THE EFFECTS OF EXERCISE ON COGNITIVE FUNCTION IN OLDER ADULTS WITH HEART FAILURE: AN INTERVENTIONAL STUDY

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by

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CHAPTER I: INTRODUCTION

Heart failure (HF) is a clinical syndrome in which the heart is unable to pump enough blood to meet the body’s metabolic needs and is characterized by the symptoms of fatigue, dyspnea and fluid retention (Roger et al., 2012). HF represents the final common pathway of many conditions that damage the heart. Hypertension is the most common risk factor for HF, with 75% of cases having antecedent hypertension (Roger et al., 2012). Another leading cause of HF is coronary artery disease, which is found in approximately two thirds of HF patients (Mehta & Cowie, 2006). Other contributors to the development of HF include chronic arrhythmias, valvular heart disease, diabetes, alcohol abuse, and infections (Cowie et al., 1997; Rosamond et al., 2008).

HF has become a worldwide epidemic as a result of an aging population, improved prognosis (Roger et al., 2004), and high rates of cardiovascular risk factors (Rich, 2001). The prevalence of HF is striking, affecting nearly 6 million adults in the United State alone. It is estimated that an additional 3 million people will develop HF by 2030, representing a 25% increase in prevalence from 2010 (Roger et al., 2012). The prevalence of HF is highest among older adults, occurring in 10 in 1000 people over the age of 65 (Roger et al., 2012).

Cardiovascular disease is the leading cause of death worldwide, with HF being responsible for more than one-third of those deaths. In 2008, HF was implicated in more than a quarter million deaths in the U.S. (Roger et al., 2012). Despite improved survival rates, the 5-year mortality rate remains at 50-60% of all HF patients (Levy, et al., 2002; Rusinaru, et al.,
2009). In addition to premature death, HF also produces significant individual and financial burden through frequent rehospitalization and high medications costs. HF is the most common reason for recurrent hospitalization and generates approximately $30 billion in health care costs per year in the United States (Dunlay et al., 2009). HF also leads to greater disability and poorer quality of life (Adams & Zannad, 1998; Bennet et al., 1997).

**Heart Failure and Neurocognitive Function**

In addition to these medical and psychosocial consequences, HF is also a risk factor for adverse neurological outcomes, including Alzheimer’s disease, vascular dementia (Qiu et al., 2006) and stroke (Wolf, Kannel, & McNamara, 1970; Witt et al., 2007). Recent work shows that HF is associated with cognitive impairment long prior to the onset of these conditions (Bennett & Sauve, 2003), with the prevalence of cognitive impairment in non-demented persons with HF estimated to be between 25 and 75 percent (Vogels, Scheltens, Schroeder-Tanka, & Weinstein 2007). Deficits in HF patients have been observed in nearly all cognitive domains, including attention, executive function, learning and memory, language, visuospatial functioning and psychomotor speed (Almeida & Flicker, 2001; Beer et al., 2009; Bennett & Sauve, 2003; Dardiotis et al., 2012; Pressler et al., 2010; Vogels et al., 2007Vogels, et al., 2007a).

Consistent with this pattern of cognitive impairment, HF patients exhibit many brain abnormalities on neuroimaging, including cortical atrophy (Woo et al., 2003), cerebral infarcts (Almeida et al., 2005; Schmidt Fazekas, Offenbacher, Dusleag, & Lechner, 1991), and white matter changes (Beer et al., 2009), such as increased white matter hyperintensities (WMH) (Schmidt et al., 1991; Vogels, et al., 2007b) and reduced white matter integrity (Kumar et al.,
Left medial temporal lobe atrophy and deep white matter hyperintensities are directly linked to poor performance on neuropsychological testing, including deficits on tests of visuospatial, executive functioning, visual memory and verbal learning (Beer et al., 2009). Similarly, greater medial temporal lobe atrophy was associated with poorer performance on tests of memory, executive function and global cognition, independent of cardiovascular risk factors in a sample of HF patients (Vogels et al., 2007).

**Can cognitive function be improved in HF?**

The trajectory of cognitive impairment and possible decline in HF remains poorly understood. Despite being a known risk factor for degenerative disorders like Alzheimer’s disease and vascular dementia (e.g., Qiu et al., 2006), two recent studies found that cognitive function remains relatively stable over short time intervals in patients with mild HF (Almeida et al., 2012; Riegel et al., 2012). Moreover, there is research to suggest that the cognitive deficits of HF may be at least partly reversible. For example, a sample of 40 well-managed HF patients showed subtle improvements in cognitive function over a 12 month period, particularly in the areas of attention and executive function (Stanek et al., 2009). Though the exact mechanisms for these cognitive gains are unclear, it appears most likely attributable to improved medical oversight for the study participants (Stanek et al., 2009). Similarly, other studies have shown improved cognitive function in persons with HF as a result of medical intervention, including cardiac transplantation (Bornstein et al., 1995; Gruhn et al., 2001; Bennet & Suave, 2003; Massaro et al., 2006) pacemaker and cardiac assist device implantation (Zimpfer et al., 2006; Petrucci et al., 2009), and initiation of treatment with ACE inhibitors (Zuccala et al., 2005;
Almeida & Tamai, 2001). In each case, improved cardiac function was associated with better cognitive function after treatment. Taken together, these results suggest that cognitive impairment in HF may be at least partially reversible through improved cardiovascular function.

**Can Exercise Improve Cognitive Function in HF?**

In addition to these medical interventions, it appears likely that structured exercise could also improve cognitive function in HF. Exercise interventions have been linked to improved neurocognitive outcomes across patient and healthy samples (Colcombe & Kramer, 2003; Palleschi et al., 1996). Aerobic exercise is linked to increased gray and white matter volume (Colcombe et al., 2006) and increased functional connectivity in the prefrontal cortex (Voss et al., 2010). The most consistent effects of aerobic exercise on cognition have been in executive functioning, although several investigations have found improvements in other domains such as attention, visuospatial functioning, processing speed (Dustman et al., 1984; Albinet, Boucard, Bouquet, & Audiffren, 2010; Blumenthal et al., 1991). For example, Voss and colleagues (2012) demonstrated that one-year of exercise training was associated with improved working memory performance. Even exercise at low intensities has been shown to improve attention (Hassmen et al., 1992), memory (Ruscheweyh et al., 2011), and concentration (Stevenson & Topp, 1990).

Research on the cognitive benefits of exercise in HF is limited, though existing work is encouraging and suggests likely benefit. Only one study has directly examined the possible effects of an exercise training program on cognitive function in patients with HF (Tanne et al., 2005). This study examined the benefits of twice weekly aerobic exercise at 60-70% of maximal heart rate for 35 minutes. Results demonstrated that individuals who participated in exercise
showed improvements in attention/psychomotor speed and executive function. Unfortunately, these findings are limited by a small number of participants in the intervention (n = 18) and control group (n = 5) and potential baseline differences in cognitive function between these groups were not examined.

Consistent with these possible benefits of exercise, two recent studies have examined the link between fitness levels and cognitive function in HF. One study found that greater metabolic equivalents (METs) from a standardized stress test was related to better performance on measures of attention ($\beta = .41, p = .03$), executive function ($\beta = .37, p = .04$), and memory ($\beta = .46, p = .04$) even after controlling for important medical and demographic characteristics, (Garcia et al., 2013). Similarly, another study examined the association between exercise capacity, estimated by distance walked on the 6-minute walk test, and cognitive function in 80 elderly patients with HF. As above, results showed that greater exercise capacity was associated with better cognitive function (Baldasseroni et al., 2010). Overall, the current evidence seems to suggest that the cognitive benefits achieved through exercise extend to persons with HF.

**CBF as mechanism for improved cognitive function with exercise in HF**

A likely mechanism is improved cerebral blood flow (CBF). Patients with HF show a 30% reduction in global cerebral blood flow (CBF) (Gruhn et al., 2001) and the degree of reduction is inversely related to HF severity (Loncar et al., 2011). Typically, CBF reductions are greatest in posterior cortical areas (Alves et al., 2005) but have also been observed in specific areas of the brain important for cognitive function including the frontal, temporal, and parietal lobes (Alves, et al., 2005; Burra et al., 2002; Vogels, et al., 2008).
A number of cardiac and vascular factors contribute to reduced CBF in HF. Briefly, HF typically involves left ventricular dysfunction resulting in reduced cardiac output (CO), or the volume of blood leaving the heart into systemic circulation per minute (Irani, 2010). Decreased CO may lead to lowered systemic blood flow, ultimately causing reduced CBF (Saxena & Schoemaker, 1993). Although autoregulatory mechanisms typically maintain CBF levels in the presence of reduced CO (van Beek et al., 2008), these mechanisms become less effective with age (Heckman, 2007) and can fail in advanced stages of HF (Choi et al., 2006). In addition to reduced CO, CBF depends on the ability of cerebral blood vessels to dilate in response to reduced pressure which may be impaired in HF. More specifically, vascular smooth muscle is located just outside of the endothelium (cells that line all of the body’s blood vessels) and controls peripheral vascular resistance, tone, blood distribution (Miller, Haynes, & Moser, 2010). However, endothelial function is often impaired in HF which can lead to sustained systemic vascular resistance and ultimately, reduced cerebral perfusion. In summary, mounting evidence suggests that it is the combination of reduced CO, impaired cerebral autoregulation, and vascular dysfunction that leads to decreased cerebral perfusion and ischemic damage in patients with HF.

**Reduced CBF leads to poor neurocognitive outcomes**

Consistent with the notion that reduced CBF produces cognitive impairment in persons with HF, reduced CBF is linked to cognitive dysfunction in persons with neurological conditions like mild cognitive impairment (Hirao et al., 2005), Alzheimer’s disease (Binnewijzend et al., 2012), and vascular dementia (Gao et al., 2012). Reductions in CBF have also been shown to predict cognitive decline in patients with MCI (Hirao et al., 2005) and in those with cerebral 

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small vessel disease (Kitagawa et al., 2009). Other research clearly links reduced CBF and neuropathology, including increased volume of WMH (Bastos-Leite et al., 2008; Tzourio et al., 2001) and decreased white matter integrity (Uh et al., 2010).

Reduced CBF is also related to poorer cognitive function in HF. In one study, resting regional CBF in elderly patients with HF was compared to healthy age-matched controls using single-photon emission computed tomography (SPECT). Individuals with HF showed reduced CBF in posterior cortical regions of the brain and lower performance in global cognition and on visual and verbal memory, learning, and language tests. Importantly, global cognition was significantly associated with CBF in the posterior cingulate cortex and precuneus (Alves et al 2005). Another study found that global cognition, measured by performance on the Mini Mental Status Exam (MMSE), was significantly positively associated with CBF velocity of the right middle cerebral artery (MCA) (Jesus et al., 2006).

Intervention studies have shown that increased CBF is linked to improvements in cognitive function in HF. As above, many of the HF treatments that have been shown to improve cognitive function (e.g., cardiac transplantation, pacemaker implantation, ACE inhibitors) are also known to improve CBF (Choi et al., 2006; Massaro et al., 2006; Gruhn et al., 2001). Several studies have shown that although CBF is reduced at baseline, they become normalized following cardiac transplantation representing an increase of up to 30% (Choi et al., 2006; Massaro et al., 2006; Gruhn et al., 2001). Similar effects have been observed following implantation of a pacemaker (van Bommel et al., 2010). Finally, in patients with severe HF, CBF improved by approximately 12ml/100g per minute following the initiation of treatment with an ACE inhibitor and normalized over time (Rajagopalan et al., 1984). Given that HF treatment such as cardiac
transplantation, pacemaker implantation and ACE inhibitors have been shown to both improve cognitive function and increase CBF, it can be reasoned that increases in CBF may be an important mechanism for improved cognitive function in HF patients.

**Can exercise improve CBF and cognitive function in HF?**

Exercise may increase CBF in HF through a series of cardiac and vascular benefits. In HF patients, exercise has been shown to improve cardiac function in terms of reducing resting HR (Dubach et al., 1997; Erbs et al., 2003; Hambrecht et al., 2000; Silva et al., 2002) and resting LV end-diastolic diameter (Hambrecht et al., 2000), and increasing CO (Hambrecht et al., 2000) and stroke volume (Dubach et al., 1997; Erbs et al., 2003; Hambrecht et al., 2000). In terms of vascular functioning, the benefits of exercise for HF patients include decreased peripheral resistance and sympathetic activation (Hambrecht et al., 2000), increased vasodilatory capacity (Linke et al., 2001) and blood flow (Hambrecht et al., 2000), and improved endothelial function (Linke et al., 2001).

Exercise likely improves CBF in HF patients through the associated improvements in cardiac and vascular function known to mediate CBF. Consistent with this notion, a growing body of literature shows aerobic exercise has beneficial effects on CBF in non-HF populations (Hellstrom et al., 1996; Ogoh and Ainslie, 2009). Recent research has demonstrated that 12 weeks of aerobic exercise was associated with both improved CBF and cognition in healthy older adults (Chapman et al., 2013). In another study, higher resting CBF levels were found among older master athletes when compared to sedentary older adults (Thomas et al., 2013). There is also a large body of literature linking increased fitness levels to increased CBF (e.g., Ainslie et
al., 2008; Brown et al., 2010). As increased fitness is the result of exercise training (Caspersen, Powell, & Christenson, 1985), it appears likely that exercise may also have beneficial effects on CBF levels. See Figure 1.

Figure 1: Mechanisms for Improved Cognitive Function with Exercise in Patient with Heart Failure

As a result, further research is much needed to clarify the possible cognitive benefits of exercise in persons with HF.

**Exercise Intensity and Cognitive Function**

When examining the benefits of exercise on cognitive function in HF, it is important to consider recent research highlighting the role of exercise intensity (Angevaren et al., 2007;
Brown et al., 2012). Specifically, higher intensity of self-reported physical activity is associated with improved processing speed, memory, executive function, and global cognition (Angevaren et al., 2007). A more recent study showed that objectively measured intensity of physical activity—not amount—was associated with cognitive function in healthy older adults (Brown et al., 2012).

No study has examined the role of exercise intensity for cognitive outcomes in HF. This omission is regrettable, as the cardiac and vascular benefits of exercise in HF appear to vary by intensity. Moderate- to high-intensity aerobic exercise has been shown to improve cardiac function in terms of increasing CO (Sullivan, Higgibotham, & Cobb, 1988; Hambrecht et al., 2000) and stroke volume (Dubach et al., 1997; Hambrecht et al., 2000; Erbs et al., 2003) and reducing LV end-diastolic diameter (Hambrecht et al., 2000) and improve vascular functioning in terms of decreasing peripheral resistance (Hambrecht et al., 2000) and increasing vasodilatory capacity (Linke et al., 2001) and blood flow (Hambrecht et al., 1997). When combined with the above findings, these results suggest that exercise will improve CBF in persons with CBF, with higher intensity exercise producing larger gains in CBF. In turn, greater CBF will lead to better cognitive function in this population at high risk for cognitive decline and neurological conditions like Alzheimer’s disease and vascular dementia.

**The Present Study**

The present study examined the neurocognitive benefits of a 12-week structured exercise program (i.e. cardiac rehabilitation (CR)) in a sample of older adults with HF. More specifically, it assessed whether participation in CR was related to increased CBF and ultimately improved
cognitive function. These aims were accomplished by examining performance on measures of cognitive function and CBF levels before and after completion of CR.

Specific Aims

Aim 1: Examine the cognitive benefits of CR on cognitive performance in older adults with HF.

Hypothesis 1: HF patients who participate in CR will exhibit improvements in attention, executive function, and memory from baseline to 12-week follow-up when compared to matched HF controls. Language function is hypothesized to remain relatively stable.

Aim 2: Investigate the relationship between exercise and cerebral blood flow (CBF) in older adults with HF.

Hypothesis 2: Participation in CR will be associated with increased CBF.

Aim 3: Determine whether changes in CBF from CR correspond to changes in cognitive function.

Hypothesis 3: Improved cognitive function in patients who participate in CR will be associated with improved CBF.

Aim 4: Examine the contribution exercise intensity to changes in cognitive function.

Hypothesis 4: Exercise at higher intensities during CR will produce greater improvements in CBF and cognitive function.
CHAPTER II: METHODS

The study protocol was approved by the Institutional Review Board at Kent State University. All subjects provided written informed consent before participating.

Participants

Participants for this study included older adults with HF who participated in a study examining the effects of CR on cognitive and physical functioning. In order to minimize potential confounds and clarify the independent effects of exercise on cognitive function, participants were selected on the basis of strict inclusion and exclusion criteria. Specifically, inclusion criteria included being 50-85 years of age, English-speaking, having a history of HF, and being eligible for CR. Exclusion criteria included a history of neurological disorder (e.g. stroke, dementia, seizures), moderate to severe head injury (defined as >10 minutes loss of consciousness), past or current severe psychiatric illness (e.g. schizophrenia, bipolar disorder, substance abuse) (defined by DSM-IV criteria), and history of learning disorder or developmental disability.

The original sample was comprised of 225 individuals, 81 of whom participated in CR. Of the entire sample of individuals who participated in CR, seven were lost to attrition (2 deceased, 5 dropped out for health reasons) and 4 were excluded due to initial exclusionary criteria (1 head injury, 3 stroke). Seven additional CR participants were excluded from final analyses due to incomplete data on key study variables. Finally, 13 participants were excluded from analyses due to having completed less than 20 CR sessions. Therefore, the main analyses
for the current study were conducted on 50 CR participants who completed at least 20 CR sessions and had complete cognitive function and self-report data and 50 control participants specifically matched on age, gender, and HF severity to participants in the CR group. These factors were chosen based on their well-documented independent associations with cognitive functioning in HF patients (e.g., Riegel et al., 2012; Pressler et al., 2010). The final sample for the main analyses included 100 participants.

Independent samples t-tests were conducted to determine whether there were significant differences between the 100 participants included in the present study and the 125 excluded individuals. Results were significant for age ($t(223) = 2.18, p < .05$) indicating that the included individuals were significantly younger ($M = 66.73$, $SD = 8.19$) than the excluded individuals ($M = 69.34$, $SD = 9.48$). Results were nonsignificant for ejection fraction ($t(223) = 0.99, p > .05$). Chi-square analyses also revealed differences in gender between the groups ($\chi^2 (1, N = 225) = 9.04$) such that there was a lower percentage of females in the included group compared to the excluded group.

**Intervention**

The intervention was the Phase II CR program at Summa Health System’s Akron City Hospital. The CR program was a comprehensive electrocardiogram (EKG)-monitored exercise and education program that lasted up to 12 weeks, with three sessions per week. Each session included one hour of aerobic exercise and 40 minutes of education. An exercise plan was customized for each individual and consisted of a warm-up, cool down, stretching, and a 40-minute, five-station circuit training regimen. Circuit training used a number of aerobic exercise
modalities including rowers, treadmills, stationary cycles, elliptical trainers, stationary steppers, and arm exercises. Education classes were designed to promote positive lifestyle changes, increase patients’ understanding of heart conditions, and reduce the risk of future cardiac events.

**Measures**

**Cognitive function.** All participants completed a brief neuropsychological test battery at baseline and 12 weeks later (corresponding to the completion of the CR program). The test battery assessed estimated IQ, as well as multiple cognitive domains including attention, executive function, memory, psychomotor speed, and language. The measures used in the current study include:

- **Estimated IQ.** The *North American Adult Reading Test* (NAART) provides a reliable estimate of IQ in medical populations. In this task, participants are asked to read a list of irregularly pronounced words. Total correctly pronounced scores are then entered into an algorithm correcting for age and education to produce an IQ estimate.

- **Memory.** The *California Verbal Learning Test-Second Edition* (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000) was used to assess memory. For this task, individuals are asked to learn and recall a 16-item word list. The four variables used in this study were total learning (the sum of trials 1-5), immediate recall, delayed recall, and recognition discriminability.
Attention.

*Trail Making Test A* (TMT; Reitan, 1958) was used to measure attention/processing speed. For this task, participants are asked to draw lines to connect numbered circles (1-25) in ascending order as quickly as possible. The variable used in this study was time to completion.

*Letter-Number Sequencing* was used to measure working memory. Participants are presented with numbers and letters in an unordered sequence and are asked to repeat the items with the numbers first in numerical order and then the letters in alphabetical order. Total number correct was the variable used for this study.

Executive Function.

*Trail Making Test B* (TMT; Reitan, 1958) is a measure of cognitive flexibility and adds a set-shifting component to Trail Making Test A. Individual are asked to draw lines connecting a series of numbers and letters in ascending order (A-1-B-2), with the variable being time to completion.

*Frontal Assessment Battery* (FAB; Dubois, Slachevsky, Litvan, & Pillon, 2000) is a measure of frontal system executive function. Participants were asked to complete several short tasks including identifying similarities among words (e.g., table, chair), name as many words as they can that start with a target letter (e.g. words that begin with ‘S’), complete frontal-motor hand movements, and tap patterns with their dominant hand. Total number correct was used as the variable for this study.
Language.

Animal Naming (Eslinger, Damasio, & Benton, 1984) is a measure of semantic verbal fluency in which participants are given 60 seconds to name as many animals as they can. Total number of animals identified was used as the variable.

Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983) is a measure of confrontation naming and language abilities in which participants are asked to name items presented to them in a picture. Items are presented in order of increasing difficulty with more difficult words being of lower frequency (e.g., abacus). Total number correct was used as the variable.

Cerebral Blood Flow Velocity (CBF-V). Transcranial Doppler (TCD) ultrasonography was performed using an expanded Stroke Prevention Trial in Sickle Cell Anemia (STOP) protocol (Bulas et al., 2000) to assess CBF-V in the major brain arteries. The insonated arteries included Middle Cerebral Artery (MCA), the Anterior Cerebral Artery (ACA), Posterior Cerebellar Artery (PCA), Intracranial Vertebral Arteries (IVA), Basilar Artery (BA), Terminal Internal Carotid Artery (TICA), Intracranial Internal Carotid Artery (ICA), and Ophthalmic Artery (OA). For each artery, a number of indices are obtained, including mean flow velocity. For this study, we used CBF-V of the MCA (mCBF-V), ACA (aCBF-V), and PCA (pCBF-V). The CBF-V measures in each artery have high test-retest reliability ($r$’s ranging from .90 to .95) (Owega et al., 1998). Additionally, TCD has been shown to reliably reflect changes in CBF (Bishop et al., 1986) and has shown concordance validity with more direct measures of cerebral perfusion (e.g., arterial spin labeling; Sorond et al., 2010). This approach has been used in past
studies in this population and shown to be related to cognitive function in persons with HF (Alosco et al., 2012).

**Depressive Symptoms.** The Beck Depression Inventory- II (BDI-II) was used to assess depressive symptoms in the current sample. BDI-II scores range from 0 to 63 with higher scores reflecting greater depressive symptomatology. The BDI-II is a widely used measure of depression and has excellent psychometric properties among older adults and adults with medical conditions (Arnau et al., 2001; Segal et al., 2008).

**Physical Activity and Fitness.**

**Exercise Intensity.** Average metabolic equivalents (METs) were obtained at each of the five stations for each session of cardiac rehabilitation. METs are in index of energy expenditure such that one MET is the ratio of the rate of energy expended during an activity to the rate of energy expended at rest. An average session METs composite variable was created for each session of CR by averaging the METs obtained for each of the five circuits. Additionally, a final session METs variable was created by using the average session METs variable for the final session for each participant.

**Two Minute Step Test** (2MST; Jones & Rikli, 2002). The 2MST is an estimate of cardiovascular fitness in which individuals are asked to walk in place, lifting their knees to a target midpoint between their kneecap and the crest of the iliac. Participants were able to place their hand on the wall for balance. Higher step count indicates better cardiovascular fitness.
**Self-reported physical activity.** The Community Health Activities Model Program for Seniors physical activity questionnaire (CHAMPS; Stewart, Mills, King, Haskell, Gillis, & Ritter, 2001) is a 41-item self-report measure that assesses the frequency and duration of typical physical activity over the past four weeks in older adults. This measure has demonstrated adequate validity, reliability, and sensitivity to change (Stewart et al., 2001).

**Demographic and Medical History.**

Participants completed self-report and demographic questionnaires at each evaluation. The self-report medical history questionnaire assessed medical and psychiatric history, including cardiovascular disease, head injury, sleep apnea, arthritis, renal problems, and surgical and psychiatric history. Participants provided and updated list of their medications. These materials were corroborated with medical record review.

**Procedure**

Each participant underwent an assessment at baseline and 12-weeks later. For the CR group, this corresponded to the beginning of and completion of CR. Controls completed identical assessments at equivalent intervals. During each session, participants presented to the research office located in the hospital. Height and weight were measured and participants completed a self-report medical history questionnaire that was later corroborated by a review of medical records. Then, they completed the neuropsychological test battery as administered by a trained research assistant under the supervision of a licensed clinical neuropsychologist. Finally,
participants completed a number of self-report questionnaires and were scheduled for TCD ultrasonography within two weeks of each evaluation. Participants were reimbursed for their participation in the study, receiving a voucher for 100 dollars for each evaluation and 50 dollars for their completion of the TCD.
CHAPTER III: RESULTS

Preliminary Analyses

To facilitate clinical interpretation, all raw scores for the cognitive tests were transformed to T-scores (distribution with a mean of 50 and a standard deviation of 10) using normative data correcting for age. Memory measures were also corrected for gender. Composite variables were created for each cognitive domain (attention, executive function, memory, and language) by averaging the T-scores for tests that comprised each domain. 2MST scores were also adjusted for age, based on published norms (Rikli & Jones, 2001). All major study variables were examined to ensure they met statistical assumptions. The skewness (≤ 2) and kurtosis (≤ 7) values for all continuous study variables indicated that these variables were normally distributed. There were also no outliers on any study variables, as defined by a cutoff of z > 3.29 (Tabachnik & Fidel, 2007). The statistical software package used for all analyses was SPSS version 20.

Association between cognitive function and study variables at baseline. Bivariate Pearson and Spearman correlations were conducted to examine the association between cognitive function and demographic/medical variables at baseline in order to determine potential covariates for use in primary analyses. Regarding medical conditions, there were significant inverse correlations between type 2 diabetes and attention ($r = .28, p < .01$), executive function ($r$
= -.30, \( p < .01 \)), and language \((r = -.23, \ p < .05)\). No other significant findings emerged between medical conditions including hypertension, high cholesterol, and type 2 diabetes and cognitive function. Results also indicated significant inverse correlations between baseline BDI scores and language \((r = -.22, \ p < .05)\) and executive function \((r = -.32, \ p < .01)\). Significant correlations were also observed between fitness and language \((r = .22, \ p < .05)\), attention \((r = .26, \ p < .05)\), and executive function \((r = .34, \ p < .01)\). Results were nonsignificant for all other variables and full results are presented in Table 1. Based on these analyses, BDI scores, fitness, and type 2 diabetes were included as covariates.

### Table 1

<table>
<thead>
<tr>
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<th>HTN</th>
<th>High Cholesterol</th>
<th>T2D</th>
<th>EF</th>
<th>BDI</th>
<th>2MST</th>
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<td>.22*</td>
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<td>-.23*</td>
<td>-.07</td>
<td>-.22*</td>
<td>.26*</td>
</tr>
</tbody>
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Note: HTN – hypertension, T2D – type 2 diabetes, EF – ejection fraction, BDI – Beck Depression Inventory score, 2MST – 2 Minute Step Test; * \( p < .05 \), ** \( p < .01 \)

### Baseline Analyses

Independent samples t-tests were used to examine between group differences on demographic and medical characteristics. Results were nonsignificant for all variables including
ejection fraction ($t(98) = .08, p > .05$), education ($t(98) = -1.14, p > .05$), and estimated IQ ($t(98) = -1.10, p = .28$). Chi-square analyses also revealed that there were no significant differences between the two groups in rates of hypertension ($\chi^2 (1, N = 100) = 0.71, p > .05$), high cholesterol ($\chi^2 (1, N = 100) = 0.04, p > .05$), type 2 diabetes ($\chi^2 (1, N = 100) = .2.94, p > .05$).

See Table 2 for full characteristics of the sample.

### Table 2

<table>
<thead>
<tr>
<th>Demographic Characteristics of the Sample</th>
<th>CR (n = 50)</th>
<th>Control (n = 50)</th>
<th>Test Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD) or %</td>
<td>Mean (SD) or %</td>
<td>(t or $\chi^2$)</td>
</tr>
<tr>
<td>Age</td>
<td>66.62 (7.81)</td>
<td>66.84 (8.63)</td>
<td>0.13</td>
</tr>
<tr>
<td>Female</td>
<td>23.5%</td>
<td>23.5%</td>
<td>0.0</td>
</tr>
<tr>
<td>EF</td>
<td>39.66 (10.96)</td>
<td>39.87 (14.14)</td>
<td>0.08</td>
</tr>
<tr>
<td>Education</td>
<td>14.30 (2.93)</td>
<td>13.70 (2.32)</td>
<td>-1.14</td>
</tr>
<tr>
<td>Estimated IQ</td>
<td>114.06 (9.67)</td>
<td>111.95 (9.69)</td>
<td>-1.10</td>
</tr>
<tr>
<td>Hypertension</td>
<td>62.0%</td>
<td>70.0%</td>
<td>0.71</td>
</tr>
<tr>
<td>High Cholesterol</td>
<td>66.0%</td>
<td>64.0%</td>
<td>0.04</td>
</tr>
<tr>
<td>Type 2 Diabetes</td>
<td>24.0%</td>
<td>40.0%</td>
<td>2.94</td>
</tr>
</tbody>
</table>

Note: CR – Cardiac rehabilitation, EF – Ejection fraction; None of the results are significant.

Independent samples t-tests were used to examine potential baseline differences in depressive symptoms between the two groups. Results indicated no significant differences, $t(98) = .48, p > .05$, between the CR group ($M = 6.04, SD = 7.25$) and the control group ($M = 6.48,$...
SD = 6.10). At baseline, BDI scores fell in the following ranges: 88.0% in the minimal range, 6.0% in the mild range, 5.0% in the moderate range, and 1.0% in the severe range.

Cognitive impairment is prevalent in older adults with HF

Cognitive impairment was common at baseline in the sample, with 22.0% of CR participants (n = 11) and 32.0% of control participants (n = 16) demonstrating clinically significant impairment (defined as a T score < 35) in at least one cognitive domain. Impairment in any across domains ranged from 2.0% to 16.0% for the CR group and from 0.0 to 22.0% in the control group. Chi-square analyses indicated that the prevalence of impairment did not differ between groups for any domain or total impairment at baseline (p’s ranged from .11 to .44).

Subclinical impairment (defined as T-score < 40) in at least one domain of cognitive function was more common and found in 37.5% of CR participants and 38.1% of control participants at baseline. Subclinical impairment in any domain ranged from 8.0 to 20.0% for the CR group and from 4.0 to 28.0% for the control group. Chi-square analyses indicated that there were no differences in subclinical impairment between the CR and control groups in any domain of cognitive function or in total impairment at baseline (p’s ranged from .24 to .94).

Baseline differences in the domains of cognitive function between the CR and control groups were also examined using independent samples t-tests. Analyses revealed no significant differences in any of the domains of cognitive function at baseline between the two groups (p’s ranged from .45 to .81). See Table 3.
Table 3

Percentage of Clinical Impairment in Cognitive Function at Baseline

<table>
<thead>
<tr>
<th></th>
<th>CR (n = 50)</th>
<th>Control (n = 50)</th>
<th>$\chi^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Attention</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td>2.0</td>
<td>0.0</td>
<td>1.01</td>
</tr>
<tr>
<td>Subclinical</td>
<td>10.0</td>
<td>4.0</td>
<td>1.38</td>
</tr>
<tr>
<td><strong>Executive</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td>16.0</td>
<td>22.0</td>
<td>0.59</td>
</tr>
<tr>
<td>Subclinical</td>
<td>18.0</td>
<td>22.0</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>Memory</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td>6.0</td>
<td>16.0</td>
<td>2.55</td>
</tr>
<tr>
<td>Subclinical</td>
<td>20.0</td>
<td>28.0</td>
<td>0.88</td>
</tr>
<tr>
<td><strong>Language</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td>3.9</td>
<td>3.9</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>Subclinical</td>
<td>8.0</td>
<td>10.0</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>Any Domain</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td>22.0</td>
<td>32.0</td>
<td>1.27</td>
</tr>
<tr>
<td>Subclinical</td>
<td>38.1</td>
<td>37.5</td>
<td>&lt; .01</td>
</tr>
</tbody>
</table>

Note: No significant differences between groups; CR – cardiac rehabilitation
Participation in CR is Heterogeneous

Individuals in the CR condition completed an average of 34.94 sessions ($SD = 3.31$). The number of completed sessions ranged from 21 to 36 sessions. For the first session, METs averaged across circuits ranged from 1.56 to 4.66 ($M = 2.75, SD = 0.84$). For the final session, average METs across circuits ranged from 2.09 to 8.30 ($M = 4.50, SD = 1.62$). Average session METs for the first and final sessions were classified into the following five categories based on the American College of Sports Medicine’s guidelines for quantifying the intensity of physical activity in adults (Garber et al., 2011). For adults aged 40-64 the guidelines are as follows: very light (< 2), light (2.0-2.9), moderate (3.0-5.9), vigorous (6.0 – 8.7) and near-maximal to maximal (> 8.70). For adults 65 and older, the guidelines are as follows: very light (< 1.6), light (1.6-3.1), moderate (3.2-4.7), vigorous (4.8- 6.7) and near-maximal to maximal (> 6.7). For the first session, 3.1% of participants were in the very light range, 71.9% were in the light range, and 25.0% were in the moderate range. For the final session, 26.6% were in the light range, 40.6% were in the moderate range, 31.3% were in the vigorous range, and 1.6% were in the near-maximal to maximal range.

Participants were classified into groups based on their progress throughout CR. Specifically, a change in intensity variable was created by subtracting first session METs from final session METs. Participants were then classified into the following three categories: minimal improvement (< 1.5 MET change), moderate improvement (1.5 – 2.99 MET change) and marked improvement (> 3.00 MET change). Of the participants, 48.0% demonstrated minimal improvement in exercise intensity over time, 32.0% demonstrated moderate improvement and 20.0% demonstrated marked improvement.
Changes in Fitness and Physical Activity Levels

**Improved fitness in the CR group.** There were no significant differences between the CR and control groups on the 2MST at baseline \( t(98) = 1.50, p > .05 \). However, there was a significant difference in fitness between groups at 12 weeks, \( t(98) = -2.37, p < .05 \), indicating that the CR group exhibited a greater level of fitness than the control group.

**No improvements in self-reported physical activity.** At baseline, there were significant differences between the CR and control groups on all variables of the CHAMPS including calories per week in all activities \( t(98) = -4.04, p < .001 \), calories per week in moderate intensity activities \( t(98) = -4.61, p < .001 \), frequency of all activities \( t(98) = 5.58, p < .001 \), and frequency per week of moderate intensity activities \( t(98) = -6.41, p < .001 \). These results indicate that the CR group participated in all activity and moderate activity more frequently than the control group and had a higher weekly caloric expenditure for all activities and moderate-intensity activities than the control group at baseline. Of note, the baseline measurements may have included participation in CR for the CR group given that the baseline measurements were taken soon after enrollment in CR.

Four separate 2(time) by 2 (group) ANOVAs were conducted to examine changes in the four primary CHAMPS variables from baseline to 12-weeks. There were no main effects of time for weekly caloric expenditure in physical activity \( F(1,98) = 0.54, p > .05 \), calories per week from moderate intensity physical activity \( F(1,98) = 2.01, p > .05 \), frequency of all physical activities \( F(1,98) = 0.09, p > .05 \), or frequency of moderate intensity physical activity \( F(1,98) = 3.59, p > .05 \). There were also no significant time by group interactions for weekly caloric expenditure in physical activity, calories per week from moderate intensity physical activity, frequency of all physical activities, or frequency of moderate intensity physical activity.
expenditure in physical activity \((F(1,98) = 0.04, p > .05)\), calories per week from moderate intensity physical activity \((F(1,98) = 0.05, p > .05)\), frequency of all physical activities \((F(1,98) = 0.10, p > .05)\), or frequency of moderate intensity physical activity \((F(1,98) = 1.20, p > .05)\).

**No Cognitive Changes from Baseline to 12-weeks**

Four separate 2 (Group) by 2 (Time) mixed analysis of covariance (ANCOVA) controlling for baseline fitness, BDI scores (baseline and 12 week), and type 2 diabetes were conducted to examine whether participation in CR was associated with improvement in each of the domains of cognitive function. Results were non-significant for all cognitive domains for a main effect of time including attention \((F(1,94) = 1.72, p > .05)\), executive function \((F(1,94) = 0.34, p > .05)\) and memory \((F(1,94) = 0.80, p > .05)\), and language \((F(1,94) = 0.11, p > .05)\)

Similarly, and contrary to expectations, there were no significant group by time interactions observed for attention \((F(1, 94) = 1.11, p > .05)\), executive function \((F(1,94) = 0.06, p > .05)\), memory \((F(1,94) = 2.17, p > .05)\) or language \((F(1,94) = 1.30, p > .05)\) suggesting that there was no effect of CR on cognitive function. See Table 4.

**No Changes in CBF-V**

At baseline, there were no differences between the CR and control groups for mCBF-V \((t(98) = -0.56, p > .05)\), aCBF-V \((t(98) = -0.20, p > .05)\), or pCBF-V \((t(98) = 0.47)\). According to published guidelines for a normal TCD study (Kassab et al., 2007) average values for each of the three arteries are as follows: mCBF-V \((55 +/- 12 \text{ cm/s})\), aCBF-V \((50 +/- 11 \text{ cm/s})\) and pCBF-V \((40 +/- 10 \text{ cm/s})\). Across all participants, average values were as follows: mCBF-V \((M = 43.12,\)
Of the sample, 48.2% of individuals were below expectation for mCBF-V, 44.7% for aCBF-V, and 49.4% for PCA.

Table 4

<table>
<thead>
<tr>
<th></th>
<th>CR (n = 50)</th>
<th>Control (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>12 Weeks</td>
</tr>
<tr>
<td>Attention</td>
<td>51.76 (7.89)</td>
<td>52.84 (7.40)</td>
</tr>
<tr>
<td>Executive Function</td>
<td>45.91 (17.31)</td>
<td>48.45 (12.86)</td>
</tr>
<tr>
<td>Memory</td>
<td>47.20 (7.65)</td>
<td>47.45 (9.51)</td>
</tr>
<tr>
<td>Language</td>
<td>53.74 (10.24)</td>
<td>55.38 (10.65)</td>
</tr>
</tbody>
</table>

Note: CR – cardiac rehabilitation

Bivariate correlations examining the relationship between baseline CBF-V levels and cognitive function revealed significant associations between mCBF-V and executive function \( (r = .14, p < .05) \) and memory \( (r = .15, p < .05) \) and between pCBF-V and executive function \( (r = .15, p < .05) \). No other significant associations emerged.

Three separate 2(time) by 2(group) ANOVAs were conducted to examine whether a significant change in CBF-V from baseline to 12-weeks was observed in any of the three arteries, Results were significant for a main effect of time for aCBF-V \( (F(1,98) = 5.63, p < .05) \) but there was no group by time interaction \( (F(1,98) = 0.79, p > .05) \). Results were nonsignificant both for a main effect of time on mCBF-V \( (F(1,98) = 0.86, p > .05) \), and pCBF-V \( (F(1,98) = 0.05, p > .05) \)
as well as a group by time interaction for mCBF-V ($F(1,98) = 0.09, p > .05$) and pCBF-V ($F(1,98) = 0.56, p > .05$). Overall, individuals in the CR condition did not experience significant improvement in CBF-V compared to control participants.

**Post-hoc analyses**

Given that the primary hypotheses were not supported with the main analyses, additional exploratory analyses were conducted to help clarify the results and examine potential subgroup or threshold effects.

**No improvements in cognitive function across individual tests.** Additional post-hoc analyses were conducted to examine whether there were changes in performance on individual cognitive tests that would not be captured using composite variables. Specifically, separate 2(time) by 2(group) ANCOVAs controlling for baseline fitness, diabetes, and BDI scores (baseline and 12-weeks) were conducted. Results were nonsignificant for all tests. Means and standard deviations for each test are presented in Table 5.

**No changes in cognitive function among non-impaired individuals.** To further clarify the results, analyses were conducted separately on only individuals who did not demonstrate impairment in a particular domain at baseline. Specifically, four separate 2 (Group) by 2 (Time) mixed analysis of covariance (ANCOVA) controlling for baseline fitness, BDI scores (baseline and 12 week), and type 2 diabetes were conducted among only those who were not impaired in
Table 5

Changes in Means (SD) for Individual Tests by Domain from Baseline to 12-Weeks

<table>
<thead>
<tr>
<th></th>
<th>CR (n = 50)</th>
<th>Control (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>12-Weeks</td>
</tr>
<tr>
<td><strong>Attention</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trails A</td>
<td>51.20(9.43)</td>
<td>52.17(8.32)</td>
</tr>
<tr>
<td>LNS</td>
<td>52.32(9.19)</td>
<td>53.52(8.89)</td>
</tr>
<tr>
<td><strong>Executive Function</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trails B</td>
<td>44.17(20.72)</td>
<td>46.79(14.44)</td>
</tr>
<tr>
<td>FAB</td>
<td>57.64(18.86)</td>
<td>50.10(17.45)</td>
</tr>
<tr>
<td><strong>Memory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Learning</td>
<td>48.99(8.01)</td>
<td>48.60(10.78)</td>
</tr>
<tr>
<td>Short Recall</td>
<td>47.50(8.59)</td>
<td>49.50(11.57)</td>
</tr>
<tr>
<td>Long Recall</td>
<td>47.10(9.37)</td>
<td>48.10(10.64)</td>
</tr>
<tr>
<td>Recognition</td>
<td>45.20(12.53)</td>
<td>43.60(11.39)</td>
</tr>
<tr>
<td><strong>Language</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BNT</td>
<td>50.87(13.94)</td>
<td>52.65(13.49)</td>
</tr>
<tr>
<td>Animals</td>
<td>56.61(10.76)</td>
<td>58.11(12.32)</td>
</tr>
</tbody>
</table>

Note: Controlling for diabetes, fitness, and BDI scores; CR – cardiac rehabilitation; LNS – letter-number sequencing; FAB- Frontal Assessment Battery; BNT – Boston Naming Test; Animals-Animal fluency test
that domain at baseline. There were no significant main effects or group by time interactions for any of the domains.

**CBF-V and cognitive changes by CR characteristics.** Exploratory analyses in the CR group only were conducted to examine the potential contributions of final session exercise intensity and improvement in exercise intensity over the course of CR to changes in CBF-V and cognitive function. For the contribution of absolute intensity, participants were stratified into three groups based on exercise intensity (METs) for the final session. The three groups included light, moderate and hard (including vigorous intensity and near-maximal to maximal groups). For improvement over time, participants were stratified as above into minimal, moderate, and marked improvement over time.

**No differences in CBF-V by exercise intensity or intensity improvement.** Three separate ANOVAs were conducted to determine whether there were differences in 12-week CBF-V for each of the three arteries among the three groups based on final session intensity. Results were nonsignificant for all arteries including mCBF-V ($F(2, 49) = 0.34, p > .05$), aCBF-V ($F(2, 49) = 0.97, p > .05$), and pCBF-V ($F(2, 49) = 0.38, p > .05$).

Three separate ANOVAs were conducted to determine whether there were differences in 12-week CBF-V for each of the three arteries among the three groups based on improvement over the course of CR. Results were nonsignificant for all arteries including mCBF-V ($F(2, 49) = 0.94, p > .05$), aCBF-V ($F(2, 49) = 0.38, p > .05$), and pCBF-V ($F(2, 49) = 0.76, p > .05$).
**Group difference in cognitive function by intensity improvement.** Four ANOVAs were conducted to examine differences in 12-week cognitive function among groups based on intensity improvement over the course of CR. Results were significant for executive function ($F(2, 49) = 3.32, p < .05$) and language ($F(2, 49) = 3.39, p < .05$). Results were nonsignificant for attention ($F(2, 49) = 0.14, p > .05$) and memory ($F(2, 49) = 0.30, p > .05$). Post-hoc analyses indicated that for both executive function and language, significantly higher scores were observed among groups with greater improvement compared to those with lower. Specifically, for executive function, there were significant differences between the minimal ($M = 43.80, SD = 15.44$) and moderate ($M = 53.14, SD = 8.89$) improvement groups. For language, there were significant differences between the minimal ($M = 51.62, SD = 12.08$) and marked ($M = 60.54, SD = 7.83$) improvement groups.

To clarify these results, four ANOVAs were conducted to examine potential baseline differences in cognitive function among improvement groups. At baseline, results were significant for executive function ($F(2, 49) = 5.80, p < .01$) and language ($F(2, 49) = 4.06, p < .05$). Results were nonsignificant for attention ($F(2, 49) = 1.04, p > .05$) and memory ($F(2, 49) = 0.13, p > .05$). In both cases, the greater improvement groups demonstrated better cognitive function at baseline. Specifically, for executive function there were significant baseline differences ($p$’s < .05) between the minimal ($M = 37.97, SD = 21.79$) and moderate ($M = 53.09, SD = 6.86$) and the minimal and marked ($M = 53.56, SD = 4.04$) improvement groups. There were no significant differences ($p > .05$) between the moderate and marked groups. For language, there were also significant differences between the minimal ($M = 49.69, SD = 11.11$)
and moderate ($M = 57.59$, $SD = 7.70$) and minimal and marked ($M = 57.30$, $SD = 8.53$) improvement groups. There were no significant differences ($p > .05$) between the moderate and marked groups.

**Group difference in cognitive function by exercise intensity.** Four ANOVAs were conducted to examine differences in 12-week cognitive function based on final session intensity between the three groups. Results were significant for attention ($F(2, 47) = 4.36$, $p < .05$), executive function ($F(2, 47) = 4.90$, $p < .05$), and language ($F(2, 47) = 7.80$, $p < .01$). Results were non-significant for memory ($F(2,47) = 0.35$, $p > .05$). In each instance, higher cognitive scores were observed among higher intensity groups. Specifically, for attention, significant differences ($p < .05$) were observed between the light ($M = 48.72$, $SD = 7.66$) and hard ($M = 56.25$, $SD = 6.93$) intensity groups. For executive function, significant differences ($p < .01$) were observed between the light ($M = 40.65$, $SD = 14.80$) and hard ($M = 54.49$, $SD = 7.54$) intensity groups. For language, significant differences ($p < .01$) were observed between the light ($M = 47.98$, $SD = 14.49$) and hard ($M = 61.62$, $SD = 7.72$) intensity groups.

To clarify these results, baseline differences in cognitive function across the intensity groups were also examined. Results were significant for executive function $F(2,47) = 4.43$, $p > .05$) and language ($F(2,47) = 11.39$, $p < .001$). No differences emerged for attention ($F(2,47) = 2.77$, $p > .05$) or memory ($F(2,47) = 0.64$, $p > .05$). In both cases, higher cognitive scores were observed among the higher intensity groups.

For executive function, significant differences ($p < .05$) were found between the light ($M = 36.37$, $SD = 29.09$) and hard ($M = 54.03$, $SD = 4.96$) intensity groups. For language,
significant differences ($p < .05$) emerged between the light ($M = 44.74$, $SD = 12.28$) and moderate ($M = 53.51$, $SD = 6.03$) and the light and hard ($M = 60.00$, $SD = 7.85$) intensity groups.
CHAPTER IV: DISCUSSION

Review of Study Goals and Rationale

HF is a well-documented risk factor for cognitive impairment and neurocognitive effects can be detected long before the development of conditions such as Alzheimer’s disease and vascular dementia (Bennett & Sauve, 2003). Although the exact mechanisms for cognitive dysfunction among HF patients are not entirely understood, prolonged cerebral hypoperfusion resulting from cardiac dysfunction is a likely contributor. Fortunately, recent research has shown that structured exercise can increase both CBF and cognition in healthy older adults (Chapman et al., 2013). However, this relationship has not been well-examined in HF samples. To date, only one study has shown that exercise can improve cognitive functioning in persons with HF. Unfortunately, that study was limited by a small sample size and it did not examine potential baseline differences between the control and intervention groups (Tanne et al., 2005).

The present study examined whether participation in a 12-week structured exercise program (i.e., CR) was related to cognitive benefits in a sample of older adults with HF. Additionally, the present study explored potential mechanisms for the cognitive benefits of exercise, such as increased CBF-V. Finally, the present study sought to examine the potential contribution of exercise intensity to the relationship between participation in CR, increased CBF-V, and improved cognitive function. It was hypothesized that: 1) individuals who participated in CR would exhibit improvements in attention, executive function, and memory compared to those who did not, while language would remain relatively stable; 2) improved cognitive function in
the CR group would be associated with improved CBF-V; and 3) exercise at higher intensities during CR would be associated with a greater magnitude of change in cognitive function and CBF-V. Overall, these hypotheses were not supported. Specifically, cognitive function and CBF-V did not improve following 12-weeks of CR compared to a well-matched control group.

Although no changes in cognitive function or CBF-V were found, exploratory analyses demonstrated a potential contribution of exercise intensity to cognitive function in this sample. Specifically, exercise at greater intensity was associated with better cognitive function, both at baseline and 12-weeks. These findings, and their potential implications are discussed in detail below.

Cognitive Function from Baseline to 12-Weeks

Consistent with previous research (e.g., Vogels et al., 2007), clinically significant cognitive impairment (> 1.5 SD below the normative mean) was found in more than one-quarter of participants and more subtle deficits (> 1 SD below the normative mean) were observed in one-third of individuals at baseline. Cognitive impairment was present in all domains, but was especially common on tests of executive function.

Overall, cognitive function in all four assessed domains (attention, executive function, memory, and language) remained stable over the course of 12 weeks in a sample of older adults with HF. This is similar to two previous studies (Almeida et al., 2012; Riegel et al., 2012) which also demonstrated stability of cognitive function in HF patients over short intervals. However, contrary to the main hypothesis of this study, participation in a structured exercise program was not associated with significant cognitive benefit from baseline to 12-weeks when compared to
the performance of a well-matched HF control group who did not participate in the exercise intervention.

These findings are surprising given that previous research has shown that attention/psychomotor speed and executive function improve in patients with severe HF following an 18-week structured aerobic exercise program (Tanne et al., 2005). These discrepant findings may be explained by group differences across studies. First, all participants in the Tanne et al (2005) study had a left ventricular ejection fraction (LVEF) of ≤ 35% while participants in the present study had an average LVEF of approximately 40%. Additionally in the present sample, 62.0% of individuals in this sample had an LVEF greater than 35% indicating that the participants in the present study had less severe HF than participants in the Tanne et al (2005) study. Similarly, exclusionary criteria for the present study were much more stringent (e.g., exclusion of neurological disorder, head injury, psychiatric illness, learning and developmental disabilities) compared to the Tanne et al. (2005) study. Additionally, it is likely that differences in the exercise interventions also partially account for these discrepant findings and will be discussed later.

Cerebral Blood Flow Velocity

The second hypothesis of the present study was that participation in CR would result in improved CBF-V. This hypothesis was also not supported. Rather, CBF-V levels in all three studied arteries (MCA, ACA, PCA) remained stable in both the intervention and control groups over the course of three months. The lack of changes in CBF-V for the intervention group likely explains why improvements in cognitive function were not observed.
There are a number of potential explanations for why CBF-V did not significantly improve among CR participants in this sample. First, CBF-V was reduced in less than half of the participants in the present study. These findings are in contrast to previous research, which includes a 31% reduction of CBF in HF patients when compared to a control group comprised of healthy adults (Gruhn et al., 2001). It is possible that the current results are attenuated by the fact that much of the sample exhibited intact CBF-V levels at baseline. Specifically, exercise may be most beneficial for individuals with significantly reduced CBF and those patients with more severe HF. Additionally, research has shown that although increases in CBF can occur during and immediately after aerobic exercise, they may not persist over time (Querido & Sheel, 2007). Finally, and similar to above, these null results may be explained by characteristics of the intervention, as described below.

**Exercise Intervention and Implications for a Potential Threshold Effect of Exercise Intensity**

Perhaps the most likely reason for the lack of significant findings for changes in cognitive function CBF-V has to do with the characteristics of the exercise intervention itself. Participants in this study exhibited a wide range of exercise intensity during CR, as defined by average session METs. While a large majority of participants (71.9%) began CR in the light range of intensity, 40.6% of the participants reached METs in the moderate range of intensity and 32.9% of individuals exceeded the moderate range of intensity by the final session. Additionally, an overall improvement in fitness level, as measured by the 2MST, was observed in the CR group.
when compared to the control group demonstrating at least some cardiovascular benefit of the CR intervention.

However, it is very important to note that more than one-quarter of participants did not exceed the light range of exercise intensity by the end of CR. Additionally, nearly half of the individuals in CR demonstrated only minimal improvement in exercise intensity from the first to final sessions. Further, examination of self-reported levels of physical activity between groups demonstrated that although physical activity levels were significantly greater in the CR group at baseline compared to the control group (presumably because the reported activities included those completed during the first week of CR), no increases in physical activity over the course of 12 weeks were observed. These results further support the notion that overall, participation in CR may not have increased absolute levels of intensity of physical activity/exercise over time.

The current results indicate that performance in CR is quite heterogeneous among participants. Results of the exploratory post-hoc analyses may help to better clarify the current findings and suggest a potential threshold effect for the benefits of exercise on cognitive function. In particular, exploratory analyses demonstrated significant differences between both absolute final session intensity and intensity improvement groups in terms of cognitive function. Specifically, better cognitive function was found in multiple domains for those individuals who exhibited greater intensity of exercise and greater improvement in exercise intensity over time. Interestingly, these effects were also present at baseline. There are a number of explanations for these interesting findings. First, CR programs are individually tailored for each patient at the start. It is possible that individuals who engaged in higher levels of physical activity prior to starting CR were able to progress more quickly through the program. If that were the case, these
results would suggest that patterns of greater physical activity may be associated with better
cognitive function in general. Similarly, such individuals may have been healthier when entering
CR and their better cognitive function is a reflection of their health status. Regardless, it does
appear that these results support the idea of a potential threshold effect such that higher levels of
exercise intensity are associated with better cognitive function. Another possibility is that
individuals with poorer cognitive function are less able to adhere to CR and derive less benefit
from it (Kakos et al, 2010). Further work is needed to clarify these and other possibilities.

These findings would also help to explain the differences between this study and the
Tanne et al (2005). Specifically, participants in the current study likely were exercising at a
lower intensity level than participants of the Tanne et al (2005) study who were all engaging in
aerobic exercise at a moderate range of intensity (60-70% max HR). This notion is also
consistent with the research that has demonstrated a strong positive association between higher
fitness levels and improved cognitive function in HF and non-HF samples (e.g., Baldasseroni,
2010; Colcombe et al., 2003). Improvements in cardiovascular fitness are strongly associated
with the intensity level of exercise. The reduced level of exercise intensity and minimal change
in exercise intensity observed in nearly half of the present sample may have limited improvement
in cardiovascular fitness. It is possible therefore that the lack of significant improvements in
cognitive functioning may be related to participants not meeting a threshold level for
improvement in fitness.

Limitations
The results of the present study must be viewed in light of a number of limitations. First, although participants in the two groups were well matched on age, gender, HF severity, IQ, education, and comorbid medical conditions, they were assigned to groups after having been referred to CR and choosing whether or not to participate. Therefore, the groups were not randomized and there may be potential group differences that were not examined. Second, the present study only examined the effects of exercise immediately after the conclusion of the CR program. Future studies should re-examine the effects of exercise in HF samples with longer follow up (i.e., 1, 3, and 5-year follow-up) to determine the long-term effects of exercise on cognitive function and to determine whether individuals continue to engage in higher levels of physical activity and exercise after finishing CR. Third, cerebral perfusion was estimated using CBF-V obtained from TCD ultrasonography. There are a number of benefits to using TCD including that it is non-invasive and less expensive than more detailed techniques. However, to further clarify the effects of exercise on cerebral perfusion and cognitive function, more detailed measures, such as positron emission tomography (PET) or arterial spin labeling (ASL), should be used in future studies. Similarly, the current study utilized the 2MST as an estimate of cardiovascular fitness because it is a brief and easily administered measure. However, future studies should examine the effects of fitness on cognitive functioning using more detailed measures of cardiorespiratory fitness, such as VO2 max from stress testing. Another limitation of the present study is the small sample size available for main analyses. Although the original sample included 225 individuals, a number of individuals were lost to attrition or excluded due to missing data for key variables. Future research should use larger samples, in order to examine
within groups effects of exercise on cognitive function and to stratify participants based on characteristics of their participation in CR.

**Future Directions**

Results from the current study are in contrast to a large body of literature demonstrating improved cognitive functioning with exercise in other samples (e.g., Colcombe & Kramer, 2003; Palleschi et al., 1996). These differences raise a number of considerations unique to HF patients such as whether HF patients are able to exercise at a level necessary to produce cognitive benefits. One possibility is that the benefits of exercise in HF differ across a variety of patient subgroups. For example, recent research demonstrated three unique profiles of cognitive functioning in older adults including intact, memory impaired, and globally impaired. These results demonstrate that cognitive impairment in patients with HF is quite heterogeneous (Miller et al., 2012) and the benefits of exercise may vary across these three groups. Additionally, the results of the current study demonstrate that individuals with HF vary greatly in their level and intensity of participation in exercise. In this study, participants varied in the number of sessions attended, average intensity of exercise, and improvement over time in exercise intensity. Importantly, this pattern suggests some contribution of exercise intensity on cognitive function as significantly higher scores were found for all domains of cognitive function except memory for the highest intensity group when stratifying individuals into groups based on final session intensity. However, more research is needed in larger samples with representation from different groups of exercise intensity to further examine the possibility of a threshold effect.
Clinical Implications

The search for interventions to improve cognitive functioning or prevent further decline in patients with HF are particularly warranted as the implications of such an intervention would be substantial. Cognitive dysfunction is a significant predictor of decreased quality of life, increased risk of disability, increased mortality (Zuccala, et al., 2001), and increased rates of hospitalization among patients with HF (Dodson et al., 2013).

Cognitive impairment in HF adversely affects activities of daily living (ADLs) in patients with HF (Zuccala et al., 2001; Putzke et al., 2000). ADLs can be divided into two categories: basic, which include feeding, bathing, toileting and dressing, and instrumental, which includes more complicated tasks required for independent living (Norberg, Boman, & Lofgren, 2008). Impairment in instrumental ADLs in this population is associated with worse outcomes such as higher rates of hospitalization, disability and reduced quality of life (Jencks, Williams, & Coleman, 2009; Campbell, Banner, Konick-McMahan, & Naylor, 1998). Such findings further highlight the potential importance of exercise for improving fitness levels, and ultimately independent functioning, of patients with HF.

Summary and Conclusions

In summary, the current study found that older adults with HF did not exhibit improved cognitive function or CBF-V following participation in a 12-week structured exercise program when compared to well-matched controls. However, exercise intensity and improvement in intensity over time was associated with better cognitive function. Such findings suggest that the effects of exercise on cognitive function and CBF-V in individuals with HF may vary based on
the intensity of exercise and raise the possibility of a threshold effect. Future research should examine the possibility of a threshold effect for cognitive benefits in large, prospective studies.
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