo, D., et al. (2009). Neurocognitive assessments in advanced heart failure patients receiving continuous-flow left ventricular assist devices. *J Heart Lung Transplant, 28*(6), 542-549.

Pressler, S. J. (2008). Cognitive functioning and chronic heart failure: a review of the literature (2002-July 2007). *J Cardiovasc Nurs, 23*(3), 239-249.

Pressler, S. J., Kim, J., Riley, P., Ronis, D. L., & Gradus-Pizlo, I. (2010). Memory dysfunction, psychomotor slowing, and decreased executive function predict mortality in patients with heart failure and low ejection fraction. *J Card Fail, 16*(9), 750-760.

Pressler, S. J., Subramanian, U., Kareken, D., Perkins, S. M., Gradus-Pizlo, I., Sauve, M. J., et al. (2010a). Cognitive deficits and health-related quality of life in chronic heart failure. *J Cardiovasc Nurs, 25*(3), 189-198.

Pressler, S. J., Subramanian, U., Kareken, D., Perkins, S. M., Gradus-Pizlo, I., Sauve, M. J., et al. (2010b). Cognitive deficits in chronic heart failure. *Nurs Res, 59*(2), 127-139.

Pullicino, P. M., & Hart, J. (2001). Cognitive impairment in congestive heart failure?: Embolism vs hypoperfusion. *Neurology, 57*(11), 1945-1946.

Pullicino, P. M., Wadley, V. G., McClure, L. A., Safford, M. M., Lazar, R. M., Klapholz, M., et al. (2008). Factors contributing to global cognitive impairment in heart failure: results from a population-based cohort. *J Card Fail, 14*(4), 290-295.

Putzke, J. D., Williams, M. A., Rayburn, B. K., Kirklin, J. K., & Boll, T. J. (1998). The relationship between cardiac function and neuropsychological status among heart transplant candidates. *J Card Fail, 4*(4), 295-303.

Randolph, C. (1998). *Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)*. San Antonio, TX: Psychological Corporation.

Randolph, C., Tierney, M. C., Mohr, E., & Chase, T. N. (1998). The repeatable battery for the assessment of neuropsychological status (RBANS): Preliminary clinical validity. *Journal of Clinical and Experimental Neuropsychology, 20*(3), 310-319.

Reitan, R. M. (1955). The relation of the Trail Making Test to organic brain damage. *Journal of Consulting Psychology, 19*, 393-394.

Rengo, F., & Acanfora, D. (1994). [Heart failure in the aged]. *G Ital Cardiol, 24*(11), 1423-1434.

Rengo, F., Acanfora, D., Trojano, L., Furgi, G., Picone, C., Iannuzzi, G. L., et al. (1996). Congestive heart failure in the elderly. *Arch Gerontol Geriatr, 23*(3), 201-223.

Rengo, F., Acanfora, D., Trojano, L., Scognamiglio, P., Ciaburri, F., Ceriello, A., et al. (1995). Congestive heart failure and cognitive impairment in the elderly. *Arch Gerontol Geriatr, 20*(1), 63-68.

Rengo, F., Ferrara, N., & Leosco, D. (1991). Ventricular function in the elderly. *Aging (Milano), 3*(1), 9-17.

Rey, A. (1941). L'examen psychologique dans les cas d'encephalopathie traumatique. . *Archives de Psychologie, 28*, 286-340.

Reynolds, C. R. (1997). Forward and backward memory span should not be combined for clinical analysis. *Arch Clin Neuropsychol, 12*(1), 29-40.

Rodeheffer, R. J., Gerstenblith, G., Becker, L. C., Fleg, J. L., Weisfeldt, M. L., & Lakatta, E. G. (1984). Exercise cardiac output is maintained with advancing age

in healthy human subjects: cardiac dilatation and increased stroke volume compensate for a diminished heart rate. *Circulation, 69*(2), 203-213.

Roine, R. O., Kajaste, S., & Kaste, M. (1993). Neuropsychological sequelae of cardiac arrest. *JAMA, 269*(2), 237-242.

Ropacki, S. A., Bert, A. A., Ropacki, M. T., Rogers, B. L., & Stern, R. A. (2007). The influence of cognitive reserve on neuropsychological functioning following coronary artery bypass grafting (CABG). *Arch Clin Neuropsychol, 22*(1), 73-85.

Ross, R. (1986). The pathogenesis of atherosclerosis--an update. *N Engl J Med, 314*(8), 488-500.

Royter, V., N, M. B., & Russell, D. (2005). Coronary artery bypass grafting (CABG) and cognitive decline: a review. *J Neurol Sci, 229-230*, 65-67.

Ruff, R. M., Light, R. H., Parker, S. B., & Levin, H. S. (1996). Benton Controlled Oral Word Association Test: reliability and updated norms. *Arch Clin Neuropsychol, 11*(4), 329-338.

Sauve, M. J., Lewis, W. R., Blankenbiller, M., Rickabaugh, B., & Pressler, S. J. (2009). Cognitive impairments in chronic heart failure: a case controlled study. *J Card Fail, 15*(1), 1-10.

Savageau, J. A., Stanton, B. A., Jenkins, C. D., & Frater, R. W. (1982). Neuropsychological dysfunction following elective cardiac operation. II. A six-month reassessment. *J Thorac Cardiovasc Surg, 84*(4), 595-600.

Savageau, J. A., Stanton, B. A., Jenkins, C. D., & Klein, M. D. (1982). Neuropsychological dysfunction following elective cardiac operation. I. Early assessment. *J Thorac Cardiovasc Surg, 84*(4), 585-594.

Schocken, D. D., Arrieta, M. I., Leaverton, P. E., & Ross, E. A. (1992). Prevalence and mortality rate of congestive heart failure in the United States. *J Am Coll Cardiol, 20*(2), 301-306.

Selnes, O. A., Goldsborough, M. A., Borowicz, L. M., & McKhann, G. M. (1999). Neurobehavioural sequelae of cardiopulmonary bypass. *Lancet, 353*(9164), 1601-1606.

Silbert, B. S., Scott, D. A., Evered, L. A., Lewis, M. S., & Maruff, P. T. (2007). Preexisting cognitive impairment in patients scheduled for elective coronary artery bypass graft surgery. *Anesth Analg, 104*(5), 1023-1028, tables of contents.

Silverberg, N. D., Wertheimer, J. C., & Fichtenberg, N. L. (2007). An effort index for the Repeatable Battery For The Assessment Of Neuropsychological Status (RBANS). *Clin Neuropsychol, 21*(5), 841-854.

Singh-Manoux, A., Britton, A., Kivimaki, M., Gueguen, A., Halcox, J., & Marmot, M. (2008). Socioeconomic status moderates the association between carotid intima-media thickness and cognition in midlife: evidence from the Whitehall II study. *Atherosclerosis, 197*(2), 541-548.

Singh-Manoux, A., Sabia, S., Kivimaki, M., Shipley, M. J., Ferrie, J. E., & Marmot, M. G. (2009). Cognition and incident coronary heart disease in late midlife: The Whitehall II study. *Intelligence, 37*(6), 529-534.

Smeulders, E. S., van Haastregt, J. C., Ambergen, T., Stoffers, H. E., Janssen-Boyne, J. J., Uszko-Lencer, N. H., et al. (2010). Heart failure patients with a lower educational level and better cognitive status benefit most from a self-management group programme. *Patient Educ Couns, 81*(2), 214-221.

Smith, A. (1973). *The Symbol Digit Modalities Test*. Los Angeles: Western Psychological Services.

Spitzer, R. L., Kroenke, K., Williams, J. B., & Lowe, B. (2006). A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med, 166*(10), 1092-1097.

Stanek, K. M., Gunstad, J., Spitznagel, M. B., Waechter, D., Hughes, J. W., Luyster, F., et al. (2011). Improvements in cognitive function following cardiac rehabilitation for older adults with cardiovascular disease. *Int J Neurosci, 121*(2), 86-93.

Stern, Y. (2002). What is cognitive reserve? Theory and research application of the reserve concept. *J Int Neuropsychol Soc, 8*(3), 448-460.

Stern, Y. (2009). Cognitive reserve. *Neuropsychologia, 47*(10), 2015-2028.

Strauss, E., Sherman, E., & Spreen, O. (2006). *A Compendium of Neuropsychological Tests* (Third ed.). New York, NY: Oxford.

Stroupe, K. T., Morrison, D. A., Hlatky, M. A., Barnett, P. G., Cao, L., Lyttle, C., et al. (2006). Cost-effectiveness of coronary artery bypass grafts versus percutaneous coronary intervention for revascularization of high-risk patients. *Circulation, 114*(12), 1251-1257.

Sun, X., Lindsay, J., Monsein, L. H., Hill, P. C., & Corso, P. J. (2012). Silent brain injury after cardiac surgery: a review: cognitive dysfunction and magnetic resonance imaging diffusion-weighted imaging findings. *J Am Coll Cardiol, 60*(9), 791-797.

Tabachnick, B. G., & Fidell, L. S. (2006). *Using Multivariate Statistics* (5th ed.).

Taylor, J., & Stott, D. J. (2002). Chronic heart failure and cognitive impairment: co-existence of conditions or true association? *Eur J Heart Fail, 4*(1), 7-9.

Thombs, B. D., de Jonge, P., Coyne, J. C., Whooley, M. A., Frasure-Smith, N., Mitchell, A. J., et al. (2008). Depression screening and patient outcomes in cardiovascular care: a systematic review. *JAMA, 300*(18), 2161-2171.

Tiemann, L., Penner, I. K., Haupts, M., Schlegel, U., & Calabrese, P. (2009). Cognitive decline in multiple sclerosis: impact of topographic lesion distribution on differential cognitive deficit patterns. *Mult Scler, 15*(10), 1164-1174.

Tiemann, L., Reidt, J. H., Esposito, L., Sander, D., Theiss, W., & Poppert, H. (2009). Neuropsychological sequelae of carotid angioplasty with stent placement: correlation with ischemic lesions in diffusion weighted imaging. *PLoS One, 4*(9), e7001.

Turner, R. G., & Gilliland, L. (1977). Comparison of self-report and performance measures of attention. *Percept Mot Skills, 45*(2), 409-410.

van den Brink, R. H., van Melle, J. P., Honig, A., Schene, A. H., Crijns, H. J., Lambert, F. P., et al. (2002). Treatment of depression after myocardial infarction and the effects on cardiac prognosis and quality of life: rationale and outline of the Myocardial INfarction and Depression-Intervention Trial (MIND-IT). *Am Heart J, 144*(2), 219-225.

van Dijk, D., Keizer, A. M., Diephuis, J. C., Durand, C., Vos, L. J., & Hijman, R. (2000). Neurocognitive dysfunction after coronary artery bypass surgery: a systematic review. *J Thorac Cardiovasc Surg, 120*(4), 632-639.

van Swieten, J. C., Geyskes, G. G., Derix, M. M., Peeck, B. M., Ramos, L. M., van Latum, J. C., et al. (1991). Hypertension in the elderly is associated with white matter lesions and cognitive decline. *Ann Neurol, 30*(6), 825-830.

Vemuri, P., Weigand, S. D., Przybelski, S. A., Knopman, D. S., Smith, G. E., Trojanowski, J. Q., et al. (2011). Cognitive reserve and Alzheimer's disease biomarkers are independent determinants of cognition. *Brain*.

Vogels, R. L., Oosterman, J. M., van Harten, B., Scheltens, P., van der Flier, W. M., Schroeder-Tanka, J. M., et al. (2007). Profile of cognitive impairment in chronic heart failure. *J Am Geriatr Soc, 55*(11), 1764-1770.

Vogels, R. L., Scheltens, P., Schroeder-Tanka, J. M., & Weinstein, H. C. (2007). Cognitive impairment in heart failure: a systematic review of the literature. *Eur J Heart Fail, 9*(5), 440-449.

Wechsler, D. (1987). *Wechsler Adult Intelligence Scale* (Revised ed.). New York: The Psychological Corporation.

Wechsler, D. (1997). *Wechsler Adult Intelligence Scale* (Third ed.). San Antonio, TX: The Psychological Corporation.

Wechsler, D. (2001). *Wechsler Test of Adult Reading*. San Antonio, TX: Pearson.

Wechsler, D. (2008). *Wechsler Adult Intelligence Scale* (Fourth ed.). San Antonio, TX: Pearson.

Wechsler, D. (2009). *Wechsler Memory Scale* (Fourth ed.). San Antonio, TX: Pearson.

What is Congestive Heart Failure? (2004). American Heart Association.

Wynands, J. E., Sheridan, C. A., Batra, M. S., Palmer, W. H., & Shanks, J. (1970). Coronary artery disease. *Anesthesiology, 33*(2), 260-281.

Xu, J., Kochanek, K. D., Murphy, S. L., & Tejada-Vera, B. (2010). *Deaths: Final Data for 2007*: U.S. Department of Health and Human Services.

Ylioja, S., Hanks, R., Baird, A., & Millis, S. (2010). Are cognitive outcome and recovery different in civilian penetrating versus non-penetrating brain injuries? *Clin Neuropsychol, 24*(7), 1097-1112.

Zuccala, G., Pedone, C., Cesari, M., Onder, G., Pahor, M., Marzetti, E., et al. (2003). The effects of cognitive impairment on mortality among hospitalized patients with heart failure. *Am J Med, 115*(2), 97-103.