Relationships Between Elements of Verbal Memory in Older People with Heart Failure

Patricia S. A. Sparacino

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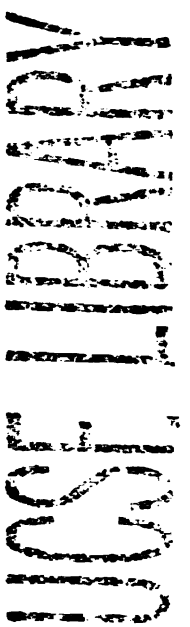

Dedication

To Bob Sparacino, my husband, who endured four years of lonely evenings and weekends but who provided inestimable moral support, love, and editorial expertise.

To Peter Sparacino, our son, who is my role model for passionate dedication to a goal.

And, to Hubert Bell Allen, my father, whose lifelong support of my education provided me with extraordinary professional opportunities, and whose 15-year struggle with heart failure infused my doctoral pursuit with equal parts of professional determination and personal sadness.

Acknowledgements

My doctoral education and the preparation of my dissertation would not have been realized without the assistance and support of many professional colleagues. I am especially grateful to

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- My Dissertation Committee, whose expertise in each of their fields provided guidance.
  - Mary Jane Sauvé, RN, DNSc – who is an expert in studying people with cognitive impairment and who so generously lent me her data base for analysis.
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RELATIONSHIPS BETWEEN ELEMENTS OF VERBAL MEMORY

IN OLDER PEOPLE WITH HEART FAILURE

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This study had two purposes: to examine the relationships among immediate memory, delayed recall, and recognition scores of older people with heart failure, using the Rey Auditory Verbal Learning Test and the Hopkins Verbal Learning Test and to determine if the relationships among verbal memory scores depended on the specific test used.

This study was a secondary analysis of data obtained from the heart failure and cardiology clinics of a Northern California, university medical center and from the heart clinic and adult general medicine clinics of an urban, teaching hospital in Indiana. A total of 99 participants were analyzed. Data elements that were obtained from each study site and analyzed included (a) demographic information; (b) New York Heart Association classification; (c) verbal memory scores (e.g., immediate memory, delayed recall, and recognition); and (d) scores of general intelligence.

There were no statistically significant, within-participant differences among the immediate memory, delayed recall, and recognition T-scores at either site or when both sites were combined. When contrasts were computed, the only significant difference was that the participants' delayed recall T-scores were better than their immediate memory T-scores. At both sites there was a statistically significant, strong correlation between immediate memory and delayed recall, and moderately strong and statistically significant

correlations between immediate memory and recognition, and between delayed recall and recognition. The very similar correlations at both sites suggest consistency of association between verbal memory elements, regardless of the test used. There were no statistically significant interactions between each of the three verbal memory T-scores and site. In this sample, therefore, it made no difference which verbal memory test was used. Age, gender, and ethnicity had little effect on any of the predictive relationships between verbal memory elements.

A more systematic evaluation is needed of the possible relationships between heart failure and associated cognitive function in general, and verbal memory impairment in particular, and between heart failure and cognitive function associated with aging.

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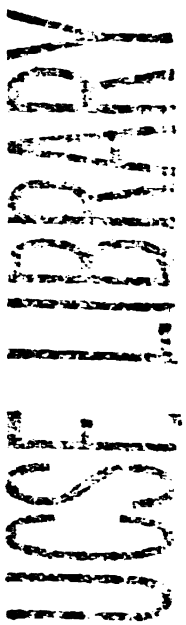
CHAPTER I

THE STUDY PROBLEM

Heart failure and cognitive impairment are well-recognized, common medical conditions in older people and, in fact, have been found to be significantly associated with each other (Acanfora et al., 1996; Antonelli Incalzi et al., 2003; Rengo et al., 1995; Trojano et al., 2003; Zuccalà, Onder, Pedone, Cocchi et al., 2001). As people live longer, they are more likely to develop heart failure (Bonow, Smaha, Smith, Mensah, & Lenfant, 2002) and other comorbidities (Blaum, Ofstedal, & Liang, 2002; Lopez, Jagust, DeKosky et al., 2003; Lopez, Jagust, Dulberg et al., 2003). Many theories have been advanced about the etiology of cognitive impairment in older people with heart failure, including impaired cerebral blood flow (Duschek, Weisz, & Schandry, 2003; Georgiadis et al., 2000; Malloy, 2001; Pullicino et al., 2001; J. Taylor & Stott, 2002; Woo, Macey, Fonarow, Hamilton, & Harper, 2003; Zuccalà, Onder, Pedone, Carosella et al., 2001), impaired cerebral oxygenation (Duschek et al., 2003; Madsen, Nielsen, & Christiansen, 2000; Roman, 2004), duration of heart failure (Almeida & Tamai, 2001b; Gorkin et al., 1993), or a dynamic related to coexisting medical conditions (Blaum et al., 2002; Zuccalà et al., 2005).

Several studies have reported that cognitive impairment is almost two times greater in people with heart failure, independent of other variables (Almeida & Tamai, 2001a; Cacciatore et al., 1998; Zuccalà et al., 1997). Heart failure and cognitive impairment may be independently associated, however (Taylor & Stott, 2002; Zuccalà et al., 2005). Bennett, Pressler, Hays, Firestine, and Huster (1997) found that attention and

memory deficits in people with heart failure were correlated with an increased risk of hospital readmissions within 6 months. Ekman, Fagerberg, and Skoog (2001) concluded that patients' Mini-Mental State Examination (MMSE) scores below the median were associated with the duration of heart failure and low hemoglobin, suggesting a causal relationship between heart failure and cognitive dysfunction. McLennan, Pearson, Cameron, and Stewart (2006) noted that an MMSE ≤ 26 was prognostically significant in patients with heart failure. The studies that have explored the association between heart failure and cognitive impairment in older people have been mostly large and cross-sectional (Antonelli Incalzi et al., 2003; Rengo et al., 1996; Zuccalà, Onder, Pedone, Carosella et al., 2001) or case-control studies (Acanfora et al., 1996; Almeida & Tamai, 2001b; Cacciatore et al., 1998; Ekman et al., 2001; Gorkin et al., 1993; Grubb, Simpson, & Fox, 2000; Trojano et al., 2003; Zuccalà, Onder, Pedone, Cocchi et al., 2001). Most of the studies attempted to prove an association between heart failure and cognitive impairment or to determine which elements of cognition are affected by heart failure.



Incidence, Prevalence, and Morbidity

Heart failure is prevalent, progressive, and costly. Of the 60 million Americans who have some form of cardiovascular disease, an estimated 5 million have heart failure. Moreover, each year there are approximately 550,000 new cases, and approximately 286,700 die with heart failure as an underlying or contributing cause (American Heart Association [AHA], 2006). The incidence of heart failure in men has remained the same over the past 3 decades, while the incidence in women has declined by 31%, and survival after the onset of heart failure has improved in both sexes (Levy et al., 2002). But, the population in the United States is living longer, and heart failure is primarily a disorder of

older adults. Although estimates of heart failure prevalence vary widely, its prevalence almost doubles with each decade of life after age 40 (Bonow et al., 2002; Eriksson, 1995; Premen, 1996; Pulignano et al., 2002; Schocken, 2000).

Heart failure is associated with considerable morbidity, and the prognosis for advanced heart failure is poor. One third of Medicare beneficiaries die within the first year of diagnosis (Braunstein et al., 2003; Croft et al., 1999). Heart failure is the most common hospital discharge diagnosis for those 65 years and older, and the number of hospital admissions has increased nearly 64% in the past 10 years (California HealthCare Foundation, 2002). Fifty-five percent of potentially preventable hospital admissions are due to heart failure exacerbations (Braunstein et al., 2003).

The Impact of Heart Failure on Cognition

Heart failure affects the brain in various ways, and cognitive functioning is affected by the pathophysiological association between heart failure and related neurological changes. The physiological mechanisms of heart failure, neuroanatomical foci, specific cognitive deficits, and reversibility of heart failure-related cognitive impairment, however, are not well-understood. The effect of heart failure on cognitive functioning is difficult to establish because of the coincidence of multiple medical comorbidities, associated polypharmacy, and neurological aging. Heart failure may have a global effect on the cerebral cortex, or there may be specific regions that appear more affected, such as the prefrontal cortex, frontal subcortical region, lateral temporal-parietal cortex, or medial temporal structures. Does hypoperfusion, a result of insufficient cardiac output, in the terminal reaches of the brain's blood supply cause structural changes in regions involved with memory, especially verbal memory?

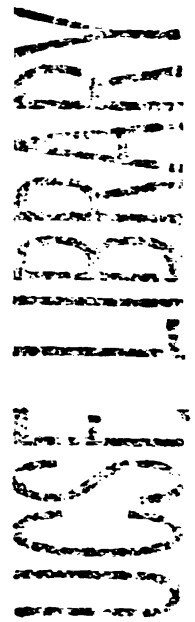
Variables significantly associated with cognitive impairment in older people with heart failure include age and female gender (Cacciatore et al., 1998; Zuccalà, Onder, Pedone, Carosella et al., 2001), educational level (Cacciatore et al., 1998), and greater comorbidity, such as hypertension (Blaum et al., 2002; Dahlstrom, 2005; in't Veld, Ruitenberg, Hofman, Stricker, & Breteler, 2001), atherosclerosis (Hofman et al., 1997), diabetes mellitus (Blaum et al., 2002; Dahlstrom, 2005; Ott, Stolk, van Harskamp, Grobbee, & Breteler, 1996), atrial fibrillation (Ott et al., 1997), and decreased blood pressure (Ruitenberg et al., 2001; Zuccalà, Onder, Pedone, Carosella et al., 2001). The specific or separate putative role of each risk factor that may be associated with memory impairment has not been confirmed.

Cognitive performance in people with heart failure has been found to be significantly worse than for older people of the same age without heart failure (Almeida & Tamai, 2001b; Staniforth, Kinnear, & Cowley, 2001). Antonelli Incalzi et al. (2003) suggested that forgetfulness increases as early as New York Heart Association (NYHA) Class[1] II, without significant decline as heart failure worsens, and that verbal memory is a significant problem, mostly evident in NYHA Classes III and IV. Some studies posit that primary (short-term) and secondary (learning) memory, particularly verbal memory and retention, are compromised in people who have heart failure but who do not have a diagnosis of dementia (Acanfora et al., 1996; Antonelli Incalzi et al., 2003; Callegari et al., 2002; Trojano et al., 2003). Almeida and Tamai (2001a) examined whether clinical

[1] Class I: Patient has no physical limitations and is asymptomatic.
Class II: Patient has mild symptoms while doing light exercise or activities of daily living (ADLs).
Class III: Patient has difficulty doing simple ADLs.
Class IV: Patient is frequently bed- or chair-ridden for most of the day and is too weak and short of breath to do simple activities.

treatment for heart failure could reverse attention deficits that are associated with severe heart failure. The study concluded that scores on tests of cognitive function improved significantly after clinical treatment, although there were many methodological inconsistencies in testing the older patients with heart failure and the comparison group.

Cognitive impairment is insidious, diminishing a person's ability to recognize symptoms, to judge when to act, and to comply with a complex health management regimen. Researchers who have studied the relationship between heart failure and cognitive function have used a variety of standard tests to detect disease-influenced fluctuations in cognition or cognitive impairment in older people with heart failure but without a diagnosis of dementia, but they have not identified which tests are sufficiently sensitive and specific.



Study Purpose

Systematic neuropsychological assessment of cognitive performance should be a part of the routine management of patients with heart failure. Recognition by a health care provider of a patient's significant cognitive fluctuations or lower cognitive functioning would indicate the need for intervention to improve the patient's clinical condition and should indicate the need to reassess how well the patient is able to manage his or her heart failure. If screening for heart failure-influenced cognitive fluctuations were practical, brief, and sensitive, health care providers could routinely assess the cognitive function of older persons with heart failure.

Clinicians use various neuropsychological tests to assess cognitive performance, impairment, and decline. Which measures of cognitive function are appropriate to detect cognitive changes, especially subtle, heart failure-influenced fluctuations? Specifically,

which test is most appropriate to measure the domain of verbal learning and retention in older people with heart failure? The Hopkins Verbal Learning Test (HVLT) and the Rey Auditory-Verbal Learning Test (RAVLT) are similar, auditorily administered tests that measure verbal learning and retention. The most appropriate test to measure the domain of verbal learning and retention in older people with heart failure is not known, however. The purpose of this study is:

1. To determine if the immediate memory, delayed recall, and recognition scores of older people with heart failure are below the age-specific normative values for two verbal memory tests.
2. To examine the relationships among immediate memory, delayed recall, and recognition scores within each of two verbal memory tests (RAVLT and HVLT), e.g., immediate memory and delayed recall, immediate memory and recognition, and delayed recall and recognition.
3. To examine if the relationships among the verbal memory scores depend on the specific test used.
4. To examine the relationship between an estimate of premobid intelligence and memory, controlling for level of education.

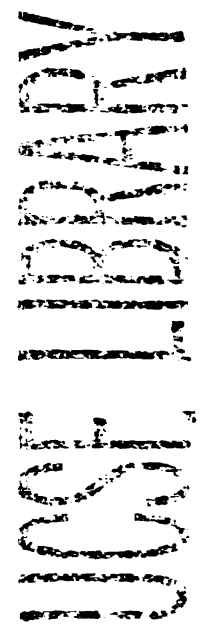
The study hypotheses are:

Hypothesis 1: Older people with heart failure have significantly greater immediate memory and delayed recall impairment than recognition impairment.

Hypothesis 2: The magnitude of the correlation between immediate memory and delayed recall is stronger than the correlation between immediate memory and recognition or delayed recall and recognition.

Hypothesis 3: The correlations among immediate memory, delayed recall, and recognition do not depend on the specific test used to measure these components of memory.

Hypothesis 4: The correlation between an estimate of premobid intelligence and verbal memory scores, controlling for level of education, is high.



CHAPTER II

HEART FAILURE AND COGNITIVE FUNCTION

Heart failure has many causes and manifestations, but the singular effect of heart failure on cognitive functioning is difficult to establish. Research has not determined if the impact of heart failure on the brain is global or specific. The challenge is to identify the most likely etiology of cognitive deficits in older patients with heart failure and the contribution of other factors (e.g., age, comorbid conditions, hypertension, and depressive symptoms) that may be associated with memory impairment.

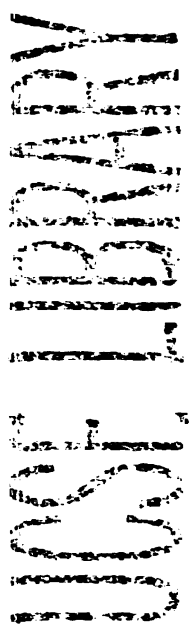
The literature review includes an overview of heart failure, the related physiology and pathophysiology, and the effects of aging and comorbid conditions on the heart; an overview of decreased cerebral blood flow, the related pathophysiology of impaired cerebral flow, and the effects of aging and comorbid conditions on the brain; an overview of cognitive function, the neural correlates of memory and attention, and the effects of aging and decreased cerebral blood flow on cognitive function; and the neurological changes associated with heart failure that affect cognitive functioning in older people.

Heart Failure

A variety of cardiovascular diseases cause or coexist with heart failure, and there are associated comorbid medical conditions and medications. Physiological changes associated with cardiovascular aging also increase the susceptibility to heart failure. Heart failure is difficult to diagnose in an older person, however, because of associated comorbidities, commingled major illnesses, or depression (Lien, Gillespie, Struthers, & McMurdo, 2002). Diffuse signs and symptoms are a challenge in making a correct

diagnosis and initiating appropriate therapy. Symptoms may not be reported because of symptom obscuration or misattribution to a comorbid condition or because of cognitive dysfunction that impairs symptom recollection or appreciation of significance. Some older people may be asymptomatic but nonetheless have clinical signs on physical examination or objective evidence such as chest x-ray findings or echocardiographic confirmation of cardiac dysfunction (Lien et al., 2002).

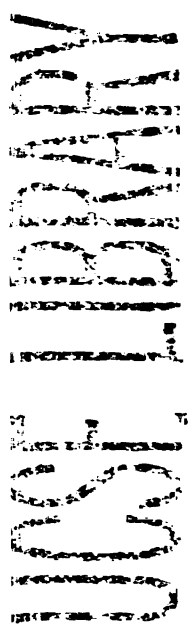
Heart failure is a syndrome rather than a disease. Heart failure occurs when there is insufficient cardiac output to meet metabolic demands at normal ventricular filling pressures. It is a chronic condition but usually associated with acute exacerbations. Heart failure has many causes, but it is most often due to atherosclerotic coronary artery disease, with or without the consequences of myocardial infarction. Other causes of heart failure include hypertension, valvular dysfunction, congenital defects, myocarditis, and cardiomyopathies. Other diseases and conditions that can lead to heart failure include, but are not limited to, congenital heart defects, severe pulmonary disease and hypoxia, diabetes, and infiltrative disease (Banasik, 2000; Chatterjee, 2002; Gaasch & Zile, 2004; Mandinov, Eberli, Seiler, & Hess, 2000). Physiological changes associated with cardiovascular aging also increase the susceptibility to heart failure.



More than half of older people diagnosed with heart failure have preserved left ventricular systolic function (ejection fraction > 45%) but have a history of hypertension and left ventricular hypertrophy. Although many of these people do not have the other typically associated contributing conditions, such as coronary, pulmonary, or valvular disease (Kitzman, 2002), confounding conditions such as hypertrophic cardiomyopathy,

infiltrative heart disease, primary valvular disease, and constrictive pericarditis must be excluded (Chatterjee, 2002).

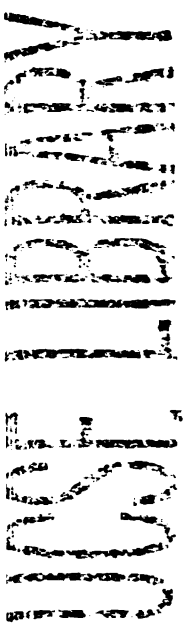
Systolic heart failure and heart failure with impaired systolic function are terms used interchangeably in the literature as are diastolic heart failure and heart failure with preserved systolic function. Left ventricular systolic dysfunction has been the more commonly recognized cause of heart failure, but heart failure can occur in the presence of either preserved or impaired ventricular systolic dysfunction (Chatterjee, 2002). Heart failure is caused by systolic dysfunction, manifested by decreased contractility which causes volume overload, and by diastolic dysfunction, manifested by increased stiffness, which causes delayed relaxation that restricts ventricular filling. Systolic and diastolic heart failure have similar signs, symptoms, and consequences, but the principal pathophysiological mechanisms are different. Several epidemiological studies have established that diastolic heart failure is more common than previously acknowledged (Kitzman, 2002; Senni & Redfield, 2001), although the accuracy of its prevalence is in question because diverse criteria have been used to diagnose it (Thomas, Fox, Coats, & Sutton, 2004).



Physiology of Circulation

Blood flow through the circulatory system is best described by the principles of resistance to flow and flow velocity. The relationship between blood flow and resistance is represented by Poiseuille's law: $Q = \frac{\Delta P}{\ell \eta} \cdot r^4 \cdot \frac{\pi}{8}$. In this equation Q is blood flow, ΔP is the pressure difference between two points, ℓ is the length of a vessel, η represents blood viscosity, r^4 is the radius of the vessel, and π and 8 are mathematical constants. Pressure is the primary determinant of flow, especially the pressure difference between

two points that creates the pressure gradient. The higher the pressure at P_1 and the lower the pressure at P_2, the greater the difference and gradient, and therefore, the better the flow. Blood flow will be slowest when there is a minimal pressure gradient between two points. Blood flow is affected by resistance $\frac{8\ell\eta}{\pi r^4}$. The two key determinants of resistance are vessel radius and length. Flow is proportional to, and resistance is inversely related to, the vessel radius (r^4); the larger the vessel radius, the less the resistance. Arterioles provide the greatest resistance to blood flow. Flow is inversely proportional to, and resistance directly related to, vessel length (ℓ) and blood viscosity (η). The shorter the vessel length, the greater the flow. Blood viscosity (η) rarely varies significantly, except in extreme situations such as dehydration or polycythemia. Ohm's law, Q = P/R, simplifies the understanding of blood flow principles. The pressure gradient has a direct effect and resistance has an indirect effect on blood flow. An increase in the pressure gradient, therefore, increases blood flow and an increase in resistance decreases blood flow.



Velocity and laminar and turbulent flow also affect blood flow. Blood flow velocity is determined by the cross-sectional area; an increase in cross-sectional area creates a decrease in flow velocity. Flow velocity is fastest in the arterial and venous systems and is slowest in the capillary system due to its very large total cross-sectional area. Laminar flow has a parabolic profile. There is a radially oriented velocity gradient of layers; maximal velocity is at the center of a vessel and is slower along the vessel wall. Blood flow, therefore, is fastest in a smooth-walled vessel. Turbulent blood flow is created by large vessel radius and velocity and by the regular branching of vessels in the circulatory system. Turbulent blood flow also occurs when there are pathological

endovascular changes, such as altered flow over an atheromatous, rough-walled intimal surface or because of abrupt variations in vessel size, as with a stenosis.

Pathophysiology of Heart Failure

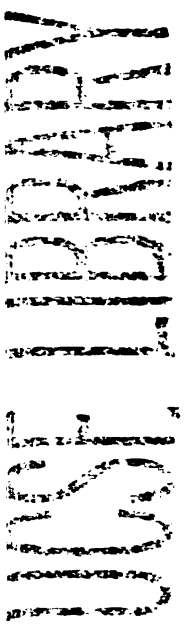
The pathophysiology of systolic and diastolic heart failure overlap substantially. Left ventricular volume, geometry, and function differ most in distinguishing between systolic and diastolic heart failure (Gaasch & Zile, 2004). The hemodynamic consequences of diastolic heart failure are similar to those of left ventricular systolic failure, except that left ventricular ejection fraction is preserved in primary diastolic heart failure. Heart failure-associated neurohumoral activation of the renin-angiotensin-aldosterone and sympathetic nervous systems contributes to the structural ventricular remodeling changes in ventricular volume, wall thickness, and chamber shape. Myocardial structural remodeling causes an increase in left ventricular volume and mass (Cohn, 1996) and reduced myocyte shortening and wall motion (Heart Failure Society of America, 1999). The result is a progressive increase in end-diastolic and end-systolic volumes (Chatterjee, 2002; Cohn, 2004). The general consequences of heart failure include decreased cardiac output, increased pulmonary venous pressure, postcapillary pulmonary hypertension, and secondary right heart failure (Chatterjee, 2002).

Systolic Heart Failure

Systolic blood pressure is the product of stroke volume and impedence to blood flow being ejected from the ventricle, but increased high-pressure aortic impedence hinders stroke volume, especially in a failing heart. Systolic heart failure begins with decreased myocardial contractility, manifested by a decreased ejection fraction. The

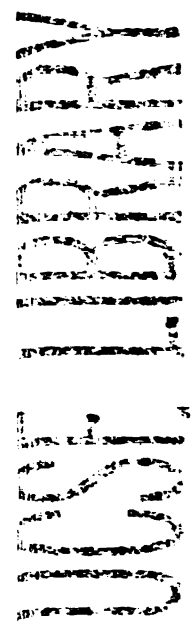
reduced ejection fraction is associated with an increase in end-systolic and end-diastolic volumes and pressures (Chatterjee, 2002).

Symptomatic left ventricular dysfunction increases plasma renin activity, angiotensin II and aldosterone levels, and tissue angiotensin activity. The increase in circulating and tissue angiotensin alters renal, peripheral, and central hemodynamics, including vascular remodeling and vasoconstriction that increase resistance to left ventricular ejection and decrease stroke volume and left ventricular ejection fraction (Chatterjee & De Marco, 1995; Cohn, 2004). Mengden, Douven, Vetter, and Dusing (1998) suggest that, in people with severe heart failure, there is a significant decrease in the capacity of resistance arteries to respond to vasodilator stimuli, resulting in increased peripheral resistance. The hemodynamic progression of systolic heart failure includes an increase in end-systolic and end-diastolic volumes, elevated left ventricular filling pressure, impaired myocardial contractility due to myofibrils that do not normally shorten against a load, reduced stroke volume, and consequent elevated left atrial and pulmonary venous pressures (Chatterjee, 2002; Cohn, 1996; Gaasch & Zile, 2004; Kitzman, 2002; Pullicino et al., 2001). As left ventricular systolic failure progresses, postcapillary pulmonary hypertension causes right heart failure, which in turn causes a diminished right ventricular stroke volume and a decrease in left ventricular preload. Thus, the decrease in left ventricular forward stroke volume and cardiac output can be due to a reduced left ventricular and/or a reduced right ventricular ejection fraction (Chatterjee, 2002).



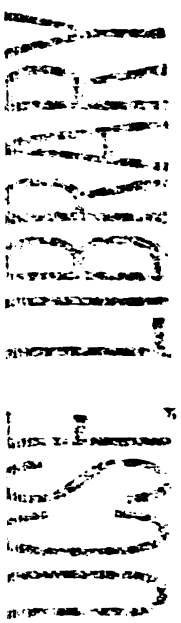
Diastolic Heart Failure

The causes of diastolic heart failure are similar to those of systolic heart failure; the most common causes are pressure-overload hypertrophy and ischemic heart disease. The dynamics of systolic heart failure and diastolic heart failure are different, however. Diastolic heart failure is elevated end-diastolic pressure in a chamber of normal size (Cohn, 1996) and a normal left ventricular ejection fraction (> 50%); 30% to 50% of people who present with signs and symptoms of heart failure have a normal left ventricular ejection fraction (Gaasch & Zile, 2004). Diastolic heart failure is a disorder of myocardial relaxation; there is decreased ventricular compliance and abnormal diastolic filling. Compliance is influenced by the process that pumps free calcium ions from cytoplasm into extracellular fluid. Compliance is hindered by fibrin and collagen deposits, associated with or resulting from ventricular wall hypertrophy (Banasik, 2000). Abnormal diastolic filling is due to a decrease in myocardial passive stretching to accommodate ventricular filling.



Without a consensus on the diagnostic criteria for heart failure with preserved systolic function, the heart failure syndrome might be better defined as a constellation of symptoms, elevated neurohormones, and impaired cardiac workload (Thomas et al., 2004). It may be that diastolic heart failure represents heterogeneous but interrelated problems (Banerjee, Clark, & Cleland, 2004). The basic elements of diastolic dysfunction include abnormal left ventricular diastolic distensibility, impaired filling, and slow or delayed relaxation (Gaasch & Zile, 2004). In the early stages of diastolic dysfunction, the diastolic pressure volume curve shifts upward, with normal end-diastolic volume but elevated end-diastolic, left atrial, and pulmonary capillary pressures. As left

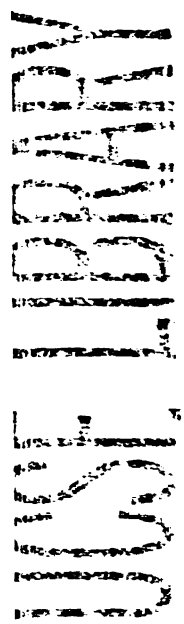
ventricular diastolic dysfunction progresses, chamber stiffness increases and diastolic compliance diminishes, and resistance to left ventricular filling increases with slowed or incomplete ventricular filling unless the atrial pressure rises. Myocardial relaxation is slowed or delayed because the myofibrils do not return to their resting length rapidly or completely. This progression of events results in a further shift to the left of diastolic pressure to volume ratio. Despite significantly increased left ventricular filling pressure, end-systolic volume (the ejection fraction) is usually normal. The neurohormonal effect probably has the most influence on whether the left ventricular ejection fraction is preserved or depressed. Increased levels of endothelin-1, norepinephrine, atrial natriuretic peptide, and brain natriuretic peptide are usually associated with a depressed ejection fraction, but increased levels have also been seen in patients with a normal ejection fraction (Chatterjee, 2002).



In diastolic heart dysfunction, myocardial stiffness inhibits an increase in end-diastolic volume, causing decreased stroke volume and the symptoms of low cardiac output (Banerjee et al., 2004; Chatterjee, 2002; Gaasch & Zile, 2004; Kitzman, 2002; Mandinov et al., 2000). As a result left atrial and pulmonary venous pressures increase (Chatterjee, 2002), and the pulmonary wedge pressure is critically elevated during exercise (Kitzman, 2002). As left ventricular diastolic failure progresses, the postcapillary pulmonary hypertension causes secondary right heart dysfunction. In turn, the right ventricular dysfunction results in a diminished right ventricular stroke volume, which contributes to a decrease in left ventricular preload, a decline in left ventricular filling, stroke volume, and finally low cardiac output (Chatterjee, 2002).

Effect of Aging on the Heart

Aging may be associated with maladaptive remodeling of myocardial interstitium, resulting in an increase in interstitial collagen content and viscoelastic burden and a change in passive myocardial elastic properties with decreased ventricular compliance (Burlew, 2004; Chatterjee, 2002; Mandinov et al., 2000). Aging is also associated with neuroendocrine changes that may contribute to myocardial structure changes, including increased myocardial cell size, increased collagen content, and decreased sarcoplasmic reticular calcium ATPase activity (Burlew, 2004; Chatterjee, 2002; Lakatta, 2000). The neuroendocrine changes include decreased β-adrenergic receptor density, decreased β-adrenergic inotropic response, and increased angiotensinogen and angiotensin-converting enzyme concentrations and angiotensin receptors (Chatterjee, 2002; Lakatta, 2000).



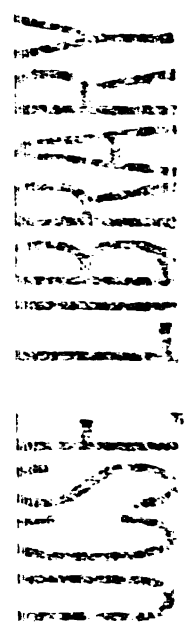
Effect of Comorbid Conditions on the Heart

Coexistent conditions, such as hypertension, diabetes and anemia, are associated with an independently increased risk of developing heart failure (Dahlstrom, 2005; Kalantar-Zadeh, Block, Horwich, & Fonarow, 2004; Meyer, Rauch, Rauch, Haque, & Crawford, 2000; Vasan et al., 2001; Yokota, Ogawa, Kurokawa, & Yamamoto, 2003; Zuccalà et al., 2005) and may be considered as predictors of heart failure. Vascular dementia and heart failure often coexist (McGann, 2000).

Hypertension is no longer considered a normal consequence of aging. It is one of the more significant risk factors for heart failure; 75% of patients with heart failure have antecedent hypertension (AHA, 2005). Systemic hypertension causes increased left ventricular filling pressures, and uncorrected and chronic left ventricular overload causes left ventricular hypertrophy, resulting in diastolic dysfunction. After a person has

developed heart failure, hypertension may not be as much a mortality risk as hypotension. Low blood pressure is the result of heart pump failure and may indicate a poor outcome in patients with heart failure; an elevated blood pressure may have a paradoxical effect on survival. Although a higher blood pressure may be associated with reduced mortality in a person with heart failure, hypertension may wreak its cardiovascular consequences nonetheless, if a person survives long enough (Kalantar-Zadeh et al., 2004).

The metabolic disturbances characteristic of diabetes cause endovascular morphological changes that alter coronary blood flow. About 20% to 30% of patients with heart failure also have diabetes. In fact, diabetes in women is the strongest risk factor for developing heart failure. The annual incidence rate of heart failure in women with diabetes, who also have an elevated body mass index or depressed creatinine clearance, is 7% and 13 % respectively. People with diabetes and with a fasting glucose greater than 300 mg/dL develop heart failure three times more frequently than diabetic people with fasting blood sugar levels within normal limits (AHA, 2005).



Anemia, which is present in about 20% to 30% of patients with heart failure, is a result of poor nutritional intake and subsequent reduced iron uptake; neurohormonal-activated increased plasma volume; impaired erythropoietin production in the kidneys due to reduced renal function and the depressive effect of angiotensin converting enzyme inhibitors on erythropoietin production in the kidneys and in bone marrow; and bone marrow depression due to high levels of cytokines. Anemia decreases red blood cell oxygen carrying capacity and creates a relative hypoxemic state, which causes myocardial functional impairment. Anemia is significant when there is increased left ventricular mass and increased left ventricular wall stress that creates an increase in

myocardial oxygen demand. Anemia might impair left ventricular function and subsequently further decrease cerebral perfusion. Treatment of anemia is associated with improved functional capability and may reduce morbidity (Dahlstrom, 2005).

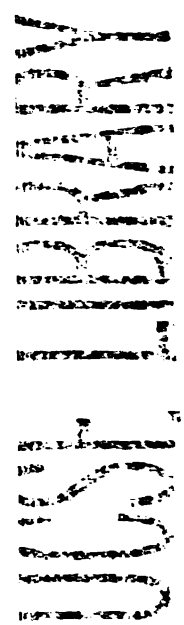
Decreased Cerebral Blood Flow and Neurological Changes

Heart failure affects the brain in various ways, including impaired cerebral blood flow, impaired cerebral oxygenation, impaired cerebrovascular reactivity, altered cerebral metabolism, and the development of white matter lesions and lacunes. The etiology of neurological changes associated with heart failure is not completely understood, however.

Cerebral Blood Flow

The internal carotid and vertebral arteries provide the brain's blood supply (Appendix A). The internal carotid arteries supply the brain's anterior circulation; they branch into the anterior (ACA) and middle cerebral (MCA) arteries and the posterior communicating arteries. The large surface branches of the ACA supply the cortex (gray matter) and white matter of the inferior frontal lobe, the medial surface of the frontal and parietal lobes, and the anterior corpus callosum. Smaller penetrating branches of the ACA supply the anterior portions of the basal ganglia, including the head of the caudate nucleus and putamen, the anterior limb of the internal capsule, and some limbic structures, including part of the cingulate gyrus. The MCA is the largest of the cerebral arteries, has the most extensive network of branching arteries, and nourishes broad territories. The large surface branches of the MCA supply most of the gray and white matter of the frontal, parietal, temporal, and occipital lobes. Smaller penetrating branches of the MCA supply deep white matter and the precuneus. The terminal reaches of the lenticulostriate arteries, which branch from the middle cerebral artery, perfuse the body

of the caudate nucleus, the putamen, and the posterior limb of the internal capsule (Appendix B). The anterior choroidal arteries, branches of the internal carotid arteries, supply the globus pallidus, part of the posterior limb of the internal capsule, and the anterior hippocampus. After passing through the dentate gyrus, the hippocampal arteries branch at right angles in a "rake-like pattern", which may explain the poor vascular supply to the CA1 sector of the hippocampus (Roman, 2004). The vertebral arteries supply the posterior circulation and join to create the basilar artery, which divides into the two posterior cerebral arteries (PCA). The large surface branches of the PCA supply the inferior temporal and medial occipital lobes, and the smaller branching arteries supply the thalamus, caudate tail, entorhinal cortex, and amygdala. The anterior and posterior inferior cerebellar arteries, terminal branches of the vertebral-basilar arterial system, provide the vascular supply to cerebellar gray matter. The anterior and posterior circulation is connected by the circle of Willis at the base of the brain. The regions, circuits, and associated functional activities or behaviors, are categorized by primary arterial supply.



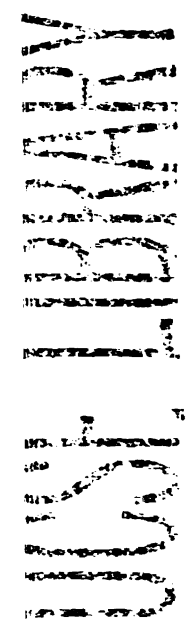
Anterior Cerebral Arteries

The deep branches of the ACA supply the head of the caudate nucleus, a part of the basal ganglia that receives input from the cerebral cortex, primarily from the anterior regions of the frontal lobe, and transmits input to the globus pallidus. The caudate nucleus controls multimodal information processing and inhibition. The smaller branches of the ACA also supply the putamen, anterior limb of the internal capsule, and part of the cingulate gyrus. The putamen acts with the caudate nucleus to influence motor activity. The internal capsule is white matter and is the major route that connects

the cerebral cortex with the brainstem and spinal cord. The cingulate gyrus allows cognitive flexibility, shifting of attention, adaptability, and cooperation.

Middle Cerebral Arteries

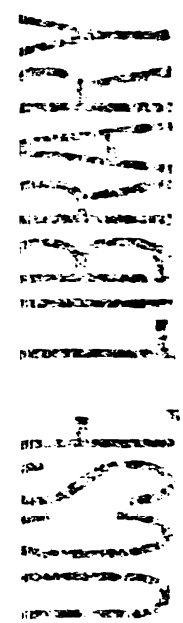
The deep branches of the MCA supply deep white matter and the precuneus. Deep white matter is the dense conduction matter that transmits neural messages within a hemisphere, between hemispheres, or between the cerebral cortex and lower centers of function. White matter, especially in the frontal lobes, is highly vulnerable to ischemia. The end result of compromised oxygen metabolism is DNA fragmentation, white matter degeneration, and incomplete necrosis (Roman, 2004). White matter lesions in the frontal lobes are associated with spatial and nonspatial deficits and with attentional impairments (Lezak, 1995a). The precuneus bilaterally, along with the posterior cingulate gyrus, is especially sensitive to heart failure-associated hypoperfusion (Alves et al., 2005; Suter et al., 2002); these areas are involved in episodic memory retrieval, especially memory and sensory integration (Grady, 2005).



Lenticulostriate arteries. The lenticulostriate arteries that branch from the MCA perfuse the body of the caudate nucleus, putamen, and the posterior limb of the internal capsule. The basal ganglia, which are actually a number of nuclear masses including the corpus striatum (caudate nucleus and putamen), translate cognition into action and are involved with procedural learning. Damage to the corpus striatum reduces cognitive flexibility (Lezak, 1995a).

Anterior choroidal arteries. The anterior choroidal arteries that also branch from the MCA supply the globus pallidus, part of the posterior limb of the internal capsule, and the anterior hippocampus. The globus pallidus is an intermediate relay system,

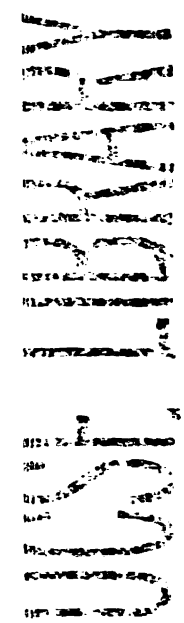
receiving input from the caudate nucleus and putamen and transmitting the input by way of the thalamus to areas of the brain that control complex motor function; the globus pallidus controls posture and movement for the most part. The hippocampus has direct connection to the entorhinal cortex, which projects to the cingulate and temporal lobe cortices, and to the amygdala. Medium-term memory is stored in the hippocampus, although it is not the only area of the brain involved in memory consolidation. The hippocampus is associated with consolidating information into long-term declarative memory, including reference learning and memory. Episodic memory consolidation requires pathway integrity between the hippocampal formation and cerebral cortex. The hippocampal complex in general, and the CA1 sector in particular, are highly susceptible to hypoxia (de la Torre, 2000; Roman, 2004). The CA1 network redistributes information before the activation of entorhinal cells initiates back projections to neocortical areas. Numerous areas are influenced by hippocampal output, especially from the CA1 sector.



Posterior Cerebral Arteries

The deep branches of the PCA supply the thalamus, caudate tail, entorhinal cortex, and amydala. Encoding and some retrieval of memory, and episodic memory, which influences performance on recognition tasks, is controlled by medial temporal structures. The thalamus is an integrative complex and is a major relay station and modulator of messages from and back to the cerebral cortex, especially visual tasks that require attentional engagement. Attention may depend on a triangular circuit in which the thalamus is thought to modulate prefrontal signals to the posterior sensory cortex (Madden, Whiting, & Huettel, 2005). The basal ganglia and thalamus may be involved in

the sensory-motor integration of executive functioning. Although the medial temporal lobes of older people show the most volume variability between tests, older people with impaired prospective memory are more likely to have difficulty with prospective cues, which is associated with the medial temporal lobe, than memory retrieval, which is associated with the frontal lobe (West, 2005). The thalamus is associated with several kinds of memory impairment: (a) defective encoding, (b) diminished capacity for exposures to new information, and (c) loss of newly acquired information (Lezak, 1995a). The caudate tail functions in motor control, especially body movement and coordination. The entorhinal cortex, the main source of input to and output from the hippocampal formation, is also sensitive to hypoxia (de la Torre, 2000). The amygdala is involved in the learning and storage of emotional aspects of experience.



Inferior Cerebellar Arteries

The inferior cerebellar arteries perfuse cerebellar gray matter and other parts of the cerebellum, pons, and medulla. The cerebellum is thought to be involved in procedural memory that is acquired through associative learning, especially verbal learning. Regional gray matter loss in the cerebellum has been associated with heart failure-related hypoperfusion (Woo et al., 2003).

Pathophysiology of Impaired Cerebral Blood Flow

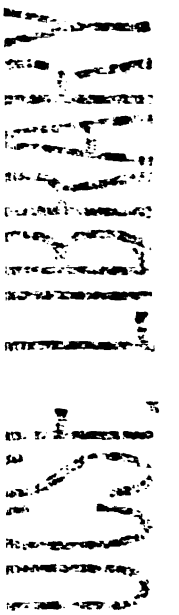
The brain is susceptible to hypoperfusion. The relationship between impaired cerebral blood flow and cognitive function is not completely clear, and what is known is extrapolated from clinical cause and effect relationships, such as carotid stenosis or occlusion and stroke; from experimental animal models of carotid occlusion; or from anatomical changes found in patients with vascular dementia. The risk of hypoperfusion

may be compounded in an older patient because of age-related or additive risk factor-modulated vascular changes, such as arteriosclerotic changes and atheromatous stenoses or occlusions.

Blood flow to the brain is usually preserved at the expense of peripheral perfusion. Cerebral circulation is autoregulated over a wide range of arterial pressures so that, in theory, a reduced ejection fraction should not affect cerebral blood flow (Duschek et al., 2003; Lee et al., 2001). In normal circumstances cerebral blood flow begins to drop when the mean arterial blood pressure is about 80% of baseline or until the arterial partial pressure of oxygen falls below 50 mmHg. Mental confusion is evident when cerebral blood flow is about 50% to 60% of normal (Brown, Wade, & Marshall, 1985; Gruhn et al., 2001). Cerebral hypoperfusion, due to left ventricular dysfunction, reduced cardiac output, and systolic arterial hypotension, is currently believed to the most likely etiology of the neurological changes associated with heart failure (Cacciatore et al., 1998; Duschek et al., 2003; Georgiadis et al., 2000; Gruhn et al., 2001; Pullicino et al., 2001; Zuccalà et al., 1997; Zuccalà, Onder, Pedone, Carosella et al., 2001). Cerebral hypoperfusion in heart failure is a consequence of combined but different mechanisms that are meant to be compensatory but are, in fact, counterregulatory. Sympathetic stimulation may significantly reduce cerebral blood flow, which cannot be compensated for by cerebral arteriolar autoregulated vasodilatation (Georgiadis et al., 2000; Gruhn et al., 2001).

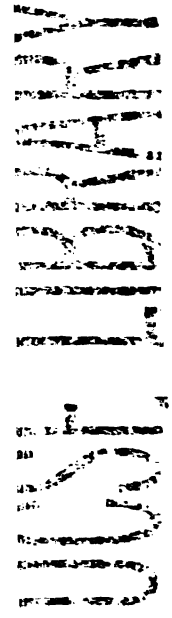
The regions and circuits perfused by the terminal reaches of the brain's blood supply, the watershed zone (Appendix C) , may be the most affected by heart failure-related hypoperfusion (Pullicino et al., 2001; Roman, 2004). A watershed area or zone is

a vascular territory that lies between two adjacent major cerebral artery territories and that is supplied by long, penetrating arteries without diffuse vascular overlap (Ball & Birge, 2002; Pullicino et al., 2001). Cerebral perfusion in these most distal regions of arterial supply, with few or no collaterals, is very dependent on perfusion pressure (Roman, 2004). The watershed zones, therefore, are the first to suffer from insufficient blood flow when cerebral hypoperfusion occurs (Ruitenberg et al., 2001; Suter et al., 2002) due to the increased resistance to blood flow in the small vessels and the additional increased resistance when there are endothelial or arteriosclerotic changes, as often occurs in an older person. The watershed zone of the anterior and middle cerebral arteries, affecting the parieto-occipital and right frontal regions, are also more affected by microinfarcts (Suter et al., 2002). Patients with heart failure have also been shown to have reduced regional cerebral blood flow bilaterally in the precuneus and cuneus, in the right lateral temporoparietal cortex, in the posterior cingulate gyrus, and the right posterior cingulate cortex (Alves et al., 2005).



The relationship between poor cardiac output and cerebral hypoperfusion creates a combined effect and risk for global ischemia. The human brain has more white matter than gray matter. There is similarity in the vulnerability of white and gray matter to hypoxemia (Stys, 1998). White matter may be more susceptible to anoxia and ischemia than gray matter due to higher amounts of fat and iron that contribute to free radical production and a lower amount of glutathione that acts as an antioxidant (Omata et al., 2003; Stys, 1998). Experimental chronic cerebral hypoperfusion of the rat brain has shown mild astrogliosis in the corpus callosum and internal capsule but significant astrocytic disintegration in the optic tract, perhaps due to glutamate damage to axonal and

myelin components (Farkas et al., 2004; Stys, 1998; Wakita et al., 2002). Chronic cerebral hypoperfusion in other animal studies has shown cognitive function changes correlated with gliosis of white matter in specific regions of the brain, such as the CA1 hippocampal sector and entorhinal cortex (de la Torre, 2000; Georgiadis et al., 2000). White matter damage has been shown to be associated with damage in the CA1 region of the hippocampus, which is in the gray matter (Sarti, Pantoni, Bartolini, & Inzitari, 2002). Woo et al. (2003) studied nine patients with advanced heart failure and found regional gray matter loss in the cerebellum and insular cortex areas that influence cognitive functioning, autonomic control, and cardiovascular regulation. Lee et al. (2001) found that occipital gray matter may be more susceptible to cerebral hypoperfusion and hypoxic injury than parietal white matter and that elevated occipital gray matter N-acetylaspartate levels may represent a terminal metabolic response to heart failure.

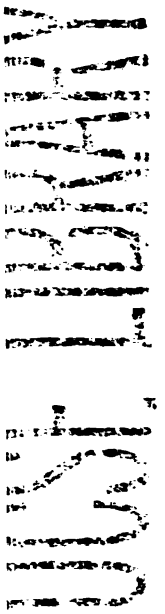


Changes associated with aging occur in the ultrastructure of the cerebral vasculature, including decreased elasticity and compliance, increased arterial tortuosity, and venous collagenosis. The effects of aging may limit the normal protective responses (Roman, 2004), or arterial stenosis, in combination with a low left ventricular ejection fraction, may cause cerebral hypoperfusion (Pullicino et al., 2001). Blood flow velocity in the middle, anterior, and posterior cerebral arteries may decrease as a person ages, resulting in significant decreases in resting blood flow in cortical and subcortical parenchyma (Gazzaley & D'Esposito, 2005).

Impaired Cerebral Oxygenation

Decreased cerebral perfusion, or ischemia, results in decreased cerebral oxygen saturation (Madsen et al., 2000) and inadequate glucose to support cellular metabolic

needs (Duschek et al., 2003; Roman, 2004). Madsen et al. (2000) studied cerebral oxygen saturation and cerebral symptoms (dizziness, drowsiness, tiredness, faintness, or light-headedness) in patients with acute heart failure; the cerebral oxygen saturation was 34% as compared to 75% in normal study participants. Although some patients in the study had a near-normal systemic mean arterial blood pressure, oxygen saturation, and carbon dioxide tension, the low cerebral oxygen saturation suggests that there is an impaired capacity for cerebrovascular dilation in a low cardiac output state. Usually when cerebral perfusion pressure falls, the blood vessels dilate to maintain normal blood flow. When there is low cardiac output resulting in a decline in cerebral blood flow, there is an initial increase in the degree of oxygen extraction fraction by cerebral cells to support cerebral oxygen metabolism. If a low perfusion pressure persists and compensatory mechanisms fail, however, impaired oxygen metabolism will lead to oxidative stress and DNA fragmentation (Roman, 2004). A decreased rate of cerebral metabolic rate of oxygen consumption has been revealed in cortical and subcortical regions in older people, and the decreased values exceeded changes in cerebral blood flow (Gazzaley & D'Esposito, 2005).

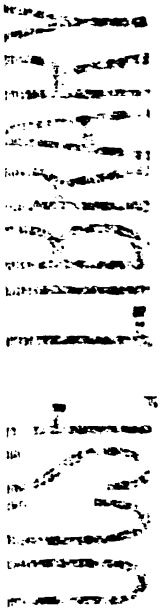


Impaired Cerebrovascular Reactivity

Protective cerebral autoregulatory mechanisms in patients with heart failure are not well-understood. In fact, peripheral afferent systems function differently in people with heart failure. The influence of both low- and high-pressure baroreceptors that modulate the sympathetic drive and vasopressin release is initially supportive. The forebrain lacks a blood-brain barrier, however, and peripherally released, blood-borne neuroactive peptides are able to reach and stimulate the forebrain, particularly the

paraventricular nucleus of the hypothalamus, and to alter volume regulation and augment sympathetic stimulation, influencing progressive deterioration of heart failure (Felder et al., 2003). The opioid receptors that are involved in cerebrovascular regulation are in the watershed periventricular regions and are highly vulnerable to hypoperfusion and hypoxemia. Damage to the periventricular regions may impair vasoreactivity in the middle cerebral artery distributions (Bonoczk, Panczel, & Nagy, 2004; Mengden et al., 1998).

Cerebrovascular reactivity decreases as left ventricular ejection fraction decreases, and cerebral arteriolar dilatory capacity is nearly exhausted in patients with severe heart failure (Georgiadis et al., 2000; Gruhn et al., 2001). Patients with severe heart failure show "a paradoxical baroreceptor-mediated peripheral vasodilation in the upright position, which may counteract flow distribution to the brain and direct flow away from the cerebral circulation" (Gruhn et al., 2001, p. 2532). The velocity of middle cerebral artery blood flow decreases with a diminished cardiac output (Gruhn et al., 2001; Saha et al., 1993). It may be that the "combination of reduced mean arterial pressure and increased neurohormonal activity cannot be compensated for by cerebral arteriolar autoregulated vasodilation and/or by systemic mechanisms available for blood flow distribution" (Gruhn et al., 2001, p. 2532). There may also be a decline in cerebral vascular reactivity to certain modulators, including carbon dioxide, in older people. The decrease in reactivity may be due to increased vessel stiffness and decreased compliance (Gazzaley & D'Esposito, 2005). Increased cerebrovascular resistance and more pronounced vasodilatory rather than vasoconstrictor capacity have been documented (Bonoczk et al., 2004).



Altered Cerebral Metabolism

Global and regional hypometabolism, measured by regional cerebral glucose metabolic rates, may be associated with cognitive dysfunction. Ischemia deprives cerebral tissue of glucose and prevents removal of metabolites. Abnormal cerebral metabolism differs regionally according to the severity of heart failure as a result of mean arterial blood pressure reduction, cerebrovascular reserve exhaustion, or systemic failure to redistribute cardiac output to the brain (Ackerman, 2001). Severe heart failure also results in abnormal neurochemistry. Activation of neurohormonal counterregulatory mechanisms causes endocrine dysfunction and results in high levels of sympathetic tone, diminished levels of parasympathetic tone, and disregulation of the renin-angiotensin system (Gruhn et al., 2001).

White matter lesions appear to be associated with a decrease in cortical metabolic rates. The relationship between cerebral metabolite levels and cognitive function in patients with heart failure is not well-understood, however. If white matter lesions impair neural transmission efficiency, then cortical connectivity and cerebral metabolism are also reduced (Reed et al., 2004). Lee et al. (2001) suggest that occipital gray matter is more susceptible to hypoxic injury than parietal white matter and that metabolite levels in occipital gray matter are prognostic of death from heart failure. When low perfusion pressure persists and compensatory mechanisms fail, however, impaired oxygen metabolism will lead to loss of N-acetylaspartate and neuronal loss (Lee et al., 2001), oxidative stress, and DNA fragmentation (Roman, 2004).

White Matter Lesions and Lacunes

White matter is extremely vulnerable to ischemia and may experience greater ischemic alterations than gray matter. In various animal models of cerebral hypoperfusion, focal necrosis and rarefaction of white matter and myelin fibers was preceded by extensive activation of glial cells, whereas gray matter manifested less prominent glial cell activation. White matter lucencies are thought to be associated with small vessel disease; severity is directly correlated with decreased cerebral blood flow and cerebral perfusion in white matter areas (Gazzaley & D'Esposito, 2005). White matter alterations have been found in the corpus callosum, cingulum, and internal capsule (Farkas et al., 2004; Sarti et al., 2002).

Cerebral white matter lesions are commonly seen in patients with dementia. The Rotterdam Scan Study (Breteler, 2000; Vermeer et al., 2003) investigated the association between vascular risk factors and white matter lesions to determine if different pathophysiological events cause different white matter lesions. Diastolic and systolic blood pressure levels were associated with both subcortical and periventricular white matter lesions, and carotid artery plaques and aortic calcifications were significantly associated with severe periventricular white matter lesions. Interestingly, periventricular lesions were associated with a higher risk of dementia and worse cognitive function.

Subcortical ischemia may contribute to age-related cognitive changes. The cognitive effects of white matter lesions caused by small vessel abnormalities or hypoperfusion are quite different than those seen in Alzheimer's disease. Cognitive function in patients with presumed small vessel disease is basically normal, though

slowed. There may also be mild memory impairment, loss of mental flexibility, and difficulty with complex situations (Lindeboom & Weinstein, 2004).

Effect of Aging on the Brain

Cognitive decline is not an inevitable consequence of aging, but it is a challenge to distinguish between normal cognitive changes associated with aging and changes associated with health, lifestyle, genes, and multiple demographic differences. Age-related cognitive changes develop as older people live longer (Anstey & Christensen, 2000; Jorm & Jolley, 1998; Meyer et al., 2000; Ostrosky-Solis, Jaime, & Ardila, 1998; Royall, Palmer, Chiodo, & Polk, 2005; Small, 2001; Verhaeghen & Salthouse, 1997), but it is not fully understood what is inevitable and what is due to disease. Researchers think that intelligence, education, and activity levels in youth might reduce the risk of age-related cognitive impairment (Fritsch et al., 2005; Plassman et al., 1995). Nonetheless they generally believe that hippocampal volume decreases with age, with a selective correlation between hippocampal size and memory functioning in older people who age either "normally" or "successfully" (Lye et al., 2004). Diffuse cortical changes may also affect the neuronal circuitry of the broad and interconnected memory network, as suggested by studies of memory in people with Alzheimer's disease (Lindeboom & Weinstein, 2004; Lopez, Jagust, DeKosky et al., 2003; Lopez, Jagust, Dulberg et al., 2003).

Most of the literature that discusses the effect of health and lifestyle on changes in cognitive functioning is specific to vascular and Alzheimer's dementias. Data on the various predictors of age-related cognitive impairment are more often from cross-sectional studies than from longitudinal studies. There are methodological problems with

and limitations of both types of studies. Methodological problems in cross-sectional studies include retrospective data collection and inclusion bias. Findings are limited by the sensitivity of cognitive tests to demographic differences, the extent to which estimates reflect actual change, and overestimation of cognitive decline because of the cohort effect (Anstey & Christensen, 2000; Ferro & Madureira, 2002; Raz, 2005; Small, 2001). Methodological problems in longitudinal studies include subjects who are their own controls, greater participant attrition due to mortality and mobility, and improved cognitive test performance over time, which underestimates cognitive decline because of learning effects or participant attrition (Raz, 2005; Small, 2001).

It is generally believed that hippocampal volume decreases with age and, therefore, plays a significant role in age-related memory decline. There is a selective correlation between hippocampal size and memory functioning in older people who age either "normally" or "successfully", although the relationship is not a simple linear one (Lye et al., 2004). Memory is complex, however, and research suggests that hippocampal dysfunction may be more specifically related to impaired delayed memory than immediate memory (Kramer et al., 2004).

White matter is more susceptible to the effects of aging than is gray matter, and the precentral gyrus region has the most significantly different age effect. One problem associated with discussing regional differences is the variability in cortical region demarcations. The entorhinal cortex may be the first cerebral structure to show pathological changes attributed to Alzheimer's disease, but the extent and significance of entorhinal cortex changes in normal aging is less clear (Raz, 2005). Besides a decrease in hippocampal volume in older adults, there is also a decrease in frontal volume. The

decrease in volume does not necessarily result in decreased attention and memory, an effect that may be mitigated by sufficient residual neural plasticity, little change in the number of neurons, or compensation by remodeled neural networks (Cabeza, Nyberg, & Park, 2005; Raz, 2005).

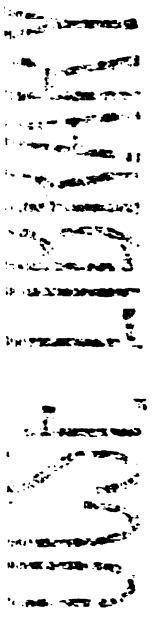
Changes in cognitive functioning in an older person are multifactorial, both biological and nonbiological. Many physiological processes change as a person ages, but the physiological changes may not result in neuronal loss (Small, 2001). Education is one of the more important nonbiological correlates. Age may not significantly influence the association between education and decline in cognitive function, but education may be protective throughout a person's life span (Anstey & Christensen, 2000). Better memory is associated with either higher levels of education (Ball & Birge, 2002) or higher estimated IQ (Lye et al., 2004).

Effect of Comorbid Conditions on the Brain

Various vascular risks may reduce or impair cerebral perfusion by causing capillary degeneration (de la Torre, 2000). Coexistent conditions, such as hypertension, hyperlipidemia, heart disease, diabetes, atherosclerosis, and atrial fibrillation, are most often reported as associated with cognitive decline and dementia (Anstey & Christensen, 2000; Meyer et al., 2000; Yokota et al., 2003). Age and vascular pathology are significantly associated (Breteler, 2000; Meyer et al., 2000), and heart failure and vascular dementia often coexist (McGann, 2000). Heterogeneous cerebrovascular disorders underlie vascular dementia. In the Rotterdam Study the investigators showed an association between vascular risks (a change in diastolic blood pressure over time, an elevated serum cholesterol, an apolipoprotein E genotype, diabetes treated with insulin,

or a history of smoking) or vascular disease (history of stroke or myocardial infarction) and impaired cognitive function (Hofman et al., 1997; Ott et al., 1997; Ott et al., 1996; Ruitenberg et al., 2001) and the presence and severity of cerebral white matter lesions in older people (Breteler, 2000).

Biological correlates of cognitive function in older people include the apolipoprotein E gene (ApoE) and hypertension. The ApoE gene expression is particularly selective in hippocampal neurons, and it appears to block the deposit of amyloid-beta protein in the repair of injured neurons in middle-aged mice but promotes amyloid-beta protein deposition and amyloid plaque formation in older mice (Ball & Birge, 2002; Small, 2001). Amyloid deposits also have vasoactive properties, as seen in cases of hemorrhagic congophilic angiopathy (Hachinski & Munoz, 2000). Studies that explored the relationship between cognitive ability and ApoE have reported that individuals with ApoE e2 had little or no cognitive decline in comparison to individuals with ApoE e4 (Anstey & Christensen, 2000; Small, 2001).



Hypertension affects about 55% of Americans (Raz, 2005) and is associated with, and may be the primary predictor of, selective cognitive impairment (Kuo et al., 2004; Meyer et al., 2000) or cognitive decline (Anstey & Christensen, 2000; Kuo et al., 2004) in otherwise healthy older persons. Prefrontal white matter is as vulnerable to the effects of hypertension as is the prefrontal cortex. An increased prevalence of white matter abnormalities and shrinkage of prefrontal gray and white matter are associated with treated hypertension, and the association suggests that chronic hypertension augments the effects of brain aging (Raz, 2005). Yet it appears that sustained low blood pressure, presumably associated with a reduction in cerebral blood flow, is also correlated with

cognitive impairment or dementia (Guo, Viitanen, & Winblad, 1997; Ruitenberg et al., 2001).

Cognitive Function

Human behavior is determined by a variety of functions, including cognition, emotion, and executive function. Cognitive function can be categorized as receptive functions, memory and learning, thinking, expressive functions, and mental activity variables, including consciousness, attention, and speed of activity (Lezak, Howieson, & Loring, 2004). Emotional function is the complex interactions of feelings and behaviors that are manifest in personality. Executive function is a multidimensional process that includes a variety of cognitive processes, such as planning, mental flexibility, and the ability to inhibit interfering influences that are necessary for effective and appropriate behavior (Gunning-Dixon & Raz, 2000; Lezak et al., 2004; Lindeboom & Weinstein, 2004; Spreen & Strauss, 1998). Although each function can be analyzed separately, the functions are more than interdependent; each function is so inextricably intertwined with the others that cognition is experienced as a single attribute (Lezak, 1995b).

Memory

Assessment of memory is more fractionated than absolute, as impairments may reflect problems in other cognitive domains, such as executive functioning or concentration. Memory impairment is primarily related to episodic memory, including problems with recall of recent (anterograde) and delayed (retrograde) information or events. Problems with semantic memory, knowledge of facts and concepts, are related to language function (Gunning-Dixon & Raz, 2000; Lindeboom & Weinstein, 2004).

Memory depends on a number of neurologic systems that determine storage and retrieval; new and initially labile memories are gradually transformed into more permanent memories. Declarative, or explicit, memory involves awareness and is the conscious recollection of information, objects, and events. Declarative memory is divided into semantic memory (factual knowledge) and episodic memory (knowledge of events). Nondeclarative, or implicit, memory is a collection of nonconscious abilities attributable to learned or acquired information that is expressed in skills or habits. Short-term memory is a limited capacity retrieval system. Short-term memory, which is an intermediate step to memory consolidation, is different from immediate memory, which is time-limited but permits a person to respond to immediate events. Primary memory, a component of short-term memory, is attention dependent and so is different than working memory, which is the ability to preserve short-term memory while paying attention to several tasks simultaneously (Lezak et al., 2004; Spreen & Strauss, 1998).

Attention

Attentional processes affect learning and memory. Attentional capacity needs to be receptive to incoming stimuli, to be able to respond to or disengage from the stimuli, and to shift between sustained or phasic stimuli. Attentional capacity varies according to person, timing, and conditions; capacity is reduced when a person is tired or depressed. Attention has a number of components, many of which are considered measures of working memory that include immediate attention, focused or selective attention, sustained attention, divided attention, and alternating attention. Immediate attention, a form of working memory, is resistant to various neurological disorders and to aging. Focused or selective attention, or concentration, attends to relevant input while

suppressing irrelevant stimuli or distractions. Sustained attention, or vigilance, is the ability to maintain an activity over a period of time. Divided attention is the ability to respond to a number of tasks at one time. Alternating attention is the ability to shift tasks or focus. Attentional deficits, which may be affected by slowed processing speed, will diminish cognitive productivity by affecting learning, although overall cognitive function may remain intact (Lezak et al., 2004; Spreen & Strauss, 1998).

Neural Correlates of Memory and Attention

The medial temporal lobes and neocortex appear to have specific but complementary roles in memory processes. The medial temporal lobes include the hippocampal region, including the CA fields and dentate gyrus, and the adjacent entorhinal, perirhinal, and parahippocampal areas. Rapid encoding and cohesion of recent memory is dependent on the hippocampus, especially the CA1 and CA3 fields, and the posterior cingulate region. The CA3 field, which has more associational connections than the CA1, may process integration of distributed memory by way of hippocampal output stored in different cortical areas. The entorhinal, perirhinal, and parahippocampal cortices may be a significant network of hierarchical associational connections that integrate information (Lavenex & Amaral, 2000). The hippocampus learns quickly, but it has a time-limited role in the processing and initial stabilization of declarative memory, perhaps so it can routinely clear redundant memories and relieve itself from the burden of long-term memory storage (Frankland & Bontempi, 2005). The hippocampus is not efficient at storing long-term memory, as shown by decreased hippocampal metabolic activity during retention testing (Alvarez & Squire, 1994; Bontempi, Laurent-Demir,

Destrade, & Jaffard, 1999; Eichenbaum, 2000; Frankland & Bontempi, 2005; Wiltgen, Brown, Talton, & Silva, 2004).

The medial temporal lobes, of which the hippocampus is a part, and the neocortical sites interact to consolidate memory. The cortex seems to learn more slowly than the hippocampus. As memory consolidation progresses, there appears to be a gradual functional disengagement of the hippocampus; this is seen as a decrease in hippocampal metabolic activity and a loss of correlation between hippocampal and neocortical metabolic activity (Bontempi et al., 1999). Consolidation is the process that stabilizes memory, but how molecular and cellular mechanisms influence cortical plasticity is not well-known, and it is cortical plasticity that determines memory consolidation (Wiltgen et al., 2004). Stable memory formation and long-term storage depend on gradual reorganization of the neuronal circuitry of the broad and interconnected network of neocortical sites, specifically the frontal, prefrontal, including the anterior cingulate and prelimbic cortices, and temporal cortical regions (Alvarez & Squire, 1994; Frankland & Bontempi, 2005; Wiltgen et al., 2004; Woo et al., 2003). Once the hippocampus is no longer involved, the prefrontal cortex may be involved in the temporary organization of information and in organizing remote memory retrieval. The anterior cingulate, prelimbic and infralimbic cortices of the prefrontal cortex may process remote memories by integrating and synthesizing information. The prefrontal cortex may be related to recollection (Yonelinas, Otten, Shaw, & Rugg, 2005) and may exert a top-down inhibition over the hippocampal function during recall of remote memories just as it inhibits posterior cortical regions during voluntary recall and sensory processing

(Bontempi et al., 1999; Frankland & Bontempi, 2005). Thus, the prefrontal cortex would be essential for the consolidation, storage, and retrieval of memory.

The multiple components of attention require integration of sensory, motor, and attentional signals. Various parts of the brain are involved during attention, depending on the specific attentional phase or function. Traditionally it has been thought that the reticular activating system arouses the cortex; the anterior cingulate cortex controls selective attention; the right hemisphere is dominant for spatial attention, or each hemisphere directs attention contralaterally; the parietal lobe disengages attention; the inferior parietal lobe, especially the left, controls auditory and visual lateralization; the posterior parietal cortex integrates sensory, motor, and attentional signals; and the prefrontal cortex mediates the ability to make and control attentional shifts, especially during working memory tasks that require dual task performance (Lezak et al., 2004).

The neural correlates of attention, specifically alerting, orienting, and reorienting, may be subcomponents of a larger attention network. Alerting, a state of general readiness after a warning signal, is primarily seen in extrastriate cortex; the source of possible top-down bias is still unknown. Orienting, the allocation of attention to a location when a cue is given, activates the anterior cingulate cortex, contradicting the belief that the parietal cortex is involved. Reorienting, which is the disengagement of attention and reorientation to a new location after a miscue, activates the parietal and frontal areas, specifically the left and right intraparietal sulcus, right temporal-parietal junction, and left and right middle frontal gyrus (Indovina & Macaluso, 2004; Thiel, Zilles, & Fink, 2004). Attentional control may involve connectivity between occipital and superior parietal regions, but the direction of the influence between cortical regions is

unknown. Indovina and Macaluso (2004) hypothesize that the temporal-parietal junction is a "circuit breaker" that interacts with the occipital cortex and mediates the shift of spatial attention.

Effecs of Aging on Cognitive Function

The risks of cognitive dysfunction and dementia increase with age; the incidence is estimated to be 8% in people older than 65 years (Erkinjuntti, Ostbye, Steenhuis, & Hachinski, 1997) and about 30% at age 85 (Lopez, Jagust, DeKosky et al., 2003; Skoog, Nilsson, Palmertz, Andreasson, & Svanborg, 1993). The incidence of cognitive impairment, however, in people older than 65 years without a diagnosis of dementia is 17%, twice the incidence of those diagnosed with dementia (Graham et al., 1997). Specifically, although mild cognitive impairment of the amnestic type may be more prevalent in people older than 80 years, mild cognitive deficits in several domains may be more commonly seen with comorbid chronic conditions, particularly diabetes, heart disease, and hypertension (Blaum et al., 2002; Lopez, Jagust, DeKosky et al., 2003; Lopez, Jagust, Dulberg et al., 2003).

Cognitive impairment is not a "normal" part of aging, but the trajectory of cognitive functioning in normal aging has not been defined (Petersen, Stevens et al., 2001). Different cognitive abilities change with aging. Even though the reasons for the rate and patterns of decline with aging are known to be multifactorial and are not well-understood, insights into the natural course of cognitive aging are gradually coming to light. Many older people have normal cognitive abilities. And certain conditions might protect them against aging-related cognitive decline, including higher intelligence, higher education, higher occupational status, regular exercise, genetics (absence of the

apolipoprotein E genotype), female gender, and good health (Fritsch et al., 2005; Lezak et al., 2004).

Education is one of the most important nonbiological correlates of cognitive performance. Assessment of intelligence examines crystallized and fluid abilities. Crystallized abilities include skills or semantic knowledge that are learned through schooling and experience, such as vocabulary, verbal fluency, and general knowledge. Fluid abilities include responses, such as reasoning or induction, to novel situations; fluid intelligence declines earlier and more rapidly than crystallized intelligence. Researchers believe that crystallized intelligence remains stable longer than fluid intelligence (Anstey & Christensen, 2000; Lezak et al., 2004). Response speed may have a confounding effect on tasks that require fluid intelligence, such as concentration, nonverbal learning and memory, retention of verbal material, and visuospatial processing speed. Verbal ability is usually well-retained, but word fluency may be reduced. Lower performance scores in older people may be more a reflection of impaired hearing or vision, diminished dexterity and coordination, and deficits in selective and sustained attention than they are evidence of cognitive decline (Lezak et al., 2004; van Boxtel et al., 2000).

There is little agreement about what constitutes normal cognitive aging. Neuropsychological test results, especially when a study has used a cross-sectional design, yield divergent and confounding effects related to many elements including aging, education, and medical status. The impact of normal aging on cognition may be due to slower information processing and primary working memory rather than the loss of cognitive capacity (de Jager, Milwain, & Budge, 2002; Lezak et al., 2004; Lindeboom & Weinstein, 2004; Verhaeghen & Salthouse, 1997). Cognitive aging and dementia are

intricately associated. Some older people develop mild cognitive impairment (subtle but measurable memory impairment) without impairment of daily activities (Petersen, Stevens et al., 2001), and others progress to dementia, the two most common types being Alzheimer's disease and vascular dementia. The predictive accuracy of the statistical relationship between increasing age and declining cognitive function depends on comprehensive longitudinal studies that compare the natural histories of older people who develop cognitive impairment to those who do not. Older persons who remain free of dementia decline very little in measures of cognition, usually at a rate of 1% to 2% a year, if at all (D. A. Bennett et al., 2002; Collie et al., 2001; de Jager et al., 2002; Petersen, Doody et al., 2001). One cannot say that older people without cognitive impairment are free from pathologic lesions, however, as the lesions may be undetected.

Mild Cognitive Impairment

Mild cognitive impairment is a heterogeneous syndrome and is distinguished by subclinical cognitive deficits. Mild amnestic cognitive impairment is characterized by delayed verbal or nonverbal recall. Mild cognitive impairment with multiple cognitive deficits is characterized by deterioration in at least one cognitive domain or abnormal test results in at least two domains, but without significant cognitive function impairment (Lopez, Jagust, DeKosky et al., 2003). People with mild cognitive impairment may have deficits in associated domains, such as verbal memory, object naming, verbal abstraction, and spatial localization (DeCarli, 2003).

Cognitive impairment, or at least poor cognitive performance, is difficult to delimit because reported studies use a composite of various types of cognitive definitions,

including age-associated memory impairment, deficits in various domains in the absence of dementia, and early or subclinical dementia (Blaum et al., 2002; DeCarli, 2003).

Mild cognitive impairment is usually limited to one domain, but the impairment does not affect activities of daily living, although it has a disorienting effect (Lezak et al., 2004; Lindeboom & Weinstein, 2004). Mild cognitive impairment, especially isolated memory impairment, may indicate preclinical Alzheimer's disease, although the inevitability of conversion has not been proved (Lindeboom & Weinstein, 2004). Older persons with mild cognitive impairment decline significantly faster than people without mild cognitive impairment, especially in tests of episodic memory, semantic memory, and perceptual speed (D. A. Bennett et al., 2002).

The reported rates of mild cognitive impairment are wide-ranging due to variability in reporting inclusion criteria, including people with mild memory impairments and with mild cognitive impairment who may be in a preclinical stage of dementia. There is also a concern about discordance in sensitivity and specificity between various diagnostic classification systems (de Jager et al., 2002; Erkinjuntti et al., 1997). The incidence of cognitive impairment in people older than 65 years without a diagnosis of dementia ranges between 8% and 17%, twice the incidence of those diagnosed with dementia (Erkinjuntti et al., 1997; Graham et al., 1997).

Dementia

Dementia is the result of an imbalance between neuronal injury, as the result of aging, environment, and genetic factors, and neuronal repair (Ball & Birge, 2002). Deterioration of episodic memory may be the initial loss in Alzheimer's disease, whereas early vascular dementia is characterized by a slowing in cognitive performance and mild

impairments in memory and executive functioning. Alzheimer's disease is progressive, but vascular dementia may not be; Alzheimer's disease and vascular dementia often coexist (Lindeboom & Weinstein, 2004). Severe memory impairment isolates a person from emotional and meaningful contexts and renders them dependent (Lezak et al., 2004).

The reported rates of conversion from mild cognitive impairment to dementia vary from 4% to 36% a year (D. A. Bennett et al., 2002; Petersen, Doody et al., 2001). In the longitudinal Religious Orders Study, 34% of those with mild cognitive impairment, compared with 7.2% without cognitive impairment, progressed over an average of 4.5 years to a diagnosis of Alzheimer's dementia (D. A. Bennett et al., 2002). In a meta-analysis of 12 studies, the average annual incidence rate of conversion to Alzheimer's disease was about 0.19% to 0.28% for ages 65 to 69 years, increasing to 0.78% to 1.17% for ages 75 to 79 years and 3.86% to 4.19% for ages 85 to 89 years. The average incidence rate for all dementias was about 0.33% to 0.46% for ages 65 to 69 years, increasing to 1.2% to 1.82% for ages 75 to 79 years and 5.33% for ages 85 to 89 years. The rate for all dementias nearly tripled in these age intervals: 65 to 69, 75 to 79, and 85 to 89 (Gao, Hendrie, Hall, & Hui, 1998; Kukull et al., 2002).

Effect of Decreased Cerebral Blood Flow on Cognitive Function

Cognitive functioning is affected by the pathophysiological association between heart failure, the brain's arterial distribution, especially the distal watershed territories, and related neurological changes. The neurocognitive consequences of heart failure in older people are due to a complex relationship of complementary influences with structural and functional manifestations. Whether there is global, hemispheric, or

regional impact, the brain functions and compensates by using its complex neural circuitry. It may be that heart failure-related hypoperfusion has a global effect on the cerebral cortex, or there may be specific regions that are more affected, such as the prefrontal cortex, frontal subcortical region, lateral temporal-parietal cortex, or medial temporal structures.

Organized behavior involves the whole brain. Cortical gray matter is interconnected over long distances by subcortical pathways. The cortex is involved in the mediation of complex behaviors by modulating complex feedback loops, linking parallel, integrative, divergent, nonlinear, recursive, and iterative processes (Lezak, 1995a). The prefrontal cortex is involved with executive control processes, but it is difficult to test regional specificity because the neuropsychological tests that assess prefrontal functioning share variance with tests of other cortical regions (Madden et al., 2005). The prefrontal cortex is active during working memory tasks, both visual and auditory (Grady, 2005). There are hemispheric differences in memory; encoding new information occurs primarily in the left prefrontal cortex and retrieval of previously learned information occurs in the right prefrontal cortex. Encoding, however, may depend on the type of information, with words lateralized to the left and faces to the right. Damage to the prefrontal cortex results in poor attention, increased distractibility, and decreased working memory. Impaired left frontal and left temporal cortex affects executive functioning. It is thought that aging affects the functional integrity of the prefrontal cortex more than other lobes, thereby affecting a number of cognitive domains (West, 2005). The insular cortex lies beneath the frontoparietal and temporal part of the paralimbic cortex; it connects the frontal lobe cortex to the parietal, occipital, and

temporal lobes. The insular cortex is involved with behaviors that require integration between extrapersonal stimuli and internal situations. The right lateral temporal-parietal cortex is involved in visual recognition, nonverbal visual memory, and visuospatial processing. The left lateral temporal-parietal cortex is involved with verbal material, such as language comprehension, word retrieval, and reading.

Conclusion

The association between heart failure and cognitive impairment is strongly supported by empirical data, but the physiological mechanisms, neurological focus, specific cognitive deficits, and reversibility of heart failure-related cognitive impairment are not well-understood. Is cognitive impairment in an older person with heart failure related to early dementia or to heart failure and associated comorbidities? If heart failure were corrected early and managed appropriately in an older person, perhaps cognitive dysfunction could be delayed or avoided.

Empirical data suggests that the cognitive impairments seen in people with heart failure are generally both memory and attention (S. J. Bennett & Sauvé, 2003). Several studies (Acanfora et al., 1996; Antonelli Incalzi et al., 2003; Callegari et al., 2002; Trojano et al., 2003) theorize that verbal memory and retention, in particular, are compromised in people who have heart failure but who do not have a diagnosis of dementia. The Rey Auditory-Verbal Learning Test (RAVLT) and the Hopkins Verbal Learning Test (HVLT) are well-recognized, frequently used, similar tests that measure verbal learning and retention. The characteristics of the RAVLT and HVLT, including their reliability, validity, and appropriateness, are discussed in Chapter 3.

CHAPTER III

NEUROPSYCHOLOGICAL TESTING

Neuropsychological tests are used to objectively assess the behavioral expression of brain dysfunction, to diagnose disease, to identify treatment needs and evaluate treatment efficacy, and to screen for cognitive impairment or dementia (Lezak et al., 2004). Clinicians use various neuropsychological tests to assess cognitive performance, impairment, and decline, but many tests were primarily developed to screen for and diagnose dementia, most commonly Alzheimer's disease. Many of the tests have been developed for ease of use and specific purposes, limiting their sensitivity to detect early cognitive changes and their generalizability to detect cognitive changes due to causes other than dementia (McDowell & Newell, 1996). And, neuropsychological tests do not have consistent diagnostic validity or predictive value if the people who are tested have cognitive performance problems that are due to a variety of neurological disorders or types of cognitive impairment (Neuropsychology Assessment Panel, 1996).

Assessment includes global cognitive functioning and the separate domains of cognition, which are not mutually exclusive but are relatively independent. Specific domains include memory, verbal function and language, visuospatial functions, executive functions, processing speed, crystallized and fluid intelligence, and motor dexterity and coordination (Lezak, 1995b). Memory testing should include three key procedures: (a) a delay trial to assess memory storage, (b) an interference strategy to interrupt continuous rehearsal, and (c) an assessment of learning, such as recognition testing, that bypasses simple recall (Lezak et al., 2004). Neuropsychological testing results are influenced by a

person's overall intelligence, but there have been many propositions for the age-related effects seen among multiple cognitive variables, including (a) control and allocation of attention or executive resources; (b) quantity of attentional resources; (c) coordination or functioning of specific cortical regions, such as the prefrontal cortex; and (d) the quantity of neurotransmitters or the intactness of myelin (Salthouse & Ferrer-Caja, 2003).

Researchers who have studied the relationship between heart failure and cognitive function have used a variety of the standard tests, but a comparison of published studies indicates that there is little agreement about which measures should be used. Researchers have not identified which tests are sufficiently sensitive and specific to detect disease-influenced fluctuations in cognition or cognitive impairment in older people with heart failure but without a diagnosis of dementia. This prompts a number of questions. Which measures of cognitive function have been used most commonly to screen older people with heart failure? Which measures of cognitive function are appropriate to test memory in older people with heart failure? Which measures of cognitive function have the greatest sensitivity and specificity to distinguish between mild cognitive impairment secondary to heart failure-influenced fluctuations and other types of cognitive changes? What is the measurement effect of the tests that have been used? Is there consensus about which measures should be used?

Testing Verbal Memory

Antonelli Incalzi et al. (2003) suggested that heart failure has a distinctive effect on primary and secondary memory in general and on verbal memory in particular. The Rey Auditory-Verbal Learning Test (RAVLT) and the Hopkins Verbal Learning Test (HVLT) are similar, auditorily administered tests that measure verbal learning and

retention. The following discussion will be limited to the HVLT and the RAVLT and to a comparison of their usefulness and appropriateness in detecting memory impairment in older people. There are no published reports that specifically compare the HVLT and the RAVLT and few reports that examine the sensitivity or specificity of memory tests in older people with heart failure. The comparison will address reliability, validity, and appropriateness for this population, realizing that the HVLT and RAVLT are not diagnostic and merely contribute information to understanding a complex phenomenon.

Rey Auditory Verbal Learning Test

In 1958 André Rey developed the RAVLT, based on a one-list word trial developed by Edouard Claparède in 1916. The original version was in French; it was translated into English without change. It has been modified several times, adding trials to test for interference effects, delayed recall, and delayed recognition. The test is also available in German, Hebrew, Spanish, Chinese, Portuguese, and Flemish (Lezak et al., 2004). The World Health Organization and the University of California, Los Angeles developed the WHO/UCLA version, which is designed to include the same list lengths and format for administration but which includes nouns that are universally familiar (e.g., body parts, animals, tools, household objects, and vehicles), rendering the test more free from cultural influences (Lezak et al., 2004; Mitrushina, Boone, Razani, & D'Elia, 2005). Correlations were in the .47 to .55 range when participants were given the WHO/UCLA list with the original word list (Lezak et al., 2004).

The RAVLT assesses several measures of learning and memory, including immediate and delayed recall, learning rate, proactive and retroactive interference effects, and recognition (Savage & Gouvier, 1992; Spreen & Strauss, 1998). There are a number

of variations of the test, but the most commonly used consists of two lists of 15 nouns each and a matrix of 50 words that includes the 30 nouns from the two lists plus 20 words that are phonemically or semantically similar to the 30 nouns. The first list of 15 nouns is read aloud to a participant who is then asked to repeat as many words as possible; this is repeated four consecutive times. After the fifth trial, the participant is read a second list of 15 nouns and is asked to repeat as many words as possible. Then the participant is asked to recall as many words as possible from the first list. After a 20- to 30-minute delay, the participant is asked to again recall as many words as possible from the first list. Finally, the patient is given the matrix list of 50 words and asked to identify words from the first list. It takes approximately 30 to 40 minutes to administer the test. Scores include, but are not limited to, the number of words correctly recalled for each of the first five immediate recall trials, with verbal learning during the five trials represented as a learning curve; the sum of words correctly recalled for the first five trials, the postdistractor trial, the delayed recall trial, and the target word recognition trial; and the number of repetitions and intrusions.

The RAVLT measures rote verbal memory and memory processes. The type and severity of a person's memory impairment is assessed by comparing verbal learning and retention, including immediate (Trial 1 score) and delayed postinterference recall (Trial 8 score), and target word recognition presented with distractors (Trial 9 score) (Lezak et al., 2004; Spreen & Strauss, 1998). Other scores that can be derived include best learning (Trial 5 score), proactive interference (Trial 6 score), retroactive interferences (Trial 7 score), temporal order (Trial 10 score), learning rate (Trial 5 minus Trial 1 score), and total learning (sum of Trials 1 through 5). The testing process and change in participant

performance over the multiple trials helps to identify the impaired memory mechanisms. The recognition score, for example, may reflect memory storage better than recall, because recognition does not use memory retrieval, which may be represented by scores of best learning, delayed recall, retroactive interference, and total learning. The temporal order score may reflect memory retrieval that relies on internal organization of information (Vakil & Blachstein, 1993).

There are large differences in reported normative data due to variation in test construct or administration, cultural differences, and, particularly in older studies, small sample size and aged data (Mitrushina et al., 2005). A number of studies have been published about recommended normative data (Bleecker, Bolla-Wilson, Agnew, & Meyers, 1988; Ferman et al., 2005; Harris, Ivnik, & Smith, 2002; Ivnik et al., 1992; Ivnik et al., 1990; Savage & Gouvier, 1992; Schmidt, 1996; Sinnett & Holen, 1999; G. E. Smith et al., 1992; G. E. Smith, Ivnik, Malec, & Tangalos, 1993; van der Elst, van Boxtel, van Breukelen, & Jolles, 2005).

The following discussion of normative data is limited to several recent studies. A study of 134 undergraduate students and healthy older people (Savage & Gouvier, 1992) found that gender had no influence on verbal acquisition or retention and that age influenced all but three trials, especially acquisition when the memory load exceeded five to six words. Sinnett and Holen (1999) studied 100 older people, aged 60 to 80, to compare several the memory measures of a variety of neuropsychological tests. Memory test performance was stable for people aged 60 to 74 years; performance dropped in the 75 to 79 year and over-80 year categories with a word loss increase from 2 to 3 in the interval from Trial V to Trial VI. Trial V of the RAVLT was very sensitive to age and to

the interaction of age and socioeconomic status ($p < .05$) and sensitive to gender ($p < .01$). Trial VI was sensitive to age and gender ($p < .05$). van der Elst et al. (2005) studied 1,855 healthy people aged 24 to 81 years. Performance results decreased for participants who were older, male, or less educated. The study also presented the word trials in written and spoken formats and compared memory performance; this is an important consideration when testing people with either vision or hearing loss. Trial 2 and 3, Delta (Trial 3 minus Trial 1 score), and repetition scores were higher when the words were visually presented, and the Trial 1 scores were higher with auditory presentation. Visual presentation is associated with better performance on tasks that rely on long-term memory processes or on mixed short- and long-term memory processes. Auditory presentation is associated with better performance on tasks that rely on short-term or working memory processes. van der Elst and colleagues posit that younger participants performed better on Trial 1 due to age-related differences in processing speed; therefore, the Total recall 1 through 5 summary score may not be an accurate estimation of learning. The investigators suggest that the Delta score may be a more appropriate measure of learning because the score difference corrects for age-related differences in processing speeds in Trial 1 and takes ceiling effects into account.

Ivnik et al. (1992) used the results from the Mayo's Older Americans Normative Studies (MOANS) test of 530 healthy, mostly well-educated, adults to convert standard RAVLT scores to age-corrected scores. Harris et al. (2002) expanded on the work of Ivnik and colleagues by combining data from 311 new participants with 530 original participants over age 55. The study focused on Recognition Trial accuracy and created norms for age- and gender-specific Recognition Percent Correct (RPC) rather than

reliance only on true-positive or false-positive variance. Age accounted for 10.2% of total RPC alone ($p < .0001$), and gender added another 7.4%, with older women performing better than older men. The MOANS RPC norms, therefore, are different for men and women. The participants were predominantly Caucasian, which is a study limitation. Ferman et al. (2005) expanded age- and education-adjusted normative data for older African Americans based on a sample of 306 healthy older participants in the Mayo's Older African American Normative Studies (MOAANS).

Schmidt (1996) provides normative data that incorporates the results of several large studies; it is a standard reference. Mitrushina et al. (2005) conducted meta-analyses of RAVLT data and concluded that age did not account for a significant amount of variability, although there is a known effect of age on list-learning scores and recommended that the mean standard deviation (SD) for the sample be used for all age groups; that education did not contribute significantly to scores, but that higher levels of education are associated with better test performance; and that the effect of gender varied according to the type of trial.

Reliability

Internal consistency. Several investigators have developed alternate forms (Crawford, Stewart, & Moore, 1989; Geffen, Butterworth, & Geffen, 1994; Lezak et al., 2004; Ryan, Geisser, Randall, & Georgemiller, 1986). Ryan et al. (1986) conducted one of the earlier tests of alternate form reliability and equivalency. They tested the original word list (List A) and an alternate form (List C) developed by Taylor (1959) and Lezak (1983) with a heterogeneous group of 85 adults. The test-retest interval was 70 to 305 minutes (mean = 140 minutes). The participants found List C more difficult when

administered after List A, but the tests were comparable when List A was given before List C; the difference lacked statistical significance, however. Of the total words recalled on Trials 1 through 6 on both forms, there was a difference of only three words. The alternate form reliability coefficients ranged from .60 to .77 and were highly significant ($p < .001$). Ryan and Geisser (1986) tested Lists A and C again with 73 inpatients and confirmed the psychometric comparability of the two word lists. Delaney, Prevey, Cramer, Mattson, and the VA Epilepsy Cooperative Study #264 Research Group (1992) also compared Lists A and C in 42 healthy adults; the retest interval was approximately one month. Lists A and C correlated highly with each other (r = .61 to .86 for the learning trials; .51 to .72 for the recall trials).

D. M. Shapiro and Harrison (1990) developed two alternate 15-word lists (List EF and List GH) to the original RAVLT (Form AB) and an alternate form (Form CD) provided by Lezak (1983). When the four alternate forms were given to a group of 42 participants, including undergraduate students and rehabilitation patients, seven of whom had a diagnosis of dementia, they yielded comparable and high alternate form reliability coefficients for each trial (.67 to .90, $p \leq .0001$). The interval for the test-retest was 2 to 13 days (mean = 5 days; $SD = 3.6$) but reliability was not reported. A practice effect was seen in the students but not in the rehabilitation patients.

Geffen et al. (1994) tested a new form (Form 4) that was equivalent to the word frequency, number of syllables, and semantic association to the original form (Form 1) on 51 normal adults, with a retest interval of 6 to 14 days. There was the expected learning across Trials 1 to 5, but there was no practice effect between the two forms. Alternate form reliability coefficients for 5 of the 13 variables ranged from .67 to .78 ($p < .01$).

There was little difference between test-retest reliability coefficients and the alternate form reliability. The reliability coefficients of participants who were given Form 1 before Form 4 were higher (9 of 13 variables ranged from .49 to .84, $p < .01$) than participants who were given Form 4 before Form 1 (6 of 13 variables ranged from .55 to .85, $p < .01$), and, although the differences between coefficients lacked statistical significance, the investigators recommended that Form 1 should be used first when retesting is anticipated. Geffen and colleagues concluded that the most reliable measures were the total number of words learned during the five learning trials ($r = .77$) and on postdistractor retention trial performance ($r = .70$).

Two alternate forms (word lists AB and BC) of the RAVLT, as listed by (Lezak, 1983), have an insignificant main effect ($p > .05$) but can be considered comparable versions because of their moderately high comparability ($p < .05$) except for the Intrusion scores. The learning curves for Trials 1 to 5 are significantly different, however ($p < .05$) (Uchiyama et al., 1995).

Test-retest reliability. There are a number of reports about the test-retest reliability of the RAVLT. Incremental improvement in learning on most variables occurs with repeated use of the same RAVLT form (Crawford et al., 1989; Uchiyama et al., 1995). Practice effects are reduced when alternate forms are used (Crawford et al., 1989; Delaney et al., 1992; Geffen et al., 1994; Ryan et al., 1986).

Crawford et al. (1989) used the RAVLT and an alternate form developed for the test-retest study of 60 healthy adults who were divided into paired groups. The mean scores for the two test forms were similar; performance improved across Trials 1 to 5 as expected. There was a significant practice effect on test performance when a participant

was retested at 27 (±3) days with the same test ($p < .0001$), but there was no significant performance improvement when a participant was retested with the alternate test form ($p = .75$). Correlation coefficients of test-retest reliability were not reported, and a less powerful between-groups analysis was conducted rather than a within-groups comparison (Geffen et al., 1994).

Uchiyama et al. (1995) reported that significant practice effects were found in a 1-year longitudinal follow-up of 2,059 young men ($p < .05$), with performance improvement similar for both forms that were tested. (In this study, Form 1 was word list AB and Form 2 was word list BC.) There was also significant equivalent form reliability ($p < .01$ to $p < .05$) for all trial scores of word lists A and C provided by Lezak (1983), except for the Intrusion scores that were lower for Form 1 than for Form 2. There were no significant differences between the two forms at 1-year retesting, supporting the psychometric equivalence of the two forms.

Validity

Construct validity. The RAVLT correlates moderately well with some other measures of verbal memory, but the CVLT has been used more frequently for comparison (Crossen & Wiens, 1994; Spreen & Strauss, 1998). The tests are not interchangeable, however, because RAVLT words do not show as clear a semantic relationship as they do on the CVLT (Spreen & Strauss, 1998), and the two tests differ in word list construction and procedure, that is, the addition of a cued recall (Vakil & Blachstein, 1993).

Macartney-Filgate and Vriezen (1988) administered the RAVLT, the Wechsler Memory Scale, and the Buschke Selective Reminding Test to 25 patients with known or

suspected cerebral dysfunction. There are significant differences between each of these tests, although each test is sensitive to long-term verbal memory. There were modest intercorrelations (r = .48 to .67, $p \leq .05$) between the RAVLT Trials 1 through 5 and all of the Wechsler Memory Scale elements, except for the delayed recall of easy associate learning (r = .35, $p > .05$). The RAVLT Trial 6 was not related to any Wechsler Memory Scale elements, and the RAVLT Trial 7 was significantly related only to the Wechsler Memory Scale elements that involved hard associate learning (r = .57 to .60, $p \leq .05$). There is sufficient variability in test format and task requirements between the three tests that each may be testing different functions of verbal memory.

Vakil and Blachstein (1993) tested 146 healthy volunteers with the RAVLT and conducted one-, two- and three-factor analysis. A single factor of memory was produced when very restrictive criteria were used for factor extraction. This suggests that, although memory may have different components, the components must relate to each other. This translates clinically to the assumption that cognitive capabilities are closely related in normal people. The distinction between memory acquisition and memory retention appeared evident in the analysis that included the learning rate score and in which two factors emerged. Clinically this difference helps in the dissociation of amnesia types. The row score analysis yielded three factors that support the three stages of the information processing of memory: acquisition, storage, and retrieval. The difference between the two- and three-factor analyses was the partitioning of memory retention into storage and retrieval; memory storage can exist with impaired retrieval.

Predictive validity. When Ryan and Geisser (1986) tested for psychometric comparability of Form A and Form C, they also examined the accuracy of the two forms

in discriminating between participants known to be cognitively intact and those known to be impaired. The two forms were identical in their highly significant hit-rate of 75.3% ($p < .001$). The RAVLT total score contributed more to the discriminant score (.95) than the contribution of age (-.12). This means that verbal memory impairment can be identified using the total score of either Form A or Form C of the RAVLT, and that either form's predictability is independent of the relationship of the verbal memory score to age.

The RAVLT is sensitive to verbal memory impairment in people with various neurological diagnoses (Lezak et al., 2004; Mitrushina et al., 2005), particularly in people with Alzheimer's disease (Mitrushina et al., 2005). Estevez-Gonzalez, Kulisevsky, Boltes, Otermin, and Garcia-Sanchez (2003) used the RAVLT to evaluate and follow 116 patients, aged 45 years or older, with subjective memory complaints, specifically to differentiate between normal aging, mild cognitive impairment, and the preclinical phase of Alzheimer's disease and to predict which patient would progress to Alzheimer's disease. Several RAVLT indices appeared to contribute to the detection of the preclinical phase of Alzheimer's disease, but recall of 0 words in Trial 6 or forgetting more than 75% of the words between Trials 5 and 6 was found to be highly sensitive ($p < .0001$) in differentiating patients who had no evidence of cognitive impairment or who had mild cognitive impairment from those with Alzheimer's dementia.

A series of studies validated the ability of the RAVLT in general, and the short delayed recall in particular, to predict conversion to and detect Alzheimer's disease. Tierney et al. (1994) compared 38 older participants with adults diagnosed with Alzheimer's dementia and dementia due to Parkinson's disease. The study concluded that some of the RAVLT indexes may be useful in determining dementia severity, while

others are more useful in distinguishing between types of dementias. In another study, Tierney et al. (2001) used 10 neuropsychological tests with 31 participants with probable Alzheimer's disease and 31 with probable subcortical ischemic vascular dementia. The recognition memory subtest of the RAVLT and the Controlled Oral Word Association Test were best able to accurately distinguish (sensitivity = 81%, specificity = 84%) between participants with Alzheimer's disease and participants with subcortical ischemic vascular dementia. The RAVLT recognition memory subtest prediction was significant ($\chi^2 = 9.77, p = .002$).

Tierney et al. (1996) reported 2-year longitudinal data for the neuropsychological testing of 123 memory-impaired participants without a dementia diagnosis and concluded that the reduced model of the delayed recall test from the RAVLT and the mental control subtest of the Wechsler Memory Scale yielded identical accuracy, sensitivity, and specificity (89%, 76%, and 94%, $p < .0001$) as the battery of 12 tests in predicting which participants would develop Alzheimer's disease. They concluded that participants with preclinical Alzheimer's disease produced delayed recall (RAVLT) and immediate recall scores that were below normative values. Tierney, Yao, Kiss, and McDowell (2005) concluded that the short delayed recall score on the RAVLT, rather than any of the other 12 neuropsychological test scores, was significant ($p < .0001$) in predicting conversion to Alzheimer's disease (sensitivity = 73%, specificity = 70%) in a 10-year longitudinal study of 263 participants. Three tests (short delayed recall on the RAVLT, animal fluency, and the information subtest on the Wechsler Memory Scale) in the 5-year longitudinal cohort (n = 551) were significant ($p < .0001$) in predicting conversion (sensitivity = 74%, specificity = 83%).

Appropriateness

The RAVLT represents and measures several different memory indices, including basic factors of acquisition and retention, with retention partitioned as storage and retrieval (Vakil & Blachstein, 1993). It is sensitive to verbal memory impairment. The RAVLT is relatively brief, but it takes slightly longer to administer than the HVLT. Because the test has been used for almost 50 years, there is extensive normative data available.

Limitations

There is considerable variability in test administration in published studies that have included the RAVLT, including different numbers of recall trials, exclusion of the interference trial, altered sequence and number of trials, altered length and format of the recognition trial, variation in the delay interval, and different rates of word list presentation and time allowed for recall (Mitrushina et al., 2005). Intelligence and educational level may exert weak and inconsistent influences on RAVLT scores (Vakil & Blachstein, 1993) due to the low reading level and very familiar words used for the RAVLT lists (Savage & Gouvier, 1992; Weins, McMinn, & Crossen, 1988). It has not been proved, however, that each score of the RAVLT is a different expression of a single factor of memory, or if each score is a measure of different memory domains (Vakil & Blachstein, 1993).

Hopkins Verbal Learning Test

In 1991 Brandt introduced the HVLT as an assessment of cognitively impaired patients who require brief and repeated assessments over time. The HVLT, a measure of verbal learning and retention, is a 12-word list that includes four words from each of

three semantic categories, and that is read to the participant during three successive learning trials, with free recall after each learning trial. Following the three free recall trials, the participant is asked to give a yes or no recognition response to a 24-word list, in which the 12 target words are mixed with 12 distractor words. Half of the distractor words are related and are drawn from the same semantic categories as the target words. The other half of the distractor words are unrelated. It takes approximately 5 to 10 minutes to administer the test. The HVLT has six parallel forms that can be used to minimize practice effects due to item familiarity (Benedict, Schretlen, Groninger, & Brandt, 1998; Brandt, 1991; Mitrushina et al., 2005).

The HVLT-R, a revised version of the HVLT that was introduced in 1998, is the same as the HVLT in all respects except for a 20 to 25 minute delayed recall trial, with recognition testing following the delayed recall (Benedict et al., 1998; Mitrushina et al., 2005). The delayed recall trial assesses learning capacity and components of memory processing, including encoding, retrieval, consolidation, and error rates (Woods et al., 2005). The addition of the delayed recall trial makes the HVLT-R more comparable to other memory tests that also include delayed recall (Lacritz, Cullum, Weiner, & Rosenberg, 2001). A participant is asked to recall the word list after a 20 to 25 minute delay that has been filled with unrelated tasks. After the delayed recall trial, the participant is asked to discriminate 24 words from 12 target words and 12 distractor words, using yes/no recognition. A score is calculated for each of the 11 HVLT-R measures including recall on each of the three learning trials, a total recall score, delayed recall, percent retention, and delayed recognition. The scores that are calculated for the recognition components include true and false positives, a recognition discrimination

index (true positive errors minus false positive errors), and the sum of "yes" responses that yields a measure of response bias for the recognition trial (Benedict et al., 1998; Lezak et al., 2004).

Benedict et al. (1998) reported a modest but significant relationship between younger participants and better performance on the HVLT-R in the initial normative data, stratified into four age ranges. The HVLT-R manual provides normative data that are stratified into eight age ranges and that are reported as raw scores (Brandt & Benedict, 2001). Tables provide raw to T-score conversions for total recall, delayed recall, percent retention, and the recognition discrimination index (Mitrushina et al., 2005). Vanderploeg et al. (2000) recommend normative data for people between 60 and 84 years of age. Age and gender had a significant effect on HVLT-R performance, but level of attained education did not. The age and gender adjustments to the HVLT-R raw scores recommended by Vanderploeg et al. are a lower level of performance, about one SD, and a slightly wider distribution than the norms published by (Benedict et al., 1998). In their study of 237 participants Friedman, Schinka, Mortimer, and Graves (2002) recommended gender and three educational level adjustments to HVLT-R raw scores for African American adults in the same age range as the Vanderploeg study. Age and education had significant, moderately large effects on performance variance. The study concluded that using Caucasian norms could result in older African Americans with mild to moderate dementia being misdiagnosed as severely demented.

Reliability

Internal consistency. Brandt (1991) determined that the six forms of the HVLT were virtually equivalent when administered to 129 normal participants. The means and

variances of the total recall scores were homogenous (Cochran's $C = .29$, *NS*). Neither the form effect ($F_{5, 123} = 1.21$, *NS*) nor the form-by-trial interaction ($F_{10,246} = .84$, *NS*) was significant. Brandt retested form equivalency a second time, using a within-subjects design with 17 normal participants who were given one form each day on six days during a 2-week period. There was no form effect ($F_{5,80} = 1.15$, *NS*), there was no trial-by-form interaction ($F_{10,160} = .82$, *NS*), the intraclass correlation coefficient was highly significant ($F_{16,85} = 4.31$, $p < .001$), and the discrimination scores for the six forms were equivalent ($F_{5,80} = 1.91$, *NS*). Frank and Byrne (2000) retested HVLT test form equivalence in a study of 56 participants' recall performance between the six forms. The alternate forms were considered comparable ($F_{5,50} = 1.27$, $p = .291$).

Interform reliability of the six forms for the HVLT-R for the free recall trials was high ($r = .55, .67, .78$, $p < .001$) when tested with 541 participants by Benedict et al. (1998). The six forms yielded small but statistically significant differences ($r = .66$, $p < .001$) for the recognition trial. Paired-T and Wilcoxin tests did not elicit any practice effects. Benedict and colleagues observed that the four recognition indices fell into two groups that were homogenous and recommended that forms 1, 2, and 4 be used together due to the higher number of false positives than forms 3, 5, and 6, which should also be used together.

Test-retest reliability. Stability coefficients for HVLT measures over nine months, a reflection of test-retest stability and alternate form reliability, were moderate but statistically significant ($r = .50$; true-positive recognitions, $r = .66$; false-positive errors, $r = .42$) for 45 healthy, older (60 to 82 years old) participants for total recall, and

comparable to test-retest reliability for similar measurements of recall and recognition (Rasmusson, Bylsma, & Brandt, 1995).

The Benedict et al. (1998) study established test-retest reliability coefficients for the primary variables of the HVLT-R over 14 to 134 days that ranged from 0.39 to 0.74 (total recall, $r = .74$; learning, $r = .41$; delayed recall, $r = .66$, percent retained, $r = .39$; recognition discrimination index, $r = .40$), with restricted and non-normal distribution of several of the variables limiting the range of the reliability coefficients. The study by Woods et al. produced modest test-retest correlations for semantic clustering ($r = .31$), semantic false-positive recognition ($r = .35$), and the retrieval index ($r = .32$), which may be related to the modest reliability between alternate forms. There was a considerable practice effect when the same HVLT-R form was given four times, each 2 weeks apart, but there was no practice effect when alternate HVLT-R forms were used for repeated administrations.

Woods et al. (2005) found modest one year HVLT-R test-retest stability coefficients for the primary test measures of total and delayed recall, percentage retained, and recognition. The coefficients for total and delayed recall were less in the study by Woods et al. (2005) than they were in the 1998 study by Benedict et al. ($r = .49$ *vs.* .74 and $r = .36$ *vs.* .66). The test-retest intervals were very different in the two studies, however; the interval in the Woods et al. study was 370 days, a more realistic interval for patient follow-up in the community, compared to 14 to 134 days in the Benedict et al. study.

Validity

Construct validity. In their study of 445 participants, Shapiro et al. (1999) determined construct and concurrent validity by correlating HVLT-R scores with a battery of tests for dementia, including a nonverbal learning test (i.e., the Brief Visuospatial Memory Test-revised [BVMT-R]), story recall and visual recall tests (i.e., the Logical Memory and Visual Reproduction subtests from the Wechsler Memory Scale-Revised); and the short form of a test of general intelligence (i.e., the Wechsler Adult Intelligence Scale-Revised). When compared to various HVLT-R measures, comparable measures of other neurological tests yielded significant moderate to high correlations that ranged from .44 to .77. The HVLT-R loaded equally on three factors with eigenvalues greater than 1, accounting for 73.2% of the total variance. Sixty percent of the variance was due to scores from the free recall trials and recognition discrimination indices of the HVLT-R and the BVMT-R. Correlation with the Wechlser Adult Intelligence Scale-Revised, a test of general intelligence, was the weakest. The results were sufficient to support the construct validity of the HVLT-R in a sample of participants with mixed dementia diagnoses. Lacritz et al. (2001) tested 40 older people with probable Alzheimer's dementia and determined that there is a relatively high correlation (r = .74) for total learning between the HVLT and the California Verbal Learning Test.

Concurrent validity. Most tests of HVLT and HVLT-R concurrent validity have compared their sensitivity and specificity to clinical diagnoses of dementia. The HVLT and HVLT-R are able to distinguish between older people with amnesic types of dementia and older people who are considered to be normal and are able to discriminate

between vascular dementia and Alzheimer's disease. In initial testing of the HVLT's six forms using patients with Alzheimer's disease and normal control participants, a score cut point between 19 and 20 for total recall yielded a sensitivity of 94% and specificity of 100%. Kuslansky et al. (2004) concluded that the HVLT is able to effectively detect dementia and the Alzheimer's disease and vascular dementia subgroups, using a cut score of 15, 16, or 17 depending on the desired sensitivity and specificity, although sensitivity rises while specificity falls when the cut point is raised. Kuslansky et al. determined that a score cut point of 20 for free recall yielded a sensitivity of 97% and specificity of 46% for detecting dementia; at a cut score of 16, the sensitivity and specificity were both 83%. When trying to detect Alzheimer's disease, sensitivity and specificity were again both 83%, if a score cut point of 16 was used. If the score cut point was raised to 17, the sensitivity increased to 88% but the specificity dropped to 67%, and, if the score cut point was lowered to 15, the sensitivity decreased to 75% and the specificity increased to 92%. When trying to detect vascular dementia, the HVLT had a sensitivity of 80% and specificity of 84%, if a score cut point of 16 was used, but, if a score cut point of 18 was used, the sensitivity increased to 90% but the specificity decreased to 68%. Kuslansky et al. concluded that that the optimal cut score for detecting mild dementia, however, was 18/19 (sensitivity = 96%, specificity = 80%. In their study to discriminate between participants with mild cognitive impairment and those who were normal, de Jager, Hogervorst, Combrinck, and Budge (2003) concluded that the HVLT total recall score had the highest sensitivity and specificity of a battery of tests. Hogervorst et al. (2002) found that the HVLT total recall score had an 87% sensitivity and 98% specificity for dementia, using a cut point of 14.5, making the HVLT useful in screening for dementia.

When the total recall and demonstration index scores were totaled for a memory score, the HVLT produced a 91% sensitivity and 98% specificity for Alzheimer's disease, using a cut point of 24.5. The Hogervorst study was limited because it excluded participants with a "questionable" diagnosis, which may overestimate test characteristics (Kuslansky et al., 2004).

The HVLT and the HVLT-R are highly sensitive for moderate to severe levels of dementia, but they are not sensitive to mild impairment. The level of sensitivity is dependent on whether study samples were recruited from the community (lower sensitivity) where participants are presumed to be normal or who have mild cognitive impairment but are functioning more independently, or from hospitals or clinics (higher sensitivity) where participants are more likely to have moderate and severe impairment.

Appropriateness

The HVLT is a screening tool that assesses basic verbal learning, especially a person's ability to learn new information, and it is a good screening tool for dementia (Hogervorst et al., 2002; Lacritz & Cullum, 1998). The HVLT and the HVLT-R are brief and repeatable, are suitable when time or clinical constraints do not allow complex measurement, and do not appear to have the ceiling effects of similar verbal learning tests for older people (Hogervorst et al., 2002; Mitrushina et al., 2005). Brandt (1991), Rasmusson et al. (1995), and Kuslanskey et al. (2004) found no correlation between HVLT performance and age. There are six equivalent forms in respect to learning and recall, and two sets of three forms can be used to assess delayed recognition (A. M. Shapiro, Benedict, Schretlen, & Brandt, 1999). And, the HVLT and the HVLT-R can compute the extent of word category clustering, a qualitative assessment of semantic

structure performance (Brandt, 1991). The HVLT-R is able to assess verbal learning and memory comparably to other commonly used verbal learning measures and may be preferred when serial testing is indicated because it is brief.

Limitations

The HVLT is not as sensitive to some types of memory skills because it does not include delayed recall, and it is limited in its ability to assess complex and qualitative aspects of verbal learning and memory (Lacritz & Cullum, 1998; Mitrushina et al., 2005). The HVLT may not be as challenging as the California Verbal Learning Test in eliciting some of the recall errors that are commonly seen in Alzheimer's disease (Lacritz et al., 2001). HVLT scores are positively correlated with education level (Benedict et al., 1998; Frank & Byrne, 2000), but the test does not appear to suffer from a ceiling effect.

The HVLT-R adds 20 to 25 minutes to the 10-minute test which may not be practical for some clinical settings or tolerated by some patients. The HVLT-R is less able to discriminate among the various subtypes of dementia than it is able to contribute to diagnosing memory impairment or dementia (A. M. Shapiro et al., 1999). The test may not be difficult enough to detect deficits in people who are young or mildly impaired or to elicit some types of recall errors in people with Alzheimer's dementia (Benedict et al., 1998; Lacritz et al., 2001).

Conclusion

Of the verbal memory tests, the verbal list learning format is the most sensitive because it does not have the contextual influences inherent in prose format (Lezak et al., 2004). The HVLT and the RAVLT are well-recognized tests of verbal memory that use this verbal list learning format. Both tests have moderate stability coefficients: the HVLT

test-retest r = .5 (Rasmusson et al., 1995) and the RAVLT r = .38 to .70 (Snow, Tierney, Zorzitto, & al., 1988). Both the HVLT (Lacritz et al., 2001; A. M. Shapiro et al., 1999) and the RAVLT (Crossen & Wiens, 1994) have recall and recognition measure comparability to other verbal memory tests. Women tend to perform better than men both on the HVLT (Vanderploeg et al., 2000) and on the RAVLT (Bleecker et al., 1988; Geffen et al., 1994). There is an age effect, especially reduced recall after age 60, on both the HVLT (Vanderploeg et al., 2000) and the RAVLT (Vakil & Blachstein, 1997). Education does not contribute significantly to the HVLT (Vanderploeg et al., 2000), but there is an education effect for the RAVLT (Bolla-Wilson, Bleecker, & Agnew, 1988). Both the HVLT (Frank & Byrne, 2000; Hogervorst et al., 2002; A. M. Shapiro et al., 1999) and the RAVLT (Tierney et al., 1996) can detect verbal memory deficits in people with Alzheimer's disease and vascular dementia.

There are slight differences between the HVLT and the RAVLT in the test administration format. Although both tests use the verbal list learning format, the lists are repeated five times for the RAVLT but only three times for the HVLT. The HVLT and the RAVLT calculate scores for learning, immediate memory, delayed recall, and recognition; the RAVLT calculates a score for early recall, but the HVLT does not. If an older person has multiple memory function deficits, it is expected that there will also be difficulty with attention and problem-solving (Lezak et al., 2004). Because primary and secondary memory are compromised in general, and verbal memory in particular, in people with heart failure (Antonelli Incalzi et al., 2003), are the HVLT and the RAVLT sufficiently sensitive and specific to detect cognitive impairment in older people with heart failure but without a diagnosis of dementia?

Both the HVLT and the RAVLT are auditorily administered verbal memory tests. Correct perception of the target words is essential to correct recall and test performance, and mild to moderate hearing loss will result in less than true memory performance. Hearing loss in older people is usually in the higher sound frequency range, and the loss of sensitivity to high frequencies accounts for about two thirds of test variance in speech perception. The interpretation of auditorily administered verbal memory test results, therefore, must consider that an older person's hearing status is often unknown (van Boxtel et al., 2000). Information processing speed and memory, both affected by age, can account for systematic variance in verbal memory test results, and intellectual performance may decline over time, especially for people whose hearing status is unknown.

If screening for heart failure-influenced cognitive fluctuations were practical, brief, and sensitive, clinicians could routinely test older persons with heart failure. A patient's significant cognitive fluctuations or lower functioning would indicate the need for interventions to improve a patient's clinical outcomes and should indicate the need to reassess how well a patient is able to manage their heart failure.

Successfully learning about heart failure is critical to patients' self-management skills (Deaton, 2000). The stabilization or improvement of heart failure, however, is based also on the ability of patients to adhere to a prescribed diet and fluid and medication regimen, to recognize and respond to symptoms, and to make appropriate decisions. Because self-management is synonymous with cognitive decision-making in response to clinical signs and symptoms (Riegel, Carlson, and Glaser, 2000), systematic neuropsychological assessment of cognitive performance should be a part of the routine

management of patients with heart failure. If screening for heart failure-influenced cognitive fluctuations were practical, brief, and sensitive, clinicians could implement routine testing in older persons with heart failure. Significant fluctuations or lower functioning would indicate needed interventions to improve patient outcomes and should cause clinicians to reassess how well patients could manage their heart failure.

CHAPTER IV

METHODOLOGY

Design

This study analyzed data that were obtained from the heart failure and cardiology clinics of a Northern California university medical center (Site 1) and from the heart clinic and adult general medicine clinics of an urban teaching hospital in Indiana (Site 2).

Sample

The UCSF Committee on Human Research approved the study with an Exempt Certification because the study is data analysis without Protected Health Identifiers (Appendix D). There were 30 participants in the Site 1 data and 70 participants in the Site 2 data.

Site 1

Participants were included if they had a current diagnosis of heart failure, with left ventricular dysfunction that was confirmed within the last 12 months by one of the following criteria: (a) an echocardiogram or a multigated acquisition scan within the last 12 months that revealed a left ventricular internal diastolic dimension of 5.5 OR a fraction of systolic shortening of less than 18% OR a left ventricular ejection fraction of less than 40% OR generalized abnormal wall motion; (b) aged 60 years or older; (c) male or female; (e) NYHA II, III, or IV functional status; and (f) understands and speaks English. Participants were excluded if they had a history of acute myocardial infarction within the last 6 months and/or a recent history of alcohol or drug abuse.

Site 2

Participants were included if they had a current diagnosis of heart failure, with left ventricular dysfunction that was confirmed within the last 12 months by one of the following criteria: (a) echocardiogram demonstrating a left ventricle internal diastolic dimension of ≥ 5.5 OR a fraction of systolic shortening of ≤ 18% OR a multigated acquisition scan with a left ventricular ejection fraction of ≤ 40% OR generalized abnormal ventricular wall motion; (b) aged 60 years or more; (c) male or female; (d) NYHA I, II, III, or IV functional status; (e) understands English as their primary language; and (f) alert and oriented to person, place, time, and purpose. Participants were excluded if they had a history of acute myocardial infarction within the last 6 months or a history of alcohol or drug abuse.

Procedure

Data elements that were obtained from each study site and analyzed included (a) demographic information (e.g., age, gender, race, marital status, and education); (b) NYHA classification; (c) verbal memory scores (e.g., immediate memory, delayed recall, and recognition); and (d) a score of general intelligence.

In administering the RAVLT, the first list of 15 nouns is read aloud to a participant who is then asked to repeat as many words as possible; this is repeated four consecutive times. The sum of words recalled for each of the five trials is the immediate memory score. After the fifth trial, a participant is read a second list of 15 nouns and is asked to repeat as many words as possible. Then the participant is asked to recall as many words as possible from the first list; this is a test of early recall after distraction but

was not included in this analysis because the HVLT does not include this step. After a 20- to 30-minute delay, the participant is asked again to recall as many words as possible from the first list; the score for this step is the delayed recall score. Finally, the patient is given a matrix list of 30 words, the 15 words nouns at the beginning of the test and 15 different nouns, and asked to identify words from the first list. The correct yes and correct no scores are totaled to calculate the recognition score.

In administering the HVLT, a 12-word list is read to a participant during three successive learning trials, with free recall after each learning trial. The sum of words recalled for each of the three trials is the immediate memory score. A participant is then asked to recall the word list after a 20- to 25-minute delay that has been filled with unrelated tasks; the score for this step is the delayed recall score. Following the delayed recall trial, the participant is asked to give a yes or no recognition response to a 24-word list in which the 12 target words are mixed with 12 distractor words. The scores that are calculated for the recognition components include true and false positives and a recognition discrimination index, which is the true-positive score minus the false-positive score (Benedict et al., 1998; Lezak et al., 2004).

Reading ability is used as a measure of premorbid intelligence, because it is thought that reading assesses previous prior knowledge of words, rather than using standard rules of pronunciation, and that reading is reasonably preserved in people with dementia (Ginsberg, 2003; Morris, Wilson, Dunn, & Teasdale, 2005). To estimate premorbid intelligence, Site 1 used the Vocabulary subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) Test. The Wechsler test vocabulary component correlates highly with education, and therefore it is used as an indicator of premorbid

intelligence (Johnstone et al., 1997; Tremont, Hoffman, Scott & Adams, 1998). While the WAIS-R computes a full-scale IQ score, a verbal IQ score, and a performance IQ score, the Site 1 participants were given the Vocabulary subtest of the WAIS-R. Scores were totaled and compared to standardized, age-corrected norms; this generated a corrected score that was converted into a T-score. Site 2 used the Wechsler Test of Adult Reading (WTAR). A participant reads a list of 50 words that have irregular spelling and therefore are difficult to enunciate. The number of correctly pronounced words are totaled, and the raw score is converted into a standard score, using published normative tables (The Psychological Association, 2001). The WTAR was developed specifically to estimate intelligence before changes from dementia or cerebral trauma and memory level of function.

Data Analysis

The Statistical Package for the Social Sciences 12.0 for Windows, was used to manage and analyze data. Descriptive statistics, means, and standard deviations for quantitative variables and frequencies and percents for categorical variables were calculated for all study variables. Study variables included demographic variables to describe the two samples and the verbal memory test and current cognitive function variables.

Hypothesis 1

Older people with heart failure have significantly greater immediate memory and delayed recall impairment than recognition impairment. Separate comparisons for the two verbal memory tests, e.g., the RAVLT obtained at Site 1 and the HVLT obtained at Site 2, were used to determine if the verbal memory scores of people with heart failure,

who are 60 years old and older, are different from the age- specific normative values. Standard deviations below the mean were used as cutoff points to distinguish between normal and impaired verbal memory. One SD below the mean was considered borderline, 1.5 SD below the mean was considered mild impairment, and 2 SD below the mean was considered moderate to severe impairment (A. Smith & Centofanti, 1975).

Hypothesis 2

The magnitude of the correlation between immediate memory and delayed recall is stronger than the correlation between immediate memory and recognition or delayed recall and recognition. Pearson's correlation coefficients were calculated among three components of verbal memory (e.g., immediate memory, delayed recall, and recognition) within each sample. For Site 1, RAVLT T-scores for immediate memory, delayed recall, and recognition were calculated by using the means and standard deviations of healthy control participants, grouped by age decade, also from Site 1. For Site 2, the HVLT T-scores for immediate memory, delayed recall, and discrimination (recognition) were obtained from Appendix A in the Hopkins Verbal Learning Test-Revised Professional Manual (Brandt & Benedict, 2001).[2]

Hypothesis 3

The correlations among immediate memory, delayed recall, and recognition do not depend on the specific test used to measure these components of memory. A multiple linear regression technique was used to examine the relationship among the verbal

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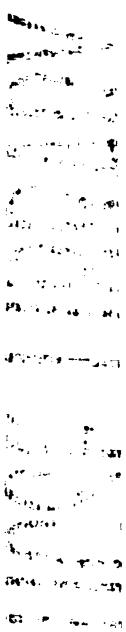
[2] Site 2 used the following criteria for scoring:
If patient is 60 years of age, use the table with midpoint = 60.
If patient age is between 61 and 65 years, use the table with midpoint = 65.
If patient age is between 66 and 70 years, use the table with midpoint = 70.
If patient age is between 71 and 75 years, use the table with midpoint = 75.
If patient age is between 76 and 80 years, use the table with midpoint = 80.
If patient age is 81 or greater, use the table for ages 80+ years.

memory scores and the possible dependence of these relationships on the instrument used. For example, to investigate the relationship between immediate memory and delayed recall, immediate memory was the independent variable and delayed recall was the dependent variable. In addition, the verbal memory instrument (HVLT and RAVLT) and the product of immediate memory and the verbal memory instrument, representing the interaction, was added to the regression model. The interaction's significance was used to determine if the relationship between immediate memory and delayed recall depended on the verbal memory instrument. If the interaction is not significant, it would provide evidence that it may be appropriate to combine the standardized verbal memory scores from the two instruments when examining the relationships among the verbal memory components. The multiple linear regression technique allowed the inclusion of other independent variables that may contribute to explaining the variance in verbal memory components including age, gender, and ethnicity.

Hypothesis 4

The correlation between estimates of premorbid intelligence and verbal memory scores, controlling for education, is high. The Vocabulary subtest of the WAIS-R and the WTAR are reading tests and considered to be general tests of intelligence. Pearson's correlation coefficients were calculated between general intelligence and verbal memory scores, controlling for years of education. At Site 1, the Vocabulary subtest of the WAIS-R was used to estimate premorbid intelligence and verbal memory was assessed by the RAVLT. At Site 2, the WTAR, a test of premorbid intellectual ability, was used, and verbal memory was assessed by the HVLT.



CHAPTER V

RESULTS

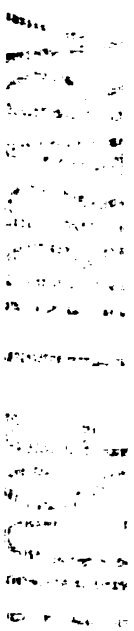
Demographic Data

A total of 99 participants were analyzed. Initially there were 30 participants from Site 1, but one participant was excluded because he was unable to recall any words, beginning with the first RAVLT trial. This participant was a single, African American man, over 80 years old, with an elementary school education and NYHA Class IV heart failure. There were 70 participants from Site 2; no participants were excluded. Demographic information and descriptive statistics for both sites are presented separately and combined in Table 1.

Differences in demographic data between the participants the two sites were assessed by *t*-tests for age and education, and by Chi-square tests for the categorical variables. Differences between the groups were not statistically significant.

Table 1. *Demographic Characteristics of Participants Grouped By Site*

	Combined	Site 1	Site 2	*p*
N	99	29	70	
Age, *M (SD)*	71.2 (7.4)	72.7 (6.6)	70.6 (7.6)	.209
Men, *n (%)*	56 (56.6)	15 (51.7)	41 (58.6)	.532
Educational levels, years, *M (SD)*	12.6 (3.1)	13.2 (3.0)	12.3 (3.1)	.210
Age by group, *n (%)*				.156
60 - 69 years old	45 (45.5)	10 (34.5)	35 (50.0)	
70 - 79 years old	40 (40.4)	16 (55.2)	24 (34.3)	
80 + years old	14 (14.1)	3 (10.3)	11 (15.7)	
Race, *n (%)*				.061
Caucasian	81 (81.8)	27 (93.1)	54 (77.1)	
Other (African American or Asian)	18 (18.2)	2 (6.9)	16 (22.9)	
Marital status, *n (%)*				.107
Partnered	50 (50.5)	11 (37.9)	39 (55.7)	
Not partnered	49 (49.5)	18 (62.1)	31 (44.3)	
Education, *n (%)*				.398
Elementary school	9 (9.1)	1 (3.4)	8 (11.4)	
High school	45 (45.5)	12 (41.4)	33 (47.1)	
College	37 (37.4)	14 (48.3)	23 (32.9)	
Postgraduate school	8 (8.1)	2 (6.9)	6 (8.6)	
NYHA Functional Class, *n (%)*				.918
I/II	47 (47.5)	14 (48.3)	33 (47.1)	
III/IV	52 (52.5)	15 (51.7)	37 (52.9)	



Hypotheses

Hypothesis 1

Older people with heart failure have significantly greater immediate memory and delayed recall impairment than recognition impairment.

Descriptive data will be discussed before an analysis of the Repeated-Measures ANOVA results that were used to analyze Hypothesis 1.

Site 1

The participants' RAVLT mean T-scores are shown in Table 2.

Table 2. *RAVLT T-scores*

RAVLT test element	*n*	Mean (± SD)	Range
Immediate memory	29	42.2 (± 16.6)	14.2-77.6
Delayed recall	29	43.0 (± 14.9)	20.0-66.4
Recognition	28	46.5 (± 14.7)	3.3-60.8

Note: T-scores, age-adjusted according to 60 to 69, 70 to 79, 80 to 89 normal control groups.

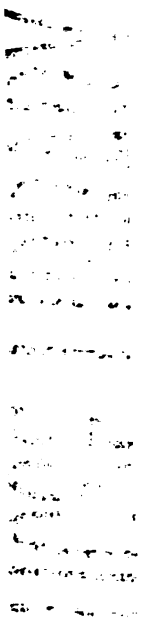
When age groups were stratified by decade (Table 3), slightly more than half of the participants' immediate memory T-scores (58.6%) and delayed memory T-scores (55.2%) were within the normal range, while a higher percentage of recognition T-scores (75%) were within the normal range. More participants had moderately low (mild impairment) and very low (impairment) delayed recall T-scores (41.4%) than moderately low (mild impairment) and very low (impairment) immediate memory T-scores (37.9%). No one had moderately low (mild impairment) recognition T-scores, but 14.3% had very low (impairment) recognition T-scores. More 60 to 69 year old participants and 70 to 79 year old participants had moderately low (mild impairment) and very low (impairment) delayed recall T-scores than moderately low (mild impairment) and very low (impairment) immediate memory or recognition T-scores. When the 60 to 69 year old

participants were combined with the 70 to 79 year olds, then delayed recall was impaired more frequently (42.3%) than immediate memory (26.9%) or recognition (16%). Although the number of participants in the 80 to 89 year old group is too small to calculate meaningful percentages, two of the three participants had very low (impairment) immediate memory T-scores, and one had a moderately low (mild impairment) delayed recall T-score. Chi-square and one-way ANOVA tests comparing the three age groups were not significant, most likely due to the small number of participants.

Table 3. *RAVLT T-scores Grouped by Standard Deviation and Stratified by Age Group*

	Age range (years)		
RAVLT T-scores	60 to 69 (n = 10) Freq (%)	70 to 79 (n = 16) Freq (%)	80 + (n = 3) Freq (%)
Immediate memory (n = 29)			
Normal: <1 SD below mean	7 (70)	9 (56.3)	1 (33.3)
Low: ≥ 1 to < 1.5 SD below mean	0	1 (6.3)	0
Moderately low: ≥ 1.5 to < 2 SD below mean	1 (10)	2 (12.5)	0
Very low: ≥ 2 SD below mean	2 (20)	4 (25)	2 (66.7)
Delayed recall (n = 29)			
Normal: <1 SD below mean	5 (50)	9 (56.3)	2 (66.7)
Low: ≥ 1 to < 1.5 SD below mean	1 (10)	0	0
Moderately low: ≥ 1.5 to < 2 SD below mean	2 (20)	3 (18.8)	1 (33.3)
Very low: ≥ 2 SD below mean	2 (20)	4 25)	0
Recognition (n = 28)			
Normal: <1 SD below mean	8 (80)	11 (73.3)	2 (66.7)
Low: ≥ 1 to < 1.5 SD below mean	1 (10)	1 (6.7)	1 (33.3)
Moderately low: ≥ 1.5 to < 2 SD below mean	0	0	0
Very low: ≥ 2 SD below mean	1 (10)	3 (20)	0

When the immediate memory, delayed recall, and recognition T-scores were grouped by standard deviations and stratified by age group (Figure 1), most participants had normal T-scores (<1 SD below the mean). Delayed recall T-scores were almost equally distributed between the normal and impaired (≥1.5 SD below the mean)



categories for the 60 to 69 year old and 70 to 79 year old participants. Few participants had impaired recognition T-scores.

Site 2

The participants' HVLT mean T-scores are shown in Table 4. Recognition scores are missing for two participants because of testing errors.

Table 4. *HVLT T-scores*

HVLT test element	*n*	Mean (± SD)	Range
Immediate memory[a]	70	37.76 (± 11.46)	20-60
Delayed recall[a]	70	40.50 (± 11.69)	20-64
Recognition[a]	68	39.28 (± 12.85)	20-62

[a] T-scores, age-adjusted according to Brandt & Benedict, 2001.

When age groups were stratified by decade (Table 5), half or more of the participants scored within the normal ranges for delayed recall T-scores (50%) and recognition T-scores (55.9%), but less than half scored within the normal range for immediate memory T-scores (44.3%). More participants had impaired immediate memory T-scores (42.9%) than impaired delayed recall (32.9%) or recognition (36.8%) T-scores. When the 60 to 69 years old participants were combined with those 70 to 79 years old, impaired immediate memory T-scores were then more frequent (31.4%) than impaired delayed recall T-scores (28.6%) or impaired recognition T-scores (26.5%). Chi-square and one-way ANOVA tests comparing the three age groups were not significant, most likely due to the small number of participants.

Table 5. *HVLT T-scores Stratified by Age Group*

	Age range (years)		
HVLT T-scores	60 to 69 (n = 35 Freq (%)	70 to 79 (n = 24) Freq (%)	80 + (n = 11) Freq (%)
Immediate memory (n = 70)			
Normal: <1 SD below mean	15 (42.9)	13 (54.2)	3 (27.3)
Low: ≥ 1 to < 1.5 SD below mean	6 (17.1)	3 (12.5)	0
Moderately low: ≥ 1.5 to < 2 SD below mean	0	4 (16.7)	5 (45.5)
Very low: ≥ 2 SD below mean	14 (40)	4 (16.7)	3 (27.3)
Delayed recall (n = 70)			
Normal: <1 SD below mean	17 (48.6)	13 (54.2)	5 (45.5)
Low: ≥ 1 to < 1.5 SD below mean	6 (17.1)	3 (12.5)	3 (27.3)
Moderately low: ≥ 1.5 to < 2 SD below mean	4 (11.4)	5 (20.8)	2 (18.2)
Very low: ≥ 2 SD below mean	8 (22.9)	3 (12.5)	1 (9.1)
Recognition (n = 68)	(n = 34)	(n = 23)	(n = 11)
Normal: <1 SD below mean	20 (58.8)	14 (60.9)	4 (36.4)
Low: ≥ 1 to < 1.5 SD below mean	1 (2.9)	4 (17.4)	0
Moderately low: ≥ 1.5 to < 2 SD below mean	5 (14.7)	1 (4.3)	0
Very low: ≥ 2 SD below mean	8 (23.5)	4 (17.4)	7 (63.6)

When the immediate memory, delayed recall, and recognition T-scores were grouped by standard deviations and stratified by age group (Figure 1), most 60 to 69 year old and 70 to 79 year old participants had normal T-scores (<1 SD below the mean). More participants who were 80 years old or more had impaired (≥1.5 SD below the mean) immediate memory T-scores (72.7%) and impaired recognition T-scores (63.6%).

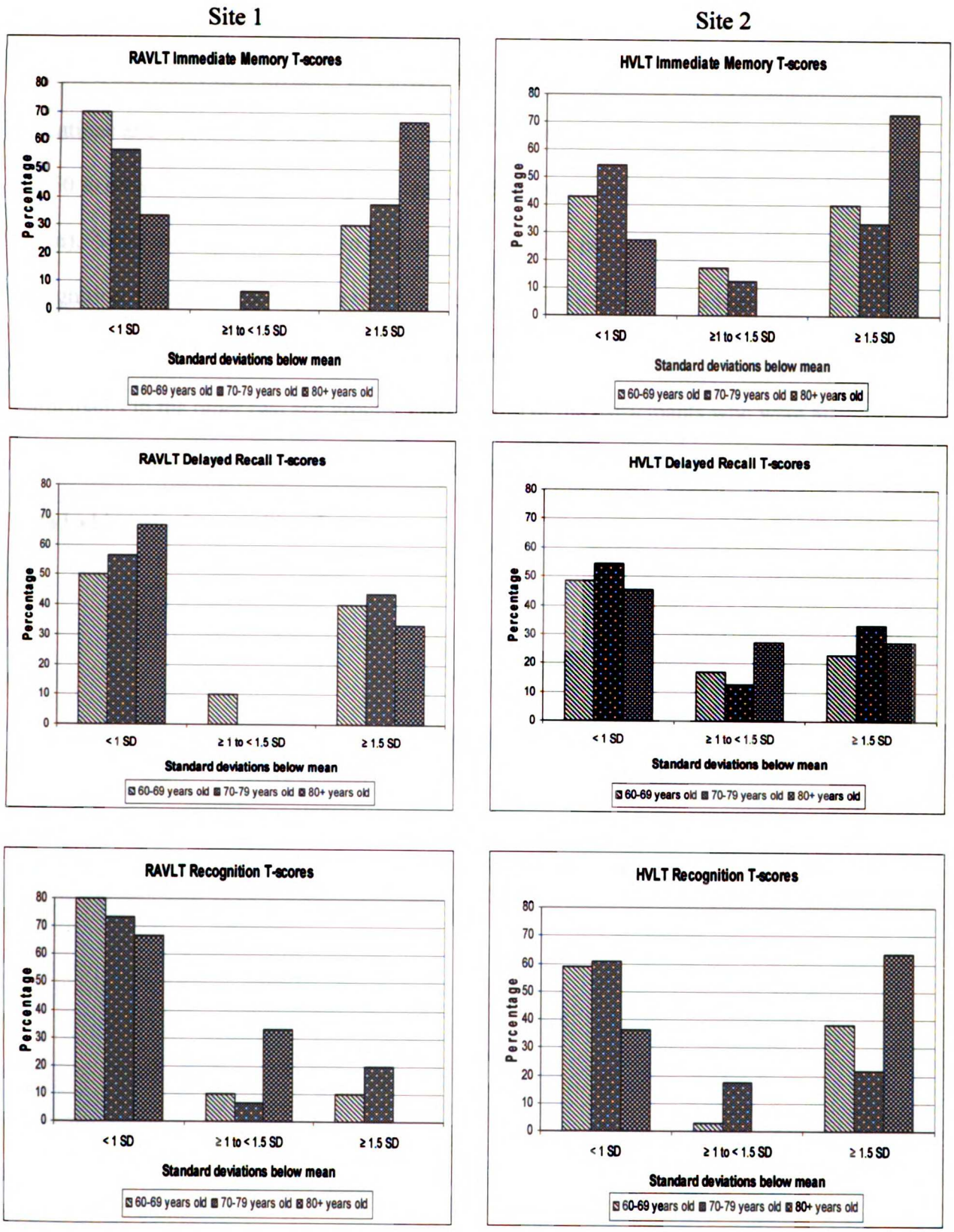
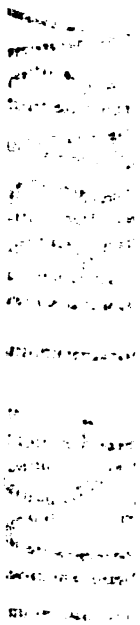
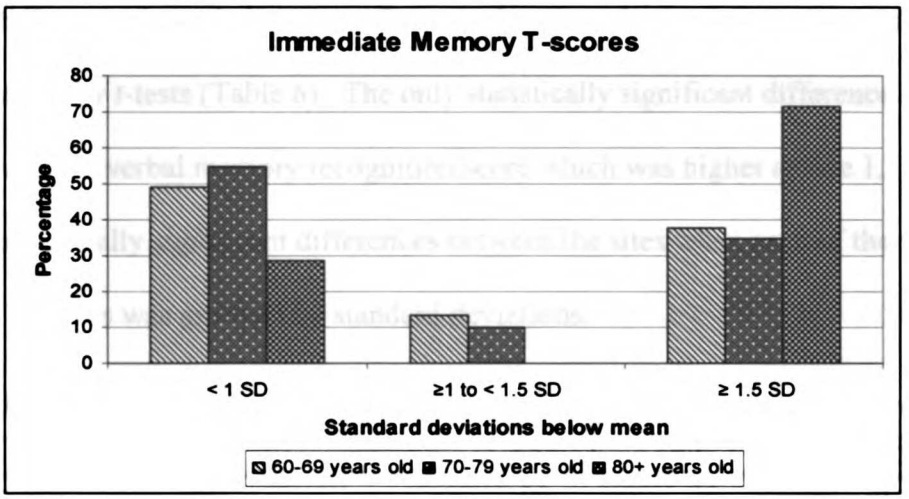


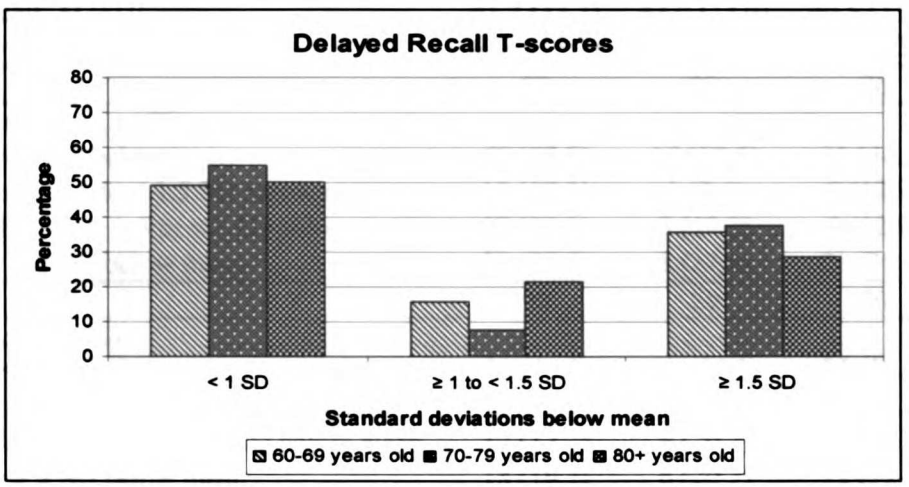
Figure 1. T-score Standard Deviation Distributions by Site and by Age Group



All Participants

When immediate memory and delayed recall T-scores were grouped by standard deviations and stratified by age group for all participants (Figure 2), half or nearly half of the 60 to 69 and 70 to 79 year old participants had normal T-scores (< 1 SD below the mean). More than 60% of the 60 to 69 and 70 to 79 years old participants had normal recognition T-scores. Participants who were 80 years old or more had a higher percentage of impaired immediate memory T-scores (71.4%) when compared to participants in the other two age groups. Only 28.6% of the participants who were 80 years old or more had impaired (≥ 1.5 SD below the mean) delayed recall T-scores, but 50% had impaired recognition T-scores.





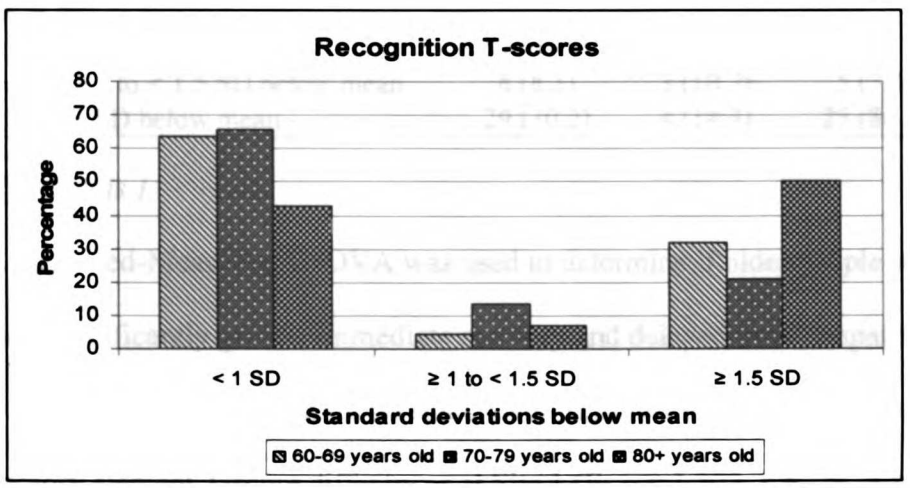


Figure 2. T-score Standard Deviation Distributions for all Participants by Age Group

Differences in verbal memory T-scores between the participants at the two sites were assessed by *t*-tests (Table 6). The only statistically significant difference between the sites was the verbal memory recognition score which was higher at Site 1. There were no statistically significant differences between the sites when each of the verbal memory T-scores was grouped by standard deviations.

Table 6. *Verbal Memory T-scores of Participants Grouped By Site and Combined*

	Combined	Site 1	Site 2	*p*
N	99	29	70	
Immediate memory, *M (SD)*	39.1 (13.3)	42.2 (16.7)	37.8 (11.5)	.200
Delayed recall, *M (SD)*	41.2 (12.7)	43.0 (14.9)	40.5 (11.7)	.422
Recognition, *M (SD)*	41.4 (13.7)	46.5 (14.7)	39.3 (12.9)	**.018**
N	99	29	70	
Immediate memory, *n (%)*				.421
Normal : < 1 SD below mean	48 (48.5)	17 (58.6)	31 (44.3)	
Low normal : ≥ 1 to < 1.5 SD below mean	10 (10.1)	1 (3.4)	9 (12.9)	
Moderately low: ≥ 1.5 to < 2 SD below mean	12 (12.1)	3 (10.3)	9 (12.9)	
Very low: ≥ 2 SD below mean	29 (29.3)	8 (27.6)	21 (30.0)	
N	99	29	70	
Delayed recall, *n (%)*				.324
Normal : < 1 SD below mean	51 (51.5)	16 (55.2)	35 (50.0)	
Low normal : ≥ 1 to < 1.5 SD below mean	13 (13.1)	1 (3.4)	12 (17.1)	
Moderately low: ≥ 1.5 to < 2 SD below mean	17 (17.2)	6 (20.7)	11 (15.7)	
Very low: ≥ 2 SD below mean	18 (19.2)	6 (20.7)	12 (17.1)	
N	96	28	68	
Recognition, *n (%)*				.092
Normal : < 1 SD below mean	59 (61.5)	21 (75.0)	38 (55.9)	
Low normal : ≥ 1 to < 1.5 SD below mean	8 (8.3)	3 (10.7)	5 (7.4)	
Impaired: ≥ 1.5 SD below mean	29 (30.2)	4 (14.3)	25 (86.2)	

Test of Hypothesis 1

A Repeated-Measures ANOVA was used to determine if older people with heart failure have significantly greater immediate memory and delayed recall impairment than recognition impairment. There were no statistically significant, within-participant, mean verbal memory element T-score differences at Site 1 ($F_{2,54} = 1.303$, $p = .28$, n = 28) or at Site 2 ($F_{2,134} = 2.84$, $p = .072$, n = 68). There were no statistically significant, within-

participant, mean verbal memory element T-score differences when both sites were combined ($F_{2,190} = 2.609$, $p = .085$, n = 96). Pair-wise contrasts are not usually computed if there is no statistical significance for the overall test, but they were calculated nonetheless. Although the overall ANOVA showed that there were no statistically significant differences among the mean T-scores of the three verbal memory elements, the biggest difference in this sample was between immediate memory and delayed recall. The pair-wise contrasts showed that participants had better delayed recall T-scores than immediate memory T-scores ($F_{(1,95)} = 7.192$, $p = .009$, adjusted $p = .0167$); the Bonferroni criteria for significance of any one of the three possible pair-wise contrasts would be $p = .0167$ (.05/3).

Hypothesis 2

The magnitude of the correlation between immediate memory and delayed recall is stronger than the correlation between immediate memory and recognition or delayed recall and recognition.

Site 1

Pearson correlations between immediate memory and delayed memory, immediate memory and recognition, and delayed memory and recognition RAVLT T-scores were calculated; all three correlations were statistically significant (Table 7).

Table 7. *Pearson Correlations between RAVLT Verbal Memory Elements*

	Delayed recall	Recognition
Immediate memory	.822*** ($n = 29$)	.635*** ($n = 28$)
Delayed recall		.655*** ($n = 28$)

*** $p < .001$.

Approximately 68% of the variance in delayed recall T-scores can be explained by the variance in immediate memory T-scores (Table 8). For every 1 point increase in

the immediate memory T-score, there was on average a 0.737 point increase in the delayed memory T-score. Approximately 40% of the variance in recognition T-scores can be explained by the variance in immediate memory T-scores. For every 1 point increase in the immediate memory T-score, there was on average a 0.574 point increase in the recognition T-score. Approximately 43% of the variance in recognition T-scores can be explained by the variance in delayed recall T-scores. For every 1 point increase in the delayed recall T-score, there was on average a 0.663 point increase in the recognition T-score.

Table 8. *RAVLT Sources of Variance*

Predictor	Dependent variable	R^2	B	CI	df	*p*
Immediate memory	Delayed recall	.676	.737	.536, .938	1, 27	.000
Immediate memory	Recognition	.403	.574	.292, .856	1, 26	.000
Delayed recall	Recognition	.430	.663	.355, .971	1, 26	.000

Site 2

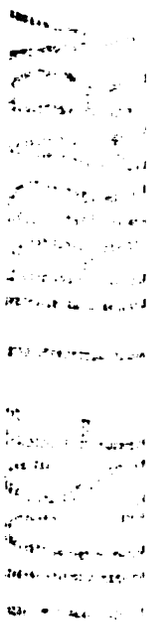
Pearson correlations between immediate memory and delayed memory, immediate memory and recognition, and delayed memory and recognition HVLT T-scores were calculated; all three correlations were statistically significant (Table 9).

Table 9. *Pearson Correlations between HVLT Verbal Memory Elements*

	Delayed recall	Recognition
Immediate memory	.802*** ($n = 70$)	.598*** ($n = 68$)
Delayed recall		.628*** ($n = 68$)

*** $p < .001$.

Approximately 64% of the variance in delayed recall T-scores can be explained by the variance in immediate memory T-scores (Table 10). For every 1 point increase in the immediate memory T-score, there was on average a 0.818 point increase in the delayed memory T-score. Approximately 36% of the variance in recognition T-scores



can be explained by the variance in immediate memory T-scores. For every 1 point increase in the immediate memory T-score, there was on average a 0.674 point increase in the recognition T-score. Approximately 40% of the variance in recognition T-scores can be explained by the variance in delayed recall T-scores. For every 1 point increase in the delayed recall T-score, there was on average a 0.697 point increase in the recognition T-score.

Table 10. *HVLT Sources of Variance*

Predictor	Dependent variable	R^2	B	CI	df	*p*
Immediate memory	Delayed recall	.643	.818	.670, .965	1, 68	.000
Immediate memory	Recognition	.358	.674	.452, .896	1, 66	.000
Delayed recall	Recognition	.395	.697	.485, .909	1, 66	.000

All Participants

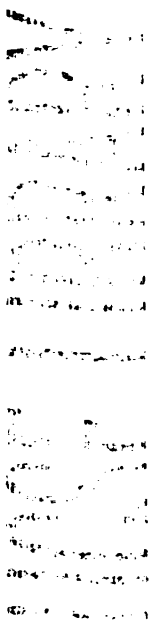
Pearson correlations between immediate memory and delayed memory, immediate memory and recognition, and delayed memory and recognition T-scores for all participants were calculated without controlling for variables, such as age, race, or gender; all three correlations were statistically significant (Table 11).

Table 11. *Pearson Correlations between Verbal Memory Elements*

	Delayed recall	Recognition
Immediate memory	.810*** ($n = 99$)	.625*** ($n = 96$)
Delayed recall		.642*** ($n = 96$)

*** $p < .001$.

Approximately 66% of the variance in delayed recall T-scores can be explained by the variance in immediate memory T-scores (Table 12). For every 1 point increase in the immediate memory T-score, there was on average a 0.776 point increase in the delayed memory T-score. Approximately 39% of the variance in recognition T-scores can be explained by the variance in immediate memory T-scores. For every 1 point



increase in the immediate memory T-score, there was on average a 0.654 point increase in the recognition T-score. Approximately 41% of the variance in recognition T-scores can be explained by the variance in delayed recall T-scores. For every 1 point increase in the delayed recall T-score, there was on average a 0.705 point increase in the recognition T-score.

Table 12. *Verbal Memory Element Sources of Variance*

Predictor	Dependent variable	R^2	B	CI	df	*p*
Immediate memory	Delayed recall	.657	.776	.662, .889	1, 97	.000
Immediate memory	Recognition	.390	.654	.486, .821	1, 94	.000
Delayed recall	Recognition	.412	.705	.533, .877	1, 94	.000

The magnitude of the correlation between immediate memory and delayed recall is stronger than the correlations between immediate memory and recognition or delayed recall and recognition.

Hypothesis 3

The correlations between immediate memory, delayed recall, and recognition do not depend on the specific test used to measure these components of memory.

Hierarchal regression analyses were performed to determine the relationships between the three elements of verbal memory (immediate memory and delayed recall, immediate memory and recognition, and delayed recall and recognition) after controlling for the contribution of other independent variables (e.g., age, gender, and ethnicity) and the possible dependence of these relationships on the specific verbal memory instrument (the interaction between a verbal memory element and site). For each of the three regression analyses performed, one of the verbal memory elements was the dependent variable and another verbal memory element was the independent variable. Age, gender,

and race[3] were entered into the model in the first step, a verbal memory element and site in the second step, and site by verbal memory element interaction in the third step.

As shown in Table 13, age, gender, and race collectively explained 6.7% (*ns*) of the variance in delayed recall T-scores. In the second step, immediate memory and site were added to determine their predictive effects; they explained an additional 61.4% ($p = .000$) of the variance in delayed recall. Female gender uniquely explained 1.7% ($p = .027$) and immediate memory uniquely explained 61.2% ($p = .000$) of the variance in delayed recall. In the third step, adding the verbal memory instrument (site) by immediate memory interaction explained only an additional 0.1% (*ns*) of the variance. Therefore, as seen in step 2, the relationship between immediate memory and delayed recall T-scores does not depend on the site, immediate memory was positively related to delayed recall, and women scored better than men.

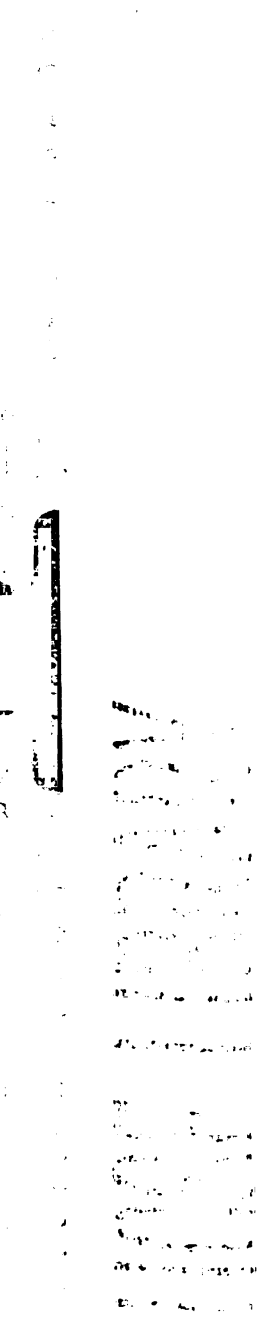
Table 13. *Age, Gender, Race, and Immediate Memory as Predictors of Delayed Recall* (n = 99)

Predictors	R^2	beta	R^2 change	df	F	*p*
Step 1	.067		.067	3,95	2.280	.084
Age		.048	.002	1,95	0.211	.647
Gender[a]		.186	.034	1,95	3.437	.067
Race[b]		-.179	.029	1,95	2.893	.097
Step 2	.681*		**.614**	2,93	89.400	**.000**
Age		.070	.004	1,93	1.259	.265
Gender[a]		.133	**.017**	1,93	5.040	**.027**
Race[b]		-.013	.000	1,93	0.041	.840
Immediate memory		.806	**.612**	1,93	178.329	**.000**
Site[c]		.052	.003	1,93	0.733	.394
Step 3	.682		.001			
Site[c] x immediate memory		.139	.001	1,92	0.342	.560

* Overall R^2 at Step 2 = .681 $F_{5,93} = 39.673$ $p = .000$

[a] Gender 1 = Male 2 = Female
[b] Race 1 = Caucasian 2 = African American and Asian
[c] Site 1 = Site 1 2 = Site 2

[3] Race was merged into two groups; there was one Asian in the entire sample and therefore that participant was added to the African American group.



As shown in Table 14, age, gender, and race collectively explained 4.7% (*ns*) of the variance in recognition. In the second step, immediate memory and site were added to determine their predictive effects; they explained an additional 38.1% ($p = .000$) of the variance in recognition. Immediate memory uniquely explained 33.4% ($p = .000$) of the variance in recognition. In the third step, adding the verbal memory instrument (site) by immediate memory interaction explained only an additional 0.3% (*ns*) of the variance. Therefore, as seen in step 2, the relationship between immediate memory and recognition T-scores does not depend on the site.

Table 14. *Age, Gender, Race, and Immediate Memory as Predictors of Recognition* (n = 96)

Predictors	R^2	beta	R^2 change	df	F	*p*
Step 1	.047		.047	3,92	1.506	.218
Age		-.053	.003	1,92	.241	.624
Gender[a]		.187	.034	1,92	3.320	.072
Race		-.142	.018	1,92	1.735	.191
Step 2	.428*		**.381**	2,90	29.957	**.000**
Age		-.042	.002	1,90	.253	.616
Gender[a]		.129	.016	1,90	2.56	.113
Race[b]		.027	.001	1,90	.096	.757
Immediate memory		.601	**.334**	1,90	52.505	**.000**
Site[c]		-.138	.018	1,90	2.819	.097
Step 3	.431		.003			
Site[c] x immediate memory		.218	.003	1,89	.449	.505

* Overall R^2 at Step 2 = .428 $F_{5,90} = 13.455$ $p = .000$

[a] Gender 1 = Male 2 = Female
[b] Race 1 = Caucasian 2 = African American and Asian
[c] Site 1 = Site 1 2 = Site 2

As shown in Table 15, age, gender, and race collectively explained 4.7% (*ns*) of the variance in recognition. In the second step, delayed recall and site were added to determine their predictive effects; they explained an additional 40.6% ($p = .000$) of the variance in recognition. Delayed recall uniquely explained 35.9% ($p = .000$) and site

uniquely explained 3.1% (p = .026) of the variance in recognition. In the third step, adding the verbal memory instrument (site) by delayed recall interaction explained less than 0.01% (*ns*) of the variance. Therefore, as seen in step 2, the relationship between delayed recall and recognition T-scores does not depend on the site. Because the main effect of site as well as delayed recall were significant in step 2, a scatter plot is included in this discussion (Figure 3). The scatter plot demonstrates nearly parallel regression lines between the two sites which indicates that, although the positive relationship between delayed recall and recognition does not depend on site, participants at Site 1 on average did have higher recognition scores.

Table 15. *Age, Gender, Race, and Delayed Recall as Predictors of Recognition* (n = 96)

Predictors	R^2	beta	R^2 change	df	F	*p*
Step 1	.047		.047	3,92	1.506	.218
Age		-.053	.003	1,92	.241	.624
Gender[a]		.187	.034	1,92	3.320	.072
Race[b]		-.142	.018	1,92	1.735	.192
Step 2	.452*		**.406**	2,90	33.334	**.000**
Age		-.089	.007	1,90	1.171	.282
Gender[a]		.050	.002	1,90	.386	.536
Race[b]		.018	.000	1,90	.044	.834
Delayed recall		.626	**.359**	1,90	58.921	**.000**
Site[c]		-.181	**.031**	1,90	5.148	**.026**
Step 3	.453					
Site[c] x delayed recall		.094	.000	1,89	.071	.791

* Overall R^2 at Step 2 = .452 $F_{5,90}$ = 14.873 p = .000

[a] Gender 1 = Male 2 = Female
[b] Race 1 = Caucasian 2 = African American and Asian
[c] Site 1 = Site 1 2 = Site 2

The correlations among immediate memory, delayed recall, and recognition did not depend on whether the RAVLT or the HVLT was used to measure these components of memory.

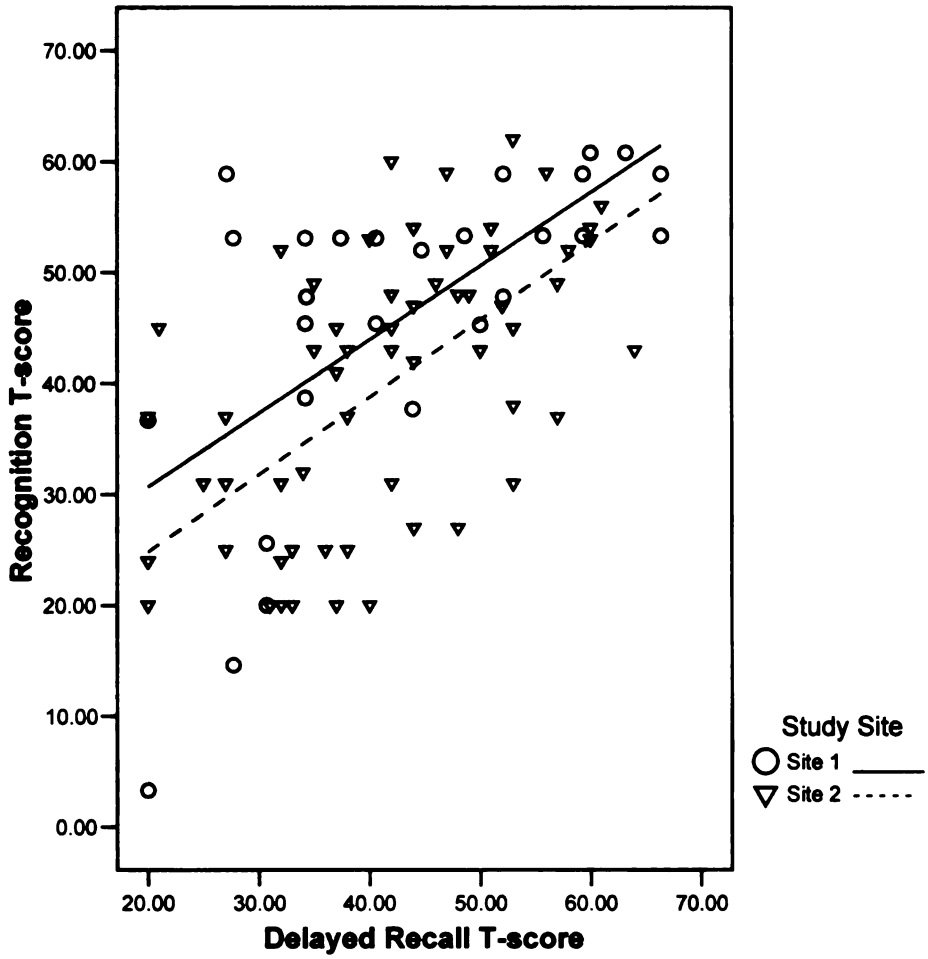


Figure 3. Scatter Plot Illustration of the Linear Relationship between Delayed Recall and Recognition T-scores for Sites 1 and 2

Hypothesis 4

The correlation between estimates of premorbid intelligence and verbal memory scores, controlling for education, is high.

Site 1

The WAIS-R Vocabulary subtest scores are missing for two participants because they were too exhausted to continue testing. The mean Vocabulary subtest score was 111.8 (± 14.8 SD, range 80-145). Pearson correlations among the WAIS-R Vocabulary subtest scores and RAVLT T-scores and education are presented in Table 16.

Table 16. *Pearson Correlations among WAIS-R Vocabulary Subtest Scores, RAVLT Memory T-scores, and Years of Education*

	n	*r*	r^2
	28		
WAIS-R and Immediate memory		.504**	.254**
WAIS-R and Education		.541**	.293**
Immediate memory and Education		.493**	.243**
	28		
WAIS-R and Delayed recall		.334*	.117*
WAIS-R and Education		.541**	.293**
Delayed recall and Education		.400**	.160**
	27		
WAIS-R and Recognition		.373*	.139*
WAIS-R and Education		.546**	.298**
Recognition and Education		.503**	.253**

*$p < .05$. **$p < .01$. *** $p < .001$.

All of the correlations between the WAIS-R Vocabulary subtest scores, RAVLT T-scores, and education are statistically significant. At least 29% of the variance in WAIS-R Vocabulary subtest scores can be explained by the variance in years of education. Likewise approximately 25.4% of the variance in WAIS-R Vocabulary subtest scores can be explained by the variance in immediate memory T-scores, but only 13.9% by recognition T-scores and 11.7% by delayed recall T-scores. Approximately

25.3% of the variance in recognition T-scores and 24.3% of the variance in immediate memory T-scores, but only 16% of the variance in delayed recall T-scores, can be explained by the variance in years of education.

Hierarchical regression analyses were performed to determine the effect of the three elements of verbal memory (immediate memory, delayed recall, and recognition) on WAIS-R Vocabulary subtest scores, after controlling for the contribution of education. As shown in Table 17, education was entered into the first step and it explained 29.3% ($p = .003$) of the variance in WAIS-R Vocabulary subtest scores. When immediate memory was added to the second step, it explained only an additional 7.5% (*ns*) of the variance. As shown in Table 18, when delayed recall was added to the second step after education, it explained only an additional 1.7% (*ns*). As shown in Table 19 education explained slightly more of the variance (29.8%, $p = .003$) in WAIS-R Vocabulary subtest scores due to the number of participants being smaller by one. But when recognition was added to the second step, it explained only an additional 1.3% (*ns*). Therefore, although there was a moderate correlation between the WAIS-R Vocabulary subtest score and education, moderate correlations among the three verbal memory elements and education, and weaker correlations among the WAIS-R Vocabulary subtest score and the three RAVLT verbal memory elements, none of the three verbal memory elements significantly explained the variance in the WAIS-R Vocabulary subtest score after controlling for education.

Table 17. *Years of Education and RAVLT Immediate Memory T-scores as Predictors of WAIS-R Vocabulary Subtest Scores* (n = 28)

Predictors	R^2	beta	R^2 change	df	F	*p*
Step 1: Education	.293	.541	**.293**	1,26	10.758	**.003**
Step 2	.367					
Education		.386	**.113**	1,25	4.461	**.045**
Immediate memory		.314	.075	1,25	2.955	.098

Table 18. *Years of Education and RAVLT Delayed Recall T-scores as Predictors of WAIS-R Vocabulary Subtest Scores* (n = 28)

Predictors	R^2	beta	R^2 change	df	F	*p*
Step 1: Education	.293	.541	**.293**	1,26	10.758	**.003**
Step 2	.309					
Education		.485	**.197**	1,25	7.145	**.013**
Delayed recall		.141	.017	1,25	.601	.445

Table 19. *Years of Education and RAVLT Recognition T-scores as Predictors of WAIS-R Vocabulary Subtest Scores* (n = 27)

Predictors	R^2	beta	R^2 change	df	F	*p*
Step 1: Education	.298	.546	**.298**	1,25	10.608	**.003**
Step 2	.311					
Education		.480	**.172**	1,24	5.988	**.022**
Recognition		.132	.013	1,24	.453	.507

Site 2

WTAR scores are missing for two participants because one was illiterate and one was visually impaired. The mean WTAR was 93.12 (± 17.28 SD, range 53-126). Pearson correlations between the WTAR and HVLT T-scores, controlling for education, are presented in Table 20.

Table 20. *Pearson Correlations among WTAR Scores, HVLT Memory T-scores, and Years of Education*

	n	*r*	r^2
	68		
WTAR and Immediate memory		.596***	.355***
WTAR and Education		.579***	.335***
Immediate Memory and Education		.355**	.126**
	68		
WTAR and Delayed recall		.561***	.315***
WTAR and Education		.579***	.335***
Delayed recall and Education		.345**	.119**
	66		
WTAR and Recognition		.335**	.112**
WTAR and Education		.596***	.355***
Recognition and Education		.126 (*ns*)	.016 (*ns*)

**$p < .01$. *** $p < .001$.

All of the correlations between the WTAR, HVLT T-scores, and education are statistically significant. At least 33% of the variance in WTAR scores can be explained by the variance in years of education. Likewise approximately 12.6% of the variance in WTAR scores can be explained by the variance in immediate memory T-scores. Approximately 11.9% of the variance in delayed recall T-scores, but only 1.6% of the variance in immediate memory T-scores, can be explained by the variance in years of education.

Hierarchical regression analyses were performed to determine the effect of the three elements of verbal memory (immediate memory, delayed recall, and recognition) on WTAR scores, after controlling for the contribution of education. As shown in Table 21, education was entered into the first step and it explained 33.5% ($p = .000$) of the variance in WTAR scores. When immediate memory was added to the second step, it explained an additional 17.5% ($p = .000$) of the variance. As shown in Table 22, when delayed recall was added to the second step after education, it explained an additional

14.8% (p = .000). As shown in Table 23 education explained slightly more of the variance (35.5%, p = .000) in WTAR scores due to the number of participants being smaller by two, but when recognition was added to the second step, it explained only an additional 6.9% (p = .008). There was a moderate correlation between the WTAR score and education, moderate correlations among the WTAR and immediate memory and delayed recall, and weaker correlations among the WTAR score and recognition and between education and the three verbal memory elements. None of the verbal memory elements explained the variance in the WTAR score more than education did; only immediate memory uniquely explained about 2% more variance than education in the WTAR score.

Table 21. *Years of Education and HVLT Immediate Memory T-scores as Predictors of WTAR Scores* (n = 68)

Predictors	R^2	beta	R^2 change	df	F	p
Step 1: Education	.335	.579	**.335**	1,66	33.316	**.000**
Step 2	.510					
Education		.421	**.154**	1,65	20.494	**.000**
Immediate memory		.447	**.175**	1,65	23.117	**.000**

Table 22. *Years of Education and HVLT Delayed Recall T-scores as Predictors of WTAR Scores* (n = 68)

Predictors	R^2	beta	R^2 change	df	F	p
Step 1: Education	.335	.579	**.335**	1,66	33.316	**.000**
Step 2	.484					
Education		.438	**.169**	1,65	21.243	**.000**
Delayed recall		.411	**.148**	1,65	18.697	**.000**

Table 23. *Years of Education and HVLT Recognition T-scores as Predictors of WTAR Scores* (n = 66)

Predictors	R^2	beta	R^2 change	df	F	p
Step 1: Education	.355	.596	**.355**	1,64	35.272	**.000**
Step 2	.424					
Education		.563	**.311**	1,63	34.106	**.000**
Recognition		.264	**.069**	1,63	7.508	**.008**

Analyses of combined sites were not conducted because Site 2 had not determined the range of scores to distinguish between normal adults and adults with cognitive impairment.

CHAPTER VI

DISCUSSION

Meaning of Findings in Relation to Hypotheses

Cognitive deficits in older people with heart failure are poorly understood and more research is needed. It is not clear if the cognitive deficits are the result of ageing in general or of heart failure in particular and if the cognitive deficits are due to global cerebral changes or to changes in specific areas of the brain. There is no agreement if it is better to use a specific and sensitive neuropsychological test to assess general cognitive performance or if it is more practical, and just as sensitive and specific, to use parts of various neuropsychological tests to assess specific regions of the brain, provided medical science knows which regions are affected by heart failure.

Hypothesis 1

Older people with heart failure have significantly greater immediate memory and delayed recall impairment than recognition impairment. Results from this study do not support the first hypothesis.

Slightly more than half of the Site 1 participants, when stratified by decade age group, scored within the normal range (< 1 SD below the mean) for immediate memory (58.6%) and delayed recall (55.2%), but most scored within the normal range for recognition (75%). Delayed recall was impaired in 41.4% of the participants, however, followed closely by impaired immediate memory in 37.9%. Only 14.3% of the Site 1 participants had impaired recognition. Less than half of the Site 2 participants, when stratified by decade age group, scored within the normal range for immediate memory

(44.3%), but half or more scored within the normal range for delayed recall (50%) and recognition (55.9%). Immediate memory was impaired in 42.9% of the participants, whereas recognition was impaired in only 36.8% and delayed recall in only 32.9% of the participants. The two sites differed in that Site 1 had more participants with 13 or more years of education, and Site 2 had more participants who were 80 years old or more, many of whom had impaired immediate memory (72.8%) and impaired recognition (63.6%).

In the analysis of the 99 older people with heart failure, however, there were no differences between the mean immediate memory, delayed recall, and recognition T-scores. There were no statistically significant, within-participant differences between the immediate memory, delayed recall, and recognition T-scores at Site 1, at Site 2, or when both sites were combined. When contrasts were computed, the only significant difference was that the participants' delayed recall T-scores were better than their immediate memory T-scores.

Immediate memory is an intermediate step to memory consolidation and is most affected by age. Duff, Schoenberg, Scott, and Adams (2005) found a significant covariation between verbal memory and executive functioning, lending strength to the suggestion that the frontal lobes might be a central system that impacts hippocampal memory, particularly immediate and delayed recall. Is there an association between heart failure in older people and frontal lobe dysfunction? And, is the often observed cognitive impairment related more to impaired executive functioning than to impaired verbal memory (Insel, Morrow, Brewer, & Figueredo, 2006)?

Hypothesis 2

The magnitude of the correlation between immediate memory and delayed recall is stronger than the correlation between immediate memory and recognition or between delayed recall and recognition. Results from this study support the second hypothesis.

In the Site 1 sample, there is a statistically significant strong correlation between immediate memory and delayed recall ($r = .822$, $p < .001$). This means that, if a participant performs well on the immediate memory element of the verbal memory test, he or she will also perform well on the delayed recall element. Likewise, if a participant performs poorly on the immediate memory element of the verbal memory test, he or she will also perform poorly on the delayed recall element. There is a moderately strong and statistically significant correlation between immediate memory and recognition ($r = .635$, $p < .001$) and between delayed recall and recognition ($r = .655$, $p < .001$). This less strong correlation may be explained by the low number of participants who had impaired recognition. The results from Site 2 are very similar; there is a statistically significant strong correlation between immediate memory and delayed recall ($r = .802$, $p < .001$). There are moderately strong and statistically significant correlations between immediate memory and recognition ($r = .598$, $p < .001$) and between delayed recall and recognition ($r = .628$, $p < .001$). These very similar correlations suggest consistency of association between verbal memory elements, regardless of the test used.

Immediate memory is a test of rote learning, but it involves a number of neurobehavioral mechanisms, including attention, hearing, short-term memory, storage, and retrieval (Lezak et al., 2004). Delayed recall measures retention and memory retrieval. Recall after 20 minutes assesses learning capacity and components of memory

processing, including encoding, consolidation, and retrieval (Woods et al., 2005); an interference introduced between learning and recall, as in the RAVLT, interrupts continuous rehearsal. When recall is poor, it cannot be determined whether the problem is due exclusively to retrieval or also to learning. Recognition, after a 20-minute delay, assesses learning and memory storage, bypassing simple recall. Recognition does not use memory retrieval and so may be a better reflection of memory storage than recall (Vakil & Blachstein, 1993). Recognition is easier than free recall, but it also assesses a person's capacity to discriminate when or with what other information a word was learned. Comparing a person's delayed recall and recognition scores may measure spontaneous retrieval efficiency, but recognition may be a little better than recall if a person simply cannot retain new information (Lezak et al., 2004).

Hypothesis 3

The correlations among immediate memory, delayed recall, and recognition do not depend on the specific test used to measure these components of memory. Results from this study support the third hypothesis.

There were no statistically significant interactions between each of the three verbal memory T-scores and site. In this sample, therefore, it did not make a difference which verbal memory test was used. Age, gender, and ethnicity had little effect on any of the predictive relationships between verbal memory elements. In each of the three relationships that were analyzed (immediate memory and delayed recall, immediate memory and recognition, and delayed recall and recognition), only the verbal memory element mean T-score had a statistically significant effect as a predictor of explained variance. Only the RAVLT delayed recall T-score had a statistically significant effect as

a predictor of the explained variance in recognition T-scores. Most likely this was due to a statistically significant difference in mean recognition T-scores between sites ($p = .018$), with the Site 1 mean score (46.5) being higher than the Site 2 mean score (39.28). Thus, in this sample the correlations among immediate memory, delayed recall, and recognition did not depend on whether the RAVLT or the HVLT was used.

The RAVLT is sensitive to verbal memory impairment in people with various neurological diagnoses (Lezak et al., 2004; Mitrushina et al., 2005), and immediate memory and delayed recall scores below the normative value may predict the development of Alzheimer's disease (Tierney et al., 1996). The HVLT is a good screening test for dementia, and it discriminates well among various subtypes of dementia, but it is not sensitive to mild cognitive impairment (Hogervorst et al., 2002; Lacritz et al., 2001). There are no published comparisons of the RAVLT and the HVLT in general, however, and none that compare the two verbal memory tests in older people with heart failure.

If there are no differences in the correlations among immediate memory, delayed recall, and recognition when larger samples are tested, the test that is used, then, may be less important than its brevity, ease of use, and its sensitivity and specificity to detect disease-influenced fluctuations in cognition or cognitive impairment in older people with heart failure but without a diagnosis of dementia. Relative to these characteristics, the HVLT is easier to administer than the RAVLT, but it may not be as sensitive to mild impairment, and it does not test for recall after a distractor (Kuslansky et al., 2004)

Hypothesis 4

The correlation between estimates of premorbid intelligence and verbal memory scores, controlling for education, is high. Results from this study do not support the fourth hypothesis. None of the RAVLT verbal memory scores significantly explained the variance in the WAIS-R Vocabulary subtest scores after controlling for education, and none of the HVLT verbal memory scores explained the variance in the WTAR more than education did. Although the WTAR was published in 2001, the few published studies involving its use investigated people with brain injuries. No conclusions can be made at this time because the WAIS-R Vocabulary subtest and the WTAR cannot be compared.

It is interesting that both the RAVLT and the HVLT immediate memory T-scores explained more variance in intelligence scores and recognition T-scores the least, when controlling for years of education. This is consistent with the theory that immediate memory reflects learning, delayed recall reflects memory processing, and recognition reflects memory storage but does not use memory retrieval. The RAVLT uses familiar words from a low reading level, so intelligence and years of education may be a weak influence (Vakil & Blachstein, 1993), although this effect cannot be seen in Site 1, perhaps due to the low number of participants. HVLT scores are positively correlated with education level (Benedict et al., 1998; Frank & Byrne, 2000); this effect was seen in Site 2 participants.

Intelligence, education, and cognitive performance in early adult years appear to reduce the impact of aging on memory (Fritsch et al., 2005; Plassman et al., 1995). General intelligence strongly affects memory scores and executive functioning scores (Duff et al., 2005). The WAIS-R Vocabulary subtest may be less affected by brain

dysfunction than tests that require oral definitions (Lezak et al., 2004). A reading test, such as the WTAR that includes reading recognition, assuming that a participant has developed reading skills normally, may provide a more accurate prediction of the premorbid intelligence that remains relatively stable during normal aging (The Psychological Association, 2001).

Significance

It is interesting to recall now the one participant who was excluded from Site 1 analysis because he was unable to recall any words, beginning with the first trial of the RAVLT . This African American man was more than 80 years old, single, had a grammar school education, and had NYHA Class IV heart failure. Self-management is synonymous with cognitive decision-making in response to clinical signs and symptoms (Riegel, Carlson, & Glaser, 2000). Given his significant memory impairment, the participant was unlikely to adhere to a prescribed diet, to comply with a fluid and medication regimen, to recognize and respond to symptoms, and to make appropriate decisions, especially because he lived alone.

If there were a pragmatic, specific, and sensitive screening tool to assess the impact of heart failure on cognitive function that could be used in varied practice settings (e.g., primary care, acute care, home health care), the test results could then be used (a) to revise treatment strategies (e.g., simplify medication regimens or clarify reportable symptom guidelines), (b) to improve symptom stability in older persons with heart failure, (c) to improve self-management, especially in older people who live alone, and (d) to decrease the risk of early rehospitalization (S. J. Bennett et al., 1997; McLennan, Pearson, Cameron, & Stewart, 2006).

Is the cognitive impairment in an older patient with heart failure exacerbation due to cardiac output that is insufficient to provide adequate cerebral perfusion, or is the cognitive impairment compounded by associated confounding comorbidities and age? If heart failure causes insufficient cardiac output to provide adequate cerebral perfusion, then cognitive dysfunction is likely due to hypoperfusion and hypoxia of vulnerable areas, especially the watershed zones of the brain (Pullicino et al., 2001; Roman, 2004). Heart failure severity and duration may have a general, global effect on the brain, or it may affect specific regions more selectively. Whether there is global, hemispheric, or regional impact, the brain compensates by using its complex neural circuitry so that functional domains in the brain interact and overlap. The challenge, therefore, is to identify which cognitive test elements sensitively measure changes in specific areas of the brain that are thought to be affected by heart failure.

Whether the impact of heart failure on the brain is global or regional, the impact on verbal memory elements is similar. If heart failure has a global effect on the brain, the impact then would be impaired learning (middle cerebral artery perfusion of most of the gray matter of the frontal, parietal, temporal, and occipital lobes) and impaired memory (anterior and middle cerebral artery perfusion of most of the white matter of the frontal, parietal, temporal, and occipital lobes). If heart failure-related hypoperfusion affects specific regions, such as the watershed zones, it should then differentially impact (a) verbal learning, immediate memory, delayed recall, and the imageability component of recognition (hippocampus, especially the CA1 and CA3); (b) memory retrieval and delayed recall (right frontal lobe); or (c) the integration of memory elements (posterior

cingulate gyrus which receives signals from the hippocampus and is part of the memory circuitry).

The hippocampus and the medial temporal lobes are critical to verbal learning. The hippocampus has direct connections to the entorhinal cortex, which projects to the cingulate and temporal lobe cortices and to the amygdala. The hippocampus is also associated with storing medium-term memory and with consolidating information into long-term declarative memory, including reference learning and memory. Memory consolidation requires pathway integrity between the hippocampal formation and the cerebral cortex. Research also suggests that hippocampal dysfunction may be more specifically related to impaired delayed memory than to immediate memory (Kramer et al., 2004) or recognition (Mayes, Holdstock, Isaac, Hunkin, & Roberts, 2002; Yonelinas et al., 2004). The anterior prefrontal cortex is probably involved with retrieval processes (Tyler, Marslen-Wilson, & Stamatakis, 2005); people with frontal lobe dysfunction and Alzheimer's disease have difficulty with delayed recall (Lezak et al., 2004).

Neural correlates associated with recognition are less well-understood, perhaps due to the integrated dynamics of verbal learning, retrieval, and recognition. Tyler et al. (2005) concluded that the anterior prefrontal cortex is involved with word recognition in addition to retrieval, and Klaver et al. (2005) concluded that medial temporal lobe processes, in general, are involved in recognition memory, and the hippocampus may be involved with imageability. Wang, Ulbert, Schomer, Marinkovic, and Halgren (2005) suggested that there are extended interactions between medial and lateral frontal and temporal sites, with anterior cingulate cortex modulation of network activity.

Understanding the impact of heart failure's trajectory and its exacerbations on specific regions of the brain and its relationship to memory impairment is not well-understood. Understanding the involvement of specific regions of the brain in memory decline, regardless of the cause, is an emerging science. Age-related hippocampal and frontal lobe cognitive changes are implicated in memory decline, as measured by recall or recognition (Huh, Kramer, Gazzaley, & Delis, 2006). Although Wixted and Squire (2004) proposed that recall and recognition are equally impaired when there is selective hippocampal damage, Yonelinas et al. (2004) disagreed, arguing that the etiology of cerebral hypoxia and amnestic severity is in dispute.

Limitations of the Study

Study Design

This study was a secondary analysis of two data sets. Secondary data analysis prevents control of data collection and entry problems, including problems with sampling, completeness of data, and data coding. Data for Site 2 normal control participants were not available, and the questions asked were limited, due to primary investigator prerogatives.

Data were obtained from two sites that are geographically distant. Despite what appeared to be differences between the two sites, each site was homogeneous and the participants' characteristics were not statistically significantly different. The sample sizes for Sites 1 and 2 were inadequate for hypothesis testing with confidence for most variables. Several participants were excluded, which reduced the total number from an ideal 100. One participant at Site 1 was completely excluded as described previously. At Site 2 two participants' recognition scores were deleted, and two could not complete the

WTAR. Heart failure severity and mortality is more prevalent in the oldest of old people (≥ 80 years old), which makes it difficult to obtain a large enough group of participants for the calculation of statistical significance. The small number of participants at each site did not allow significance in detecting site-specific R^2 changes when analyzing regressions for immediate memory, delayed recall, and recognition T-scores. Because the interaction between sites was not significant, however, the participants from both sites were merged, after which the hierarchal regression analyses did yield significant R^2 changes.

The participants at each site were predominantly Caucasian; there was one Asian participant and the others were African American. When the participants from both sites were merged for analysis, race was collapsed into two categories, Caucasian and African American/Asian. It is understood that each ethnic group has unique characteristics, but the African American/Asian label was preferred over *Other*.

Verbal Memory Tests

This study had two purposes: to examine the relationships among three elements of the RAVLT and the HVLT and to determine if the relationships among the verbal memory scores depended on the specific test used. The HVLT and the RAVLT are similar, auditorily administered tests that measure verbal learning and retention. The two verbal learning tests are considered by some, however, to be sufficiently different in construct as to be not comparable. The standard RAVLT test format has five trials, two word lists of 15 nouns each, a distractor, a 50-word matrix used to test recognition that includes the 30 nouns from the two word lists and 20 words that are phonemically or semantically similar to the 30 nouns, and the test takes 30 to 40 minutes to administer.

The HVLT has only three trials, a 12-word list from three semantic categories, no distractor, a 24-word list of 12 target words mixed with 12 distractor words to test recognition, and it takes only 5 to 10 minutes to administer. It would be interesting to compare participants' learning curves in the RAVLT (five trials) compared to the HVLT (three trials).

The RAVLT T-scores for immediate memory, delayed recall, and recognition were calculated for this study by using the means and standard deviations of healthy control participants, grouped by age decade, from the same study. Published norms for the RAVLT (Ferman et al., 2005; Ivnik et al., 1990) were not used. The HVLT T-scores were obtained from the Hopkins Verbal learning Test-Revised Professional Manual. Most participants had either normal (<1 SD below the mean) or impaired (≥1.5 SD below the mean) T-scores. The question therefore arises whether either test was sufficiently sensitive to detect more low normal scores (≥1 to <1.5 SD below the mean) that might be expected in older people with heart failure who might have cognitive impairment due to causes other than aging or heart failure, such as low premorbid intelligence or depression. Is recognition, which is stable in the presence of age-associated decline, less likely to be impaired than immediate memory or delayed recall in older people with heart failure? The degree of improvement in interpretative accuracy achieved by creating education-adjusted norms is not clear; age and general intellectual function may be better associated with test performance (Steinberg, Bieliauskas, Smith, & Ivnik, 2005).

To detect verbal memory impairment using a single test may be too difficult. Cognitive dysfunction may be reflected in many different processes: (a) impaired multimodal information processing, (b) cognitive flexibility, (c) attentional shifting,

(d) defective memory encoding and sensory integration, (e) episodic memory consolidation and retrieval, (f) declarative memory, (g) procedural learning, and (h) sensory-motor integration of executive functioning (Alves et al., 2005; Georgiadis et al., 2000; Lee et al., 2001; Pullicino et al., 2001; Roman, 2004; Woo et al., 2003).

Implications and Recommendations

Is limited neuropsychological testing sufficiently sensitive and specific to detect cognitive and verbal memory changes in older people with heart failure? Until more is known about the impact of heart failure-related hypoperfusion on specific regions of the brain, a comprehensive battery is required to detect the global cognitive versus specific verbal memory changes. The tests that are used with older people also need to differentiate between the different, cognitive functional abilities and to discriminate impairment associated with aging. There may also be sufficient differences in ceiling and floor sensitivities that significant measurement error occurs within and between neuropsychological tests (Mungas, Reed, & Kramer, 2003)?

Differences in verbal memory performance may also be affected by select variables, such as NYHA class, comorbid conditions, attention, depression, hearing, age, visual learning style, and education. The relationship between verbal memory scores and NYHA class need to be examined, especially if immediate memory, delayed recall, and recognition scores decline with progression in severity of NYHA classification.

Does it matter clinically which test is used? In this secondary analysis, there were no statistically significant differences between the RAVLT and the HVLT. Whatever test is used to assess recognition memory will need to include (a) more items, (b) fewer

learning trials to decrease the risk of a ceiling effect in normal participants, and (c) equal numbers of target and distractor words (Huh et al., 2006).

Future Research

Although inferences about causality cannot be made, the association between heart failure and verbal memory impairment appears to be sufficiently strong to support further research. It is important, however, to differentiate between difficulties with learning and poor retention that are associated with heart failure severity and aging. Heart failure symptom severity, stratified by NYHA class, however, may not correlate with heart function as measured by ejection fraction. Most studies do not differentiate between systolic and diastolic heart failure, but their findings imply that heart failure-associated hypotension is secondary to decreased left ventricular ejection fraction. Diastolic heart failure is associated with a normal left ventricular ejection fraction, and its prevalence increases with age and is highest in patients over the age of 75 years (Redfield et al., 2003). Future studies, therefore, should include the specific type of heart failure, as approximately half of older patients with chronic heart failure have diastolic heart failure with a normal ejection fraction. No published studies, however, have shown if the neurological effect of systolic heart failure is the same as diastolic heart failure.

To determine if verbal memory impairment is associated with heart failure severity, the consequences of the trajectory of heart failure, or with aging, a prospective, repeated measures study with age-matched, normal, control participants is needed. General intellectual functioning, ejection fraction, NYHA classification, and comprehensive memory testing would be assessed at baseline, and NYHA classification and limited memory testing would be repeated during each heart failure exacerbation.

Repeated measures of ejection fraction and comprehensive memory testing would not be tolerated or feasible during an episode of heart failure exacerbation. A comparison of memory scores in general and verbal memory scores in particular, NYHA class, and ejection fraction support the hypothesis that impaired cognition is due more to reduced cerebral blood flow during an exacerbation of heart failure, within the context of the heart failure trajectory, than to aging.

Clinicians could benefit from a pragmatic, specific, and sensitive tool to screen patients for heart failure-influenced cognitive fluctuations, so that they could revise treatment strategies to improve symptom stability, especially for the older person with heart failure who lives alone. If, for example, further research suggests that heart failure compromises verbal memory more than other elements of cognition, can one element of verbal memory be selected from memory test performance and used clinically. If a screening tool for heart failure-influenced, cognitive fluctuations were relevant, practical, brief, and sensitive, clinicians could assess cognitive performance as part of the routine management of older patients with heart failure. Significant fluctuations or lower functioning may herald an exacerbation of heart failure, indicating the need for immediate treatment. Clinicians could then evaluate their patients for impaired cognitive function, and their interventions would include simplifying medication regimens, clarifying guidelines for reportable symptoms, issuing written instead of verbal instructions, and involving family members or other caregivers. The expected outcome is to improve a patient's immediate health, but it should also prompt clinicians to reassess how well their patients can manage their heart failure.

Conclusion

Antonelli Incalzi et al. (2003) concluded that memory deficits are relatively common in people with heart failure; immediate memory was affected by worsening heart failure, whereas forgetting was uniformly high but did not increase with the severity of heart failure. Cognitive performance in people with heart failure has been found to be significantly worse than for older people of the same age without heart failure (Acanfora et al., 1996; Almeida & Tamai, 2001a; Cacciatore et al., 1998; Staniforth et al., 2001). The degree of heart failure severity, when classified by the NYHA system, may also be correlated with cognitive performance (Antonelli Incalzi et al., 2003; Cacciatore et al., 1998; Callegari et al., 2002; Gorkin et al., 1993), especially verbal memory (Antonelli Incalzi et al., 2003). Attention, memory, learning, executive function, working memory, and psychomotor speed may be affected by exacerbations of heart failure or by the cumulative effects of heart failure's trajectory.

Heart failure severity, heart failure duration, comorbid conditions, and age may have different effects on verbal memory. A more systematic evaluation is needed of the possible relationships between heart failure and associated cognitive function in general, and verbal memory impairment in particular, and between heart failure and cognitive function associated with aging.

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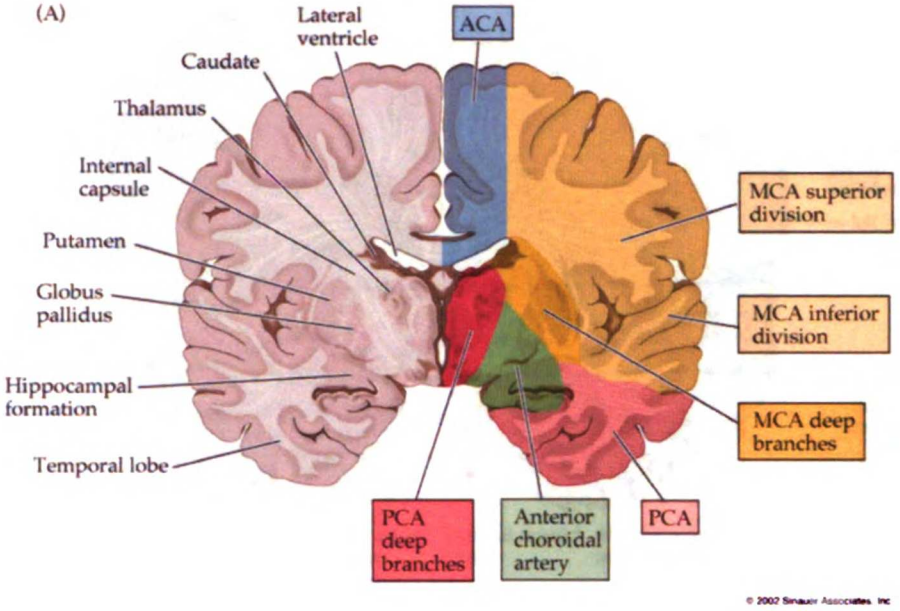
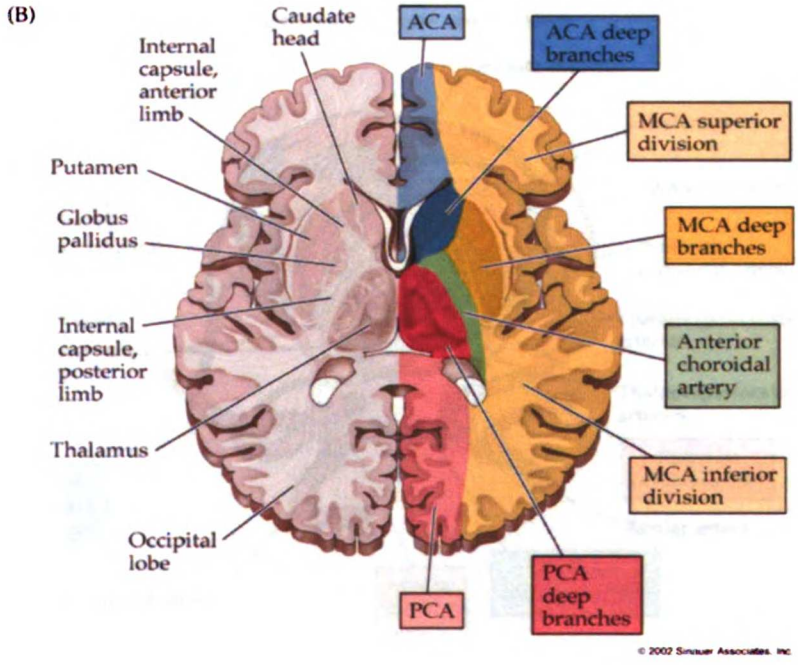
APPENDIX A. Internal Carotid and Vertebral Artery Cerebral Blood Supply

Superficial and Deep Arterial Supply to the Cerebral Hemispheres: Coronal Plane



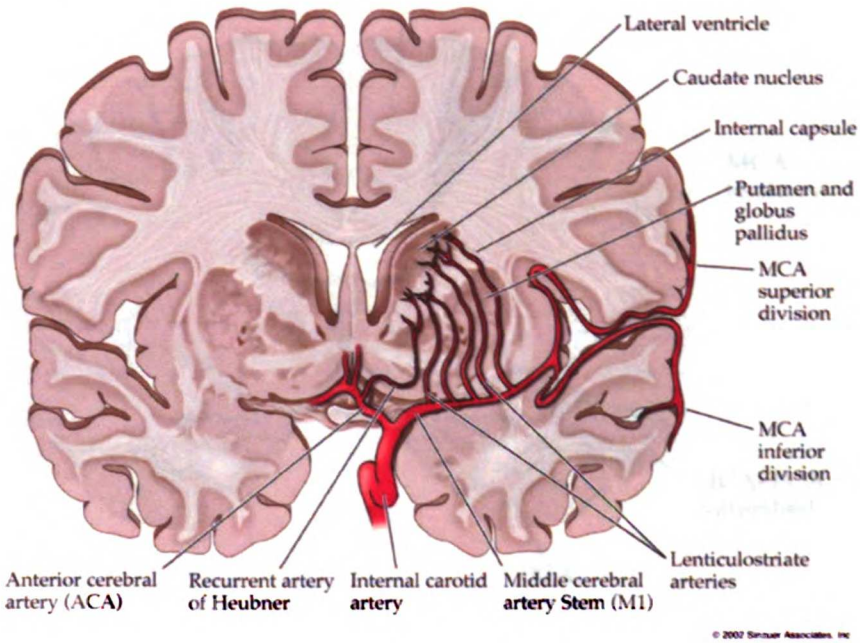
Superficial and Deep Arterial Supply to the Cerebral Hemisphere: Horizontal Plane



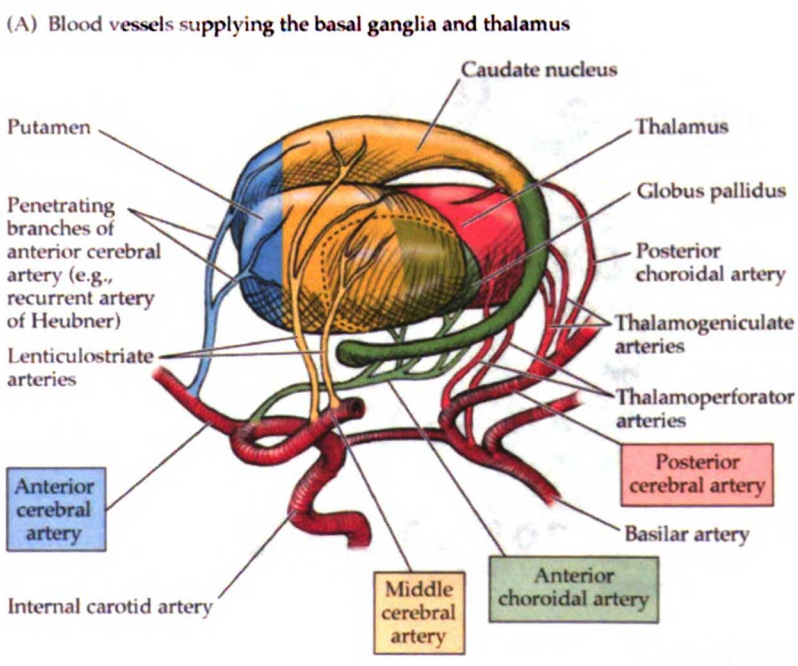
Source: http://web.odu.edu/webroot/instr/sci/kcarson.nsf/files/Chapter10.ppt/$file/Chapter10.ppt

APPENDIX B. Terminal Artery Cerebral Blood Supply

Lenticulostriate Arteries Supply the Basal Ganglia and Internal Capsule



Arterial Supply of the Thalamus and Basal Ganglia



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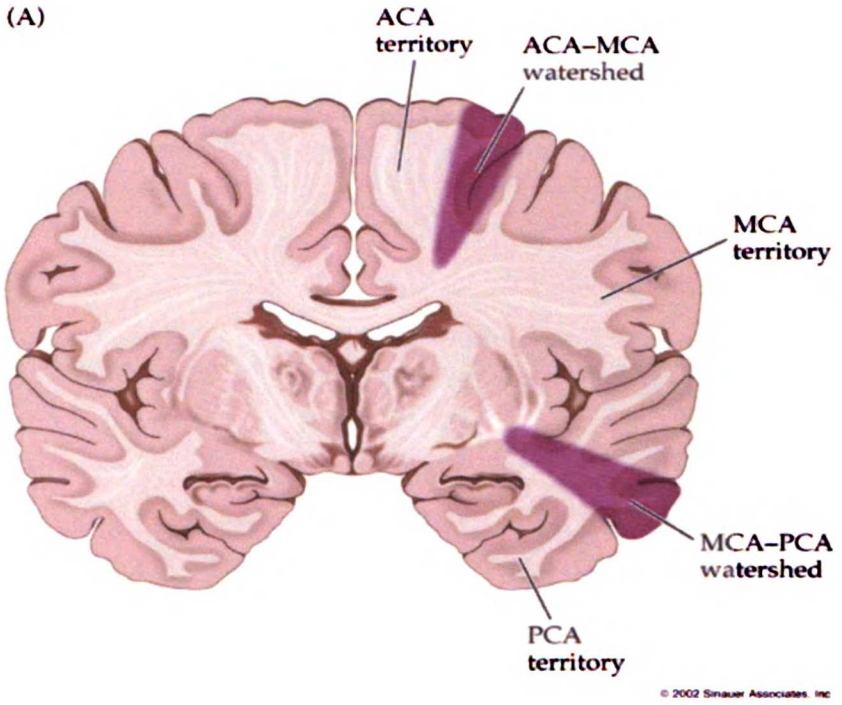
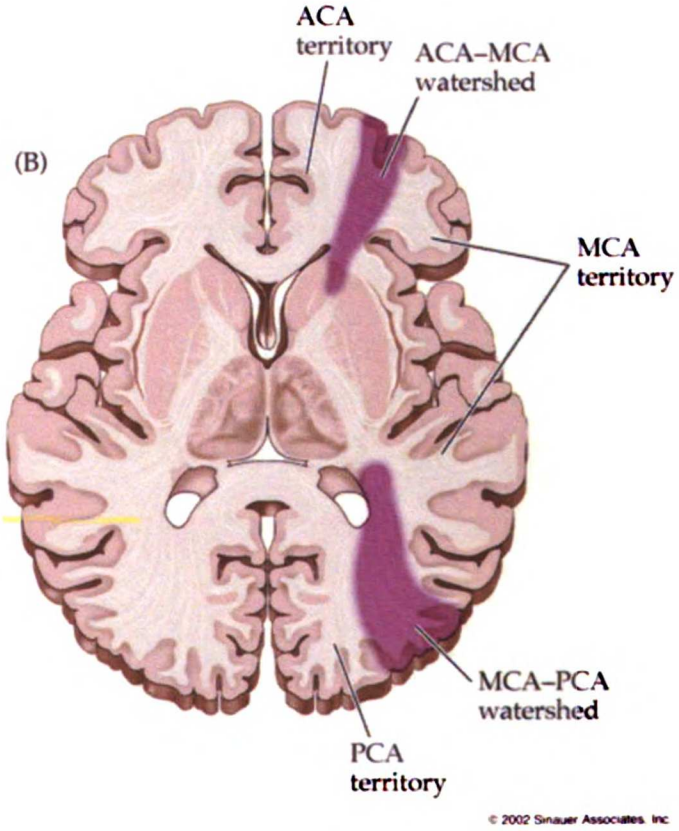
APPENDIX C: Watershed Zones





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