ASSOCIATIONS AMONG CARDIAC OUTPUT, CEREBRAL BLOOD FLOW, AND COGNITIVE FUNCTION IN HEART FAILURE

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by

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Introduction

Over 81 million Americans are afflicted with one or more types of cardiovascular disease (CVD), with the prevalence of such disease increasing with age. When including hypertension, coronary heart disease, HF, and stroke, the prevalence of CVD increases from approximately 40% of adults aged 40 to 59 years to 79-85% of persons aged 80 and above (American Heart Association, 2010). CVD is the most costly disease in the United States (National Heart, Lung, and Blood Institute, 2009) with the direct and indirect costs estimated at over $503 billion for 2010 alone (American Heart Association, 2010).

In addition to being an economic burden, CVD is a leading cause of death in the United States. Of the 15 leading causes of death in 2007, diseases of the heart, cerebrovascular diseases, and hypertension ranked 1, 3, and 13, respectively. While the mortality rate of CVD in the United States has declined from 1999 to 2007, CVD accounted for more than a third of all deaths in 2007. Additionally, the life expectancy for persons with CVD is nearly 4 years less than the national average (Xu, Kochanek, Murphy, & Tejada-Vera, 2010).

Within the United States, nearly 6 million persons have HF and an estimated 670,000 new cases are reported each year. The most common risk factor for the development of HF is hypertension, as 75% of HF cases have antecedent hypertension. Given the increasing age of the population and the increased survival rate of persons with other forms of CVD, HF has become more prevalent. The prevalence of HF increases from approximately 2% of adults aged 40-59 years to 14.7% of men and 12.8% of women aged 80 and above (American Heart Association, 2010). While the incidence of HF in women has declined over recent decades, the incidence among men remains unchanged (Levy, et al., 2002), and despite improved survival rates, the 5-

year mortality rate among both genders remains high at 50-60% (Levy, et al., 2002; Rusinaru, et al., 2009).

In addition to being a significant clinical problem, HF produces a significant economic burden, costing an estimated $40 billion annually with more than half of these costs attributable to direct hospital costs (American Heart Association, 2010). A recent cohort study of Medicare beneficiaries indicated that over 2.5 million persons were hospitalized with HF between 2001-2005. Of those, 65% were readmitted to the hospital within one year, and nearly 40% were readmitted twice (Curtis et al., 2008).

The Pathophysiology of Heart Failure

Individuals with HF experience numerous pathophysiological changes within the cardiovascular system that are not consistent with normal aging. The cardiovascular system functions to bring oxygen and nutrients to, and carbon dioxide and wastes away from, metabolic tissues. The left and right sides of the heart work as a circuit to meet this goal, with the left side pumping to complete the high-resistance systemic circulation and the right side pumping to complete low-resistance pulmonary circulation (Hoit & Walsh, 2008). In normal aging, the cardiovascular system undergoes both structural and functional changes that can have negative consequences. For example, the heart increases in weight, the number of cardiomyocytes decreases, artery walls thicken, there is an increase in the amount of inflammatory and/or atherosclerotic substances, and arterial distensibility (i.e., the ability of an artery to dilate and contract) decreases. However, many functions of the heart remain preserved in normal aging. For example, both ejection fraction (i.e., the fraction of blood ejected with each heart beat) and stroke volume (i.e., the volume of blood pumped out per heart beat) remain relatively unchanged and resting heart rate is unchanged or only slightly reduced, thus preserving cardiac output (i.e. the

amount of blood pumped from the heart over a one minute interval; Ferrari, Radaelli, & Centola, 2003).

In contrast to the processes of normal cardiovascular aging, heart failure is a complex clinical syndrome associated with structural or functional damage such that the heart is unable to pump blood sufficiently enough to meet the body's metabolic needs. Any form of heart disease can lead to HF and thus no single cause can be pinpointed. The condition of HF usually evolves over time and progresses as the body tries to compensate for the work the damaged heart can no longer perform (Francis, Sonnenblick, Wilson Tang, & Poole-Wilson, 2008). For example, left ventricular dysfunction, a common abnormality in HF, results in a decrease of cardiac output. In response, activation of neurohormonal compensatory mechanisms, such as sympathetic nervous system activation (e.g., increase in heart rate, peripheral vasoconstriction) occurs in an attempt to maintain cardiac output. While this initially maintains cardiac output, chronic sympathetic nervous system activation ultimately leads to further weakening of the heart and is also related to cardiac muscle cell death, hypertrophy, and focal myocardial necrosis (Jackson, Gibbs, Davies, & Lip, 2000). Such compensatory mechanisms prove to be insufficient and ultimately have additional negative effects on the heart and these initially adaptive responses contribute to the progression of HF (Jackson, Gibbs, Davies, & Lip, 2000; Francis, Sonnenblick, Wilson Tang, & Poole-Wilson, 2008).

Heart Failure & Cognition

In addition to the common symptoms of fatigue and lethargy, shortness of breath, and edema (Watson & Gibbs, 2000), cognitive impairment is also common in HF and is associated with adverse outcomes. The prevalence rates of cognitive impairment in HF typically range from approximately 30-50%, though impairment has been found in up to 80% of this population

(Bennett & Sauvé, 2003). Moreover, risk for cognitive impairment is higher with greater HF severity as measured by the New York Heart Association (NYHA) Class criteria (Vogels, et al., 2007a; Pressler et al., 2010). The risk of cognitive impairment in persons with HF is 4-times that of matched controls without HF (Sauvé, Lewis, Blankenbiller, Rickabaugh, & Pressler, 2009), and impairment is found in multiple domains including memory, attention, executive function, psychomotor speed, and language (Almeida & Flicker, 2001; Vogels, Scheltens, Schroeder-Tanka, & Weinstein 2007; Vogels, et al., 2007a; Bennett & Sauvé, 2003; Pressler et al., 2010). Such impairment in this population is associated with a 5-fold increase in risk of mortality (Zuccala, et al., 2003) and a 6-fold increase in disability (Zuccala, et al., 2001).

The Etiology of Cognitive Impairment in HF

While the research examining the etiology of cognitive dysfunction in HF is limited and mixed, several potential mechanisms have been proposed. It is likely that the pattern of impairment seen is a result of multiple factors including structural brain changes and reduced cerebral blood flow.

Structural brain changes. It is well established that HF is a risk factor for vascular dementia (Román, 2005) and stroke (Siachos, et al., 2005; Wang et al., 2003). However, prior to the onset of such conditions, adverse brain changes that can negatively affect cognitive functioning emerge on neuroimaging of HF patients. For example, individuals with HF show cerebral atrophy and infarcts (Schmidt, Fazekas, Offenbacher, Dusleag, & Lechner, 1991; Vogels, et al., 2007b) as well as white matter hyperintensities (WMH) (Vogels, et al., 2007b; Almeida et al., 2005). In addition, a reduction in gray matter volume is seen in areas such as the parahippocampal gyrus, cingulate gyrus, and frontal cortex (Woo, Macey, Fonarow, Hamilton, & Harper, 2003).

Despite these findings, few studies have directly examined the association between structural brain changes and cognitive performance in HF, and those that have, reported mixed findings. For example, Vogels and colleagues (2007c) investigated the relationship between brain abnormalities and cognitive performance in 58 HF patients. Patients completed a neuropsychological battery and underwent magnetic resonance imaging (MRI). On MRI, deep periventricular and total WMH, lacunar and global infarcts, and global and total medial temporal lobe atrophy were visually quantified. Medial temporal lobe atrophy was found to be associated with decreased performance on tasks of memory and executive function, such that increased medial temporal lobe atrophy was associated with a decrease in cognitive performance. Moreover, this finding was independent of cardiovascular risk factors (e.g., hypertension). However, contrary to expectations there was no association between WMH (periventricular or total) and cognitive performance. While adding to the literature, the study is not without limitations. The sample is limited in that only those without MRI contraindications (e.g., pacemaker) were included. Patients requiring such devices may have more advanced HF and as a result have a different cognitive profile and differential pattern of abnormalities on neuroimaging. In addition, analyses of the imaging data is limited due to the visual rating scales used to quantify atrophy, and, while infarcts were recorded in terms of number and location, no analyses are provided in regard to their relation to cognitive performance. In addition, while a control group (n = 26) was used to obtain a "normative" cognitive performance value, these individuals were not included in any further analyses. The generalizability of these findings is further limited due to the fact that the HF patients appear generally intact based on a measure of global cognitive performance. Moreover, the cutoff Z-score (-0.45) used to determine impairment was based on the performance of the healthy controls, rather than age and education corrected normative data.

In a more recent study, Beer and colleagues (2009) examined the associations between cognitive outcomes and neuroimaging in 31 patients with HF and 24 controls with no symptoms of HF. The HF patients performed significantly worse than controls on neuropsychological tests of multiple domains and also showed significantly more right (but not left) medial temporal lobe atrophy than controls. However, in contrast to expectations HF patients (n = 19 for MRI) had significantly less severe periventricular WMH than controls (n = 20 for MRI). Moreover, the two groups did not differ on other MRI measures. While some measures of structural brain change were associated with poorer cognitive performance in HF patients, the authors were unable to consistently differentiate HF patients from controls (Beer et al., 2009). Similar to the work of Vogels and colleagues (2007c), the generalizability of this study is lacking in terms of some patients not completing MRI due to contraindications and use of visual ratings.

An obvious possible explanation for the mixed findings of these studies lies, at least in part, with the methodological limitations of these studies discussed above. However, when considered in the context of similar work with other populations, these results also suggest that structural brain changes cannot fully account for the pattern of cognitive impairment seen in HF. The relationship between structural brain changes and cognitive performance is well established in other populations, such as persons with more generalized CVD. For example, Raz and colleagues (2003) examined the neural correlates of cognitive function in middle-aged adults with treated hypertension compared to normotensive adults. Neuroimaging revealed that those with hypertension had reduced volume and elevated WMH when compared to their normotensive peers. Moreover, these abnormalities were more specific to the frontal regions of the brain, including the prefrontal cortex, and were associated with deficits on tasks of executive function (Raz, Rodrigue, & Acker, 2003). In addition, Paul and colleagues (2005) examined neuroimaging correlates of cognitive function in a group of cardiac patients with heterogeneous forms of CVD

(e.g., hypertension, myocardial infarction). Whole brain volume was found to be associated with overall cognitive performance as well as performance on tasks of attention and executive function. Moreover, subcortical hyperintensities were also associated with attention and executive function performance (Paul et al., 2005). Considering that other forms of CVD are often comorbid with HF (Metra et al., 2011), it appears likely that there are similar structural mechanisms contributing to cognitive dysfunction in HF. However, given the mixed findings in the literature, it is evident that other mechanisms interact with structural changes to impact cognitive performance in HF.

Reduced cerebral blood flow. Given that structural brain changes do not fully explain the cognitive dysfunction seen in HF, other pathophysiological mechanisms that negatively impact functional capacity are clearly involved. One likely contributor to cognitive decline in HF is reduced cerebral perfusion. It is hypothesized that the reduced cardiac function in HF alters systemic blood flow, which can ultimately disrupt cerebral blood flow and cognitive function (Jefferson, 2010). Previous work with CVD patients found that systemic hypoperfusion (i.e., cardiac output < 4.0 liters/minute) was associated with poorer performance on tasks of executive functioning (Jefferson, Poppas, Paul & Cohen, 2007). Extending this work, Hoth and colleagues (2008) found reduced cognitive performance in individuals with moderate to severe HF compared to normative data and cardiac controls, with poorer performance on tasks of memory, executive function, and global cognition associated with reduced systemic perfusion (Hoth, Poppas, Moser, Paul, & Cohen, 2008). Previous work has also demonstrated an association between WMH and cardiac output, such that decreased cardiac output is associated with an increase in subcortical WMH (Jefferson, et al., 2007). Moreover, improvements in mean flow velocities in cerebral arteries (Massaro, Dutra, Almeida, Diniz, & Malheiros, 2006) and cognitive function (Bornstein et al., 1995; Deshields et al., 1996) have been demonstrated following cardiac transplant. Taken

together, these findings suggest a reduction in cerebral perfusion, to some extent, in the brain regions that mediate the mental abilities commonly impaired in HF.

The negative impact that even temporary periods of reduced cerebral blood flow (CBF) can have on cognition can be highlighted by the short-term cognitive dysfunction seen in some individuals undergoing coronary artery bypass graft surgery (CABG) with cardiopulmonary bypass. Recent work has examined CBF during the various phases of cardiopulmonary bypass and found disruptions in CBF autoregulation. Brady and colleagues (2010) monitored real-time CBF during cardiopulmonary bypass using transcranial Doppler monitoring and near-infrared spectroscopy monitoring and found a disruption of CBF in the middle cerebral artery. In addition, Joshi and colleagues (2010) found abnormal CBF autoregulation during the re-warming phase of hypothermic cardiopulmonary bypass. To that end, a recent review examined neuropsychological outcomes after CABG with cardiopulmonary bypass and found cognitive decline in 4-33% of patients seven days following surgery, with cognitive decline seen in the domains of attention, processing speed, and memory (Selnes & Gottesman, 2010). While it is hypothesized that the etiology of cognitive decline following CABG with cardiopulmonary bypass is multifactorial, cerebral hypoperfusion is suspected to play an important role (Selnes & Gottesman, 2010).

It appears likely that a similar effect is found in persons with HF. Despite autoregulatory mechanisms present in the brain that work to maintain adequate blood flow across ranges of cerebral perfusion pressures (Serrador & Milberg, 2010), persons with HF show a 19-30% decrease in cerebral perfusion when compared to healthy controls (Choi et al., 2006; Gruhn, et al., 2001). Moreover, the reduction of global CBF is associated with the severity and chronicity of HF (Choi et al., 2006). In addition to these generalized reductions, decreased cerebral perfusion is found 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 recent

review of the functional imaging literature on HF found reduced perfusion in posterior cortical regions, similar to the pattern of decreased regional brain activity seen in Alzheimer's disease (Alves & Busatto, 2006). Additionally, both reduced cerebral and systemic perfusion increase the risk of WMH development (Tzourio, Levy, Dufouil, Touboul, Ducimetiere, & Alperovitch, 2001; Jefferson, et al., 2007) and are associated with cognitive decline (Román, 2004; Jefferson, Poppas, Paul, & Cohen, 2006).

The likely association between cerebral perfusion and cognitive function is also highlighted when examining the benefits of cardiovascular fitness on cognition. Several studies have shown that healthy older adults who engage in regular physical activity demonstrate improved performance on neuropsychological tests and fewer pathological changes on neuroimaging (Colcombe & Kramer, 2003; Colcombe et al., 2003; Colcombe et al., 2006; Kramer, Colcombe, McAulley, Scalf, & Erickson, 2005). Recent work has extended these findings to older adults with CVD and found that participation in a cardiac rehabilitation program not only improved cardiovascular fitness, but was also associated with improvements in global cognition, attention, executive function, psychomotor speed, and memory (Gunstad et al., 2005; Stanek et al., 2011). Such findings suggest that similar benefits would likely be seen in individuals with HF as it is also established that increased levels of cardiovascular fitness provide multiple gains for persons with HF. Specifically, in addition to reductions in symptom severity, increases in quality of life, and gains in functional performance (Austin, Williams, Ross, Moseley, & Hutchison, 2005), the physiological changes that occur as an outcome of exercise may in turn be associated with cognitive gains. For example, increased fitness levels have been shown to improve cardiac output, functional work capacity, and vascular function (Jonsdottir, Andersen, Sigurosson, & Sigurosson, 2006; Linke, Erbs, & Hambrecht, 2006; van Tol, Huijsmans, Kroon, Schothorst, & Kwakkel, 2006; You Fang & Marwick, 2003), which in turn

increase CBF. Thus, it appears likely that HF patients who have higher levels of cardiovascular fitness would show increased levels of cerebral perfusion and in turn less cognitive decline.

Despite the likely link between cerebral perfusion and cognitive performance, few studies have directly examined this association in persons with HF, and those that have yielded mixed findings. Using transcranial Doppler sonography (TCD), Jesus and colleagues (2006) examined the association between CBF measures and cognition in a sample of 83 HF patients. Results demonstrated a significant positive association between mean blood flow velocity of the right middle cerebral artery (MCA) and performance on the Mini Mental State Exam (MMSE), a measure of global cognition. Specifically, increased blood flow velocity of the right MCA was associated with increased performance on the MMSE. In addition, there was an inverse relationship between MMSE performance and the right MCA pulsatility index (PI), a measure of vascular resistance. That is, greater vascular resistance (i.e., higher PI values) was associated with poorer performance on the MMSE. However, the initial analyses conducted included individuals with a history of stroke. When those with stroke history were excluded, only the inverse association between right MCA PI and MMSE performance remained significant (Jesus et al., 2006). While these findings are consistent with what would be expected, the MMSE is a brief, global screening measure of cognitive function and is not equivocal to a comprehensive neuropsychological battery, limiting the generalizability of the findings. The evaluation of just the MCA is another limitation of this study, as indices of other arteries could easily have been obtained. In addition, the authors do not provide normative data on TCD indices or include a control group.

A more recent study examined the associations among CBF, neuroimaging, and cognitive performance in persons with mild to moderate HF (n = 43), cardiac controls without HF (n = 33), and healthy controls (n = 22; Vogels, et al., 2008). Through the use of TCD, the authors found

that those with mild HF had lower mean blood flow velocities of the MCA when compared to healthy controls, but did not differ from cardiac controls. The HF patients also had significantly higher MCA PI values than the healthy controls, but not the cardiac controls. In addition, those with mild HF performed significantly poorer than healthy controls when an overall composite cognitive performance was tabulated. More specifically, reduced performance was seen in the domains of memory, executive function, and mental speed/attention. However, MMSE scores between all groups were similar. Despite the differences in individual cognitive domain performance and CBF indices among the groups, the reduction in CBF in was not related to cognitive performance. In addition, HF patients without contraindications also underwent MRI to quantify WMH and medial temporal atrophy, though neither measure was associated with mean blood flow velocity or PI of the right MCA (Vogels, et al., 2008). While a more comprehensive neuropsychological battery was used and control groups were included, the generalizability of these results are limited by the range restriction of neurocognitive performance, as persons in all groups exhibited generally intact cognitive function across all measures. Similar to the limitations in the work done by Jesus and colleagues (2006), this study is further limited by the lack of examination of other cerebral arteries and a comparison of the obtained TCD indices to a normative sample. Moreover, additional information could have been added to the literature had they examined the associations between cognitive performance and MRI findings.

Alves and colleagues (2005) employed a more sophisticated functional technique and used single-photon emission computed tomography (SPECT) to examine and compare resting regional cerebral blood flow in elderly adults with HF (n = 17) to age-matched healthy controls (n = 18). Prior to completing SPECT scanning, participants completed cognitive testing which included the MMSE and the cognitive function assessment portion of the Cambridge Mental Disorders of the Elderly Examination (CAMCOG). SPECT scans were completed following

intravenous injection of 30-mCi technetium-99m hexamethylpropyleneamine-oxime (^{99m}Tc-HMPAO). In addition, structural brain scans were completed on all participants, with those with MRI contraindications completing CT scans. Overall, individuals with HF demonstrated lower global cognition and poorer performance on subtests of the CAMCOG, including visual and verbal memory, learning, and language, when compared to controls. In addition, individuals with HF showed a reduction in regional cerebral blood flow in posterior cortical regions of the brain, and total score on the CAMCOG was correlated to regional cerebral blood flow in a voxel cluster including the right posterior cingulate cortex and precuneus. Within the subsamples of individuals who completed MRI, no significant differences emerged between HF and controls participants in terms of total WMH (Alves et al., 2005). While the use of SPECT allows for more precise functional quantification, the study is limited in several ways. In addition to a small sample size, normative data is not provided for the cognitive measures used, and while finding a significant difference in MMSE scores between the HF and control groups, the mean MMSE score for the HF group would still be considered intact (M = 26.6).

In sum, the mechanisms linking HF to cognitive dysfunction are still being elucidated, though likely contributors have been identified. It is well established that individuals with HF experience irreversible brain changes such as atrophy, infarcts, and WMH (Schmidt, Fazekas, Offenbacher, Dusleag, & Lechner, 1991; Vogels, et al., 2007b; Almeida et al., 2005) which can negatively impact cognitive functioning. However, findings from work in this area have been inconsistent indicating that structural changes do not fully account for the pattern of cognitive decline seen in HF. Thus, it appears likely that functional brain changes, specifically reduced cerebral perfusion, play an important role. The disruption in cerebral autoregulation that occurs during CPB has been implicated in the short-term cognitive dysfunction seen after CABG (Selnes & Gottesman, 2010). This suggests that even transient periods of hypoperfusion can have a

negative, albeit temporary, impact on cognition. Individuals with HF experience a 19-30% (Choi et al., 2006; Gruhn, et al., 2001) decrease in cerebral perfusion which likely has a more severe and enduring negative impact on cognition. The limited work examining the association between reduced CBF and cognition in HF has yielded mixed results, warranting further examination of this potential relationship.

Study Aims

The current study aimed to elucidate the relationship among cardiac function, CBF, and cognitive performance in HF. Given the positive association demonstrated between increased levels of cardiovascular fitness and neurocognitive outcomes in CVD (Gunstad et al., 2005; Stanek et al., 2011), it was expected that individuals with higher levels of cardiac output would perform better on cognitive tasks. In addition, it was expected that increased CBF mean velocity and decreased PI would be associated with better cognitive performance. Lastly, it was hypothesized that cardiac output would moderate the relationship between cerebral perfusion measures and cognitive performance, such that higher levels of cardiac output would yield better cognitive performance for those with higher cerebral mean flow velocities and lower pulsatility indices.

Method

Participants

A total of 100 older adults who are enrolled in a longitudinal study examining the effects of cardiac rehabilitation on neuropsychological functioning in HF were included in the current study. Participants from the parent longitudinal study were recruited from outpatient cardiology clinics and were eligible for participation if they were between 50-85 years of age, English-speaking, and had a history of HF. Exclusion criteria included a history of neurological disorder (e.g., stroke, Alzheimer's disease, severe head injury), history of significant psychological problems (e.g., schizophrenia, bipolar disorder, substance abuse), or developmental disability. See Table 1 for demographic and clinical characteristics.

Table 1. Demographic and Clinical Characteristics of 100 Older Adults with HF.

Demographic Characteristics	Mean (SD)	Range
Age (years)	67.85 (9.06)	50 - 85
Female (%)	27	
Clinical Characteristics	Mean(SD)/%	Range
Education (years)	13.50 (2.52)	8 - 23
Hypertension	65	
Myocardial Infarction	58	
Diabetes	34	
Sleep Apnea	20	

Measures

Neuropsychological test battery. Participants completed a battery of well established neuropsychological measures that assessed multiple domains (see Table 2). Specifically, cognitive performance in the domains of memory, attention/psychomotor speed, executive function, and language was assessed. Raw test scores were converted into T-scores using normative data based on age, and when possible, education and gender, prior to running analyses to facilitate interpretation. A composite score was then created for each cognitive domain by averaging the scores of each domain's subtests. In addition, global cognitive functioning was assessed and premorbid IQ was estimated. Participants completed the following measures:

Memory

California Verbal Learning Test-Second Edition (CVLT; Delis, Kramer, Kaplan, & Ober, 2000). Individuals are asked to learn and recall a 16-item word list. Specifically, indices of learning (Sum of Trials 1-5), Immediate Recall (Short Free Recall), and Delayed Recall (Long Free Recall) was examined.

Attention/Psychomotor Speed

Trail Making Test A (Reitan, 1958). Individuals are asked to connect a series of 25 numbered dots in ascending order as quickly as they can (e.g. 1-2-3, etc.). Time to completion is recorded.

Letter Number Sequencing (Wechsler, 1997). This test is a measure of complex attention and working memory. Participants are read strings of numbers and letters of increasing length, and asked to reorganize the numbers and letters according to predetermined rules.

Grooved Pegboard (Klove, 1963). Individuals are asked to place notched pegs into a 5 X 5 board as quickly as possible. Time to completion for the dominant hand performance was recorded.

Executive Function

Trail Making Test B (Reitan, 1958). Trail Making B adds a set-shifting component to Trail Making Test A and requires participants to alternate between numbers and letters in ascending order (e.g. 1-A-2-B, etc.). Time to completion was recorded.

Frontal Assessment Battery (Dubois, Slachevsky, Litvan, & Pillon, 2000). This test employs several short tasks to assess frontal system executive function. More specifically, participants are asked to identify similarities among two 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.

Stroop Test (Golden, 1978). This test measures selective attention and mental flexibility. Participants are asked to first read columns of words spelling out colors printed in black ink (word subtest). They are then asked to identify the color a series of Xs is printed in (color subtest), and finally to indicate the color of the ink of a word (which spells out a color) is printed in, regardless of the verbal content (color-word subtest). An interference score was calculated based on word and color subtest performances to determine expected performance on the color-word subtest; this was then compared to actual color-word test performance.

Language

Animal Naming (Eslinger, Damasio, & Benton, 1984). This test is a measure of semantic verbal fluency. Participants are asked to name as many different kinds of animals as they can in 60 seconds.

Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983). This test is a measure of confrontation naming and language abilities. Participants are shown pictures and asked to name the depicted item. Items difficulty increases from high-frequency objects (e.g., bed) and lower-frequency objects (e.g., trellis).

Global Cognitive Functioning

Modified Mini Mental Status Examination (3MS; Teng & Chui, 1987). This test is a brief screening measure of global cognitive function and is an extension of the MMSE (Folstein, Folstein, & McHugh, 1975). Much like the MMSE, the 3MS is comprised of several short tasks, including orientation, learning and brief recall of a short list of target words, and a copy of a simple geometric figure. However, the 3MS also includes a delayed free recall of target words, additional orientation questions, animal fluency, and a measure of executive function (i.e., similarities). Previous work has found the 3MS to be better at identifying cognitive impairment and dementia among elderly individuals when compared to the MMSE (McDowell, Kristjansson, Hill, & Hébert, 1997; Bland & Newman, 2001).

Estimated Premorbid Intelligence.

North American Adult Reading Test (NAART; Blair & Spreen 1989). Individuals are asked to read a list of irregularly pronounced words. This test provides a reliable estimate of IQ in medical populations.

Cardiac function. Impedance cardiography was used to determine cardiac output. Impedance cardiography is considered a safe and reliable means of assessing hemodynamic function, including cardiac output, in HF (Rosenberg & Yancy, 2000). Impedance cardiography signals were recorded via a Hutcheson Impedance Cardiograph (Model HIC-3000, Bio-Impedance Technology, Chapel Hill, NC) using a tetrapolar band-electrode configuration. The electrocardiogram (ECG) was recorded from the Hutcheson Impedance Cardiograph using disposable ECG electrodes. The basal thoracic impedance (Zo), the first derivative of the pulsatile impedance (dZ/dt) and the ECG waveforms were processed using specialized ensemble-averaging software (COP, BIT Inc., Chapel Hill, NC), which was used to derive stroke volume using the Kubicek equation. Following instrumentation, Impedance cardiographic signals were

recorded for seven 40 second periods during a 10 minute resting baseline. Heart rate was assessed using an automated oscillometric blood pressure device (Accutor Plus Oscillometric BP Monitor, Datascope Corp, Mahwah, NH) which when initiated triggered a concurrent 40 second impedance cardiography measure. The last six measurements were averaged to determine cardiac output (stroke volume x heart rate). See Table 2.

Cerebral blood flow. TCD was used to quantify cerebral perfusion. Specifically, an expanded STOP protocol was completed for all study participants (Bulas, et al., 2000). Briefly, the STOP protocol assesses blood flow velocity in the major arteries of the brain, including the MCA, anterior cerebral artery (ACA), terminal internal carotid artery (TICA), posterior cerebellar artery (PCA), intracranial vertebral arteries (IVA), basilar artery (BA), intracranial internal carotid artery (ICA), and opthalamic artery (OA). For each artery, several indices are generated including peak systolic flow velocity, end diastolic flow velocity, mean flow velocity, and pulsatility index [PI = (peak systolic – end diastolic)/mean velocity]. The current study examined the mean flow velocity and pulsatility index in areas of the brain known to be affected in HF. Indices of the ACA, MCA, PCA were examined, as these arteries perfuse regions of the brain critical for the cognitive abilities affected by HF. Specifically, the ACA perfuses the frontal to anterior parietal lobes, the MCA perfuses portions of the frontal, temporal and parietal lobes, and the PCA perfuses the inferior and medial temporal lobe, as well as the occipital cortex (Blumenfeld, 2002). The average of multiple reads will be taken and the measures from the left and right arteries were combined (see Table 2), as previous work suggests there are no significant interhemispheric differences (Krejza, et al., 1999; Demirkaya, Uluc, Bek, & Vural, 2008).

Table 2. Cognitive, Cardiac, and Cerebrovascular Characteristics of 100 Older Adults with HF.

Cognitive Characteristics	Mean (SD)	Range
Estimated IQ	111.28 (9.87)	84 - 131
3MS	93.59 (4.73)	73 - 100
Memory	47.79 (9.69)	17.33 - 73.67
Attention/Psychomotor Speed	46.93 (7.99)	21.40 - 60.50
Executive Function	47.54 (10.93)	3.27 - 64.20
Language	53.51 (8.57)	27.45 - 75.75
Cardiac Function		
Cardiac Output (l/min)	5.11 (1.63)	2.10 - 9.92
Cerebrovascular Function		
ACA mean flow velocity (cm/sec)	35.72 (10.28)	16.75 - 71.36
MCA mean flow velocity (cm/sec)	40.55 (10.43)	16.00 - 73.29
PCA mean flow velocity (cm/sec)	27.44 (6.08)	14.00 - 40.00
ACA pulsatility index	1.09 (0.25)	0.71 - 1.91
MCA pulsatility index	1.05 (0.21)	0.67 - 1.63
PCA pulsatility index	1.01 (0.21)	0.60 - 1.53

Procedure

Informed consent was provided by all study participants prior to beginning any part of the study. Participants completed study procedures over two visits. On the first visit, participants provided medical history information through self-report measures, which were corroborated by medical records whenever possible. Participants then completed measures of cardiac function followed by the neuropsychological test battery. The TCD was completed on a different day, within 2-weeks of completing the first visit.

Statistical Analyses

Analysis plan. Hierarchical multiple regression was used to examine the potential moderating effect of cardiac output on the relationship between cerebral perfusion and cognitive performance. Six analyses were conducted for each cognitive domain to examine the relationships between cognition and cardiac output with the mean flow velocities and PIs of the ACA, MCA, and PCA. The composite cognitive score served as the dependent variable in all analyses. Cardiac output, mean flow velocity, and PI were standardized within the sample to facilitate interpretation. Block 1 included the TCD measure (i.e., mean flow velocity or PI), Block 2 included the TCD measure and cardiac output, and the interaction between TCD and cardiac output wasadded in Block 3. Since composite/average scores were calculated, all missing data was excluded listwise.

Preliminary statistical analyses. The data was first examined for group differences in mean cardiac output among individuals with and without a pacemaker/cardiac device. There was no significant difference in cardiac output between the groups [t (98)= 1.32, p = .19] and pacemaker status was therefore not included in further analyses. Prior to testing study hypotheses, the data was also examined to ensure the assumptions of regression were met. First, the data was screened for univariate outliers by examining standardized scores. Three cases were found to

have extreme outliers and these cases were dropped from further analyses. With the remaining cases, the data was then checked for the presence of multivariate outliers by examining Mahalanobis distance and an additional nine cases were excluded from further analyses. The final sample size was 100. Regression analyses were conducted and normality, linearity, homoscedasticity, and multicollinearity were assessed on an analysis to analysis basis by examining plots/histograms of the residuals (normality, linearity, and homoscedasticity) and correlations among variables (multicollinearity). No violations of these assumptions were evident and no additional transformations were made.

Results

Memory

The full model including the mean flow velocity of the ACA was a statistically significant predictor of memory performance [$F(3,96) = 6.51$, $p < .001$] and accounted for 16.9% of the variance in memory performance (see Table 3). Mean flow velocity of the ACA [$\beta = 0.28$, $t(96) = 2.91$, $p = .01$] was a significant individual predictor of memory performance, with increased mean flow velocity associated with better memory performance, while cardiac output was not a significant individual predictor [$\beta = -0.05$ $t(96) = -0.55$, $p = .59$]. However, cardiac output moderated the association between mean flow velocity of the ACA and memory [$\beta = -0.32$, $t(96) = -3.32$, $p < .01$; $\Delta R^2 = 0.10$, $F(1,96) = 11.03$, $p < .01$]. Specifically, the combination of group mean levels of cardiac output and increased mean flow velocity of the ACA was associated with better memory performance; the combination of below average cardiac output and higher mean flow velocities was associated with even greater gains in memory performance. In contrast, the combination of higher than average cardiac output and increased velocity did not greatly impact memory performance (see Figure 1).

The remaining full models examining memory performance were not significant: pACA [$F(3,96) = 0.58$, $p = .63$]; mMCA [$F(3,96) = 2.19$, $p = .09$]; pMCA [$F(3,96) = 0.68$, $p = .57$]; mPCA [$F(3,96) = 2.14$, $p = .10$]; pPCA [$F(3,96) = 0.31$, $p = .82$].

Table 3. Full Model Results of Hierarchical Regression Analyses for Memory.

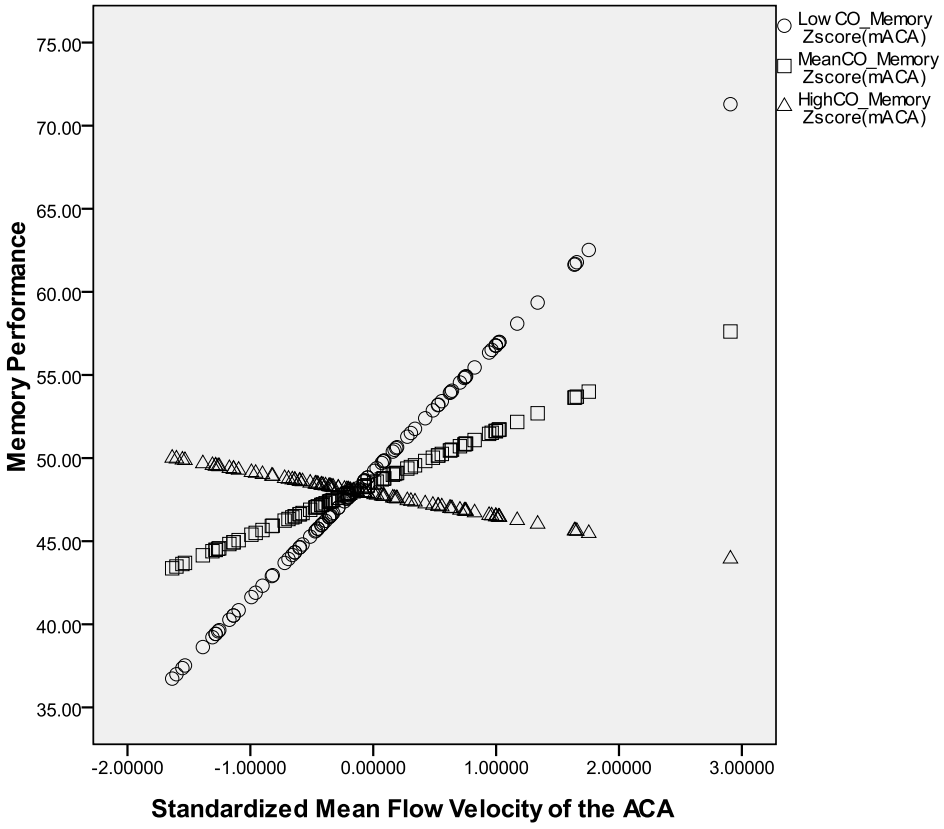
Cerebrovascular Measure	B	SE	β	t	*p*
ACA - mean flow velocity					
mACA	3.14	1.08	0.28	2.91	.01
CO	-0.68	1.25	-0.05	-0.55	.59
mACA*CO	-4.47	1.35	-0.32	-3.32	<.01
MCA - mean flow velocity					
mMCA	2.34	1.04	0.23	2.24	.03
CO	-1.07	1.30	-0.08	-0.83	.41
mMCA*CO	-1.34	1.52	-0.09	-0.88	.38
PCA - mean flow velocity					
mPCA	3.08	1.29	0.25	2.39	.02
CO	-0.99	1.28	-0.08	-0.77	.44
mPCA*CO	0.12	1.67	0.01	0.07	.94
ACA - pulsatility index					
pACA	-1.46	1.24	-0.13	-1.17	.25
CO	-0.90	1.34	-0.07	-0.67	.51
pACA*CO	-1.12	1.82	-0.07	-0.61	.54
MCA - pulsatility index					
pMCA	-2.43	2.24	-0.12	-1.09	.28
CO	-0.97	1.33	-0.08	-0.73	.47
pMCA*CO	-3.31	2.99	-0.13	-1.11	.27
PCA - pulsatility index					
pPCA	-0.55	1.16	-0.05	-0.47	.64
CO	-0.85	1.32	-0.07	-0.64	.52
pPCA*CO	-1.11	1.57	-0.07	-0.70	.48

*Note.*ACA = anterior cerebral artery; MCA = middle cerebral artery;

PCA = posterior cerebral artery; m = mean flow velocity; CO = cardiac output;

p = pulsatility index.

Figure 1. Interactive Effect of Cardiac Output and Mean Flow Velocity of the ACA on Memory.



Executive Function

The full model including the mean flow velocity of the ACA was a significant predictor of executive function performance [F (3,96) = 2.80, p = .04] and accounted for 8.1% of the variance in performance (see Table 4). While no significant individual predictors emerged, cardiac output moderated the relationship between mean flow velocity of the ACA and executive function [β = -0.26, t (96) = -2.56, p = .01; ΔR^2 = 0.06, F(1,96) = 6.56, p = .01]. Specifically, the combination of below group average levels of cardiac output and increased mean flow velocity of the ACA was associated with better performance, while the combination of above average cardiac output and higher mean flow velocities was associated with a decline in performance. The combination of average cardiac output and increased velocity did not greatly impact executive function performance (see Figure 2).

Analyses indicated no other significant full models for predicting executive function: pACA [F (3, 96) = 1.64, p = .19]; mMCA [F (3,96) = 0.92, p = .44]; pMCA [F (3,96) = 0.38, p = .77]; mPCA [F (3,96) = 2.15, p =.10]; pPCA [F (3,96) = 0.71, p = .55].

Table 4. Full Model Results of Hierarchical Regression Analyses for Executive Function.

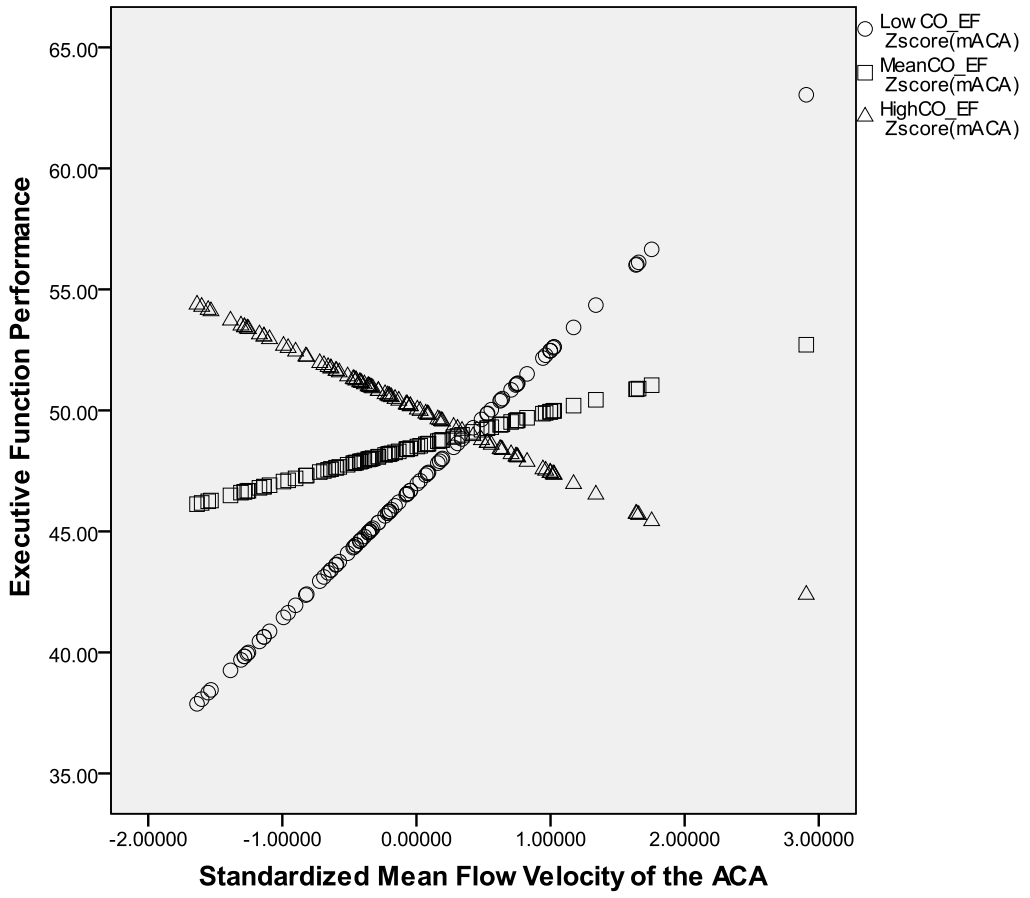
Cerebrovascular Measure	B	SE	β	t	*p*
ACA - mean flow velocity					
mACA	1.45	1.28	0.11	1.13	.26
CO	1.56	1.48	0.11	1.05	.30
mACA*CO	-4.09	1.60	-0.26	-2.56	.01
MCA - mean flow velocity					
mMCA	1.36	1.20	0.12	1.13	.26
CO	1.03	1.49	0.07	0.69	.49
mMCA*CO	-1.41	1.75	-0.08	-0.80	.42
PCA - mean flow velocity					
mPCA	1.98	1.45	0.14	1.36	.18
CO	1.20	1.44	0.08	0.83	.41
mPCA*CO	-2.90	1.88	-0.16	-1.54	.13
ACA - pulsatility index					
pACA	0.35	1.38	0.03	0.25	.80
CO	1.92	1.49	0.13	1.29	.20
pACA*CO	4.05	2.02	0.22	2.01	.05
MCA - pulsatility index					
pMCA	-1.17	2.53	-0.05	-0.46	.64
CO	1.31	1.50	0.09	0.87	.39
pMCA*CO	1.03	3.39	0.03	0.30	.76
PCA - pulsatility index					
pPCA	-0.24	1.30	-0.02	-0.19	.85
CO	1.46	1.48	0.10	0.99	.33
pPCA*CO	2.01	1.76	0.12	1.14	.26

Note. ACA = anterior cerebral artery; MCA = middle cerebral artery;

PCA = posterior cerebral artery; m = mean flow velocity; CO = cardiac output;

p = pulsatility index.

Figure 2. Interactive Effect of Cardiac Output and Mean Flow Velocity of the ACA on Executive Function.



Attention/Psychomotor Speed

The full model including the pulsatility index of the PCA was a significant predictor of attention/psychomotor speed performance [F (3,96) = 2.98, p = .04] and accounted for 8.5% of the variance (see Table 5). The pulsatility index of the PCA was a significant predictor of performance [β = -0.28, t(96) = -2.75, p = .01], with higher pulsatility indices associated with decreased attention/psychomotor speed performance. No moderation was observed.

Analyses indicated no other significant full models for predicting attention/psychomotor speed performance: mACA [F (3,96) = 0.52, p = .67]; pACA [F (3,96) = 1.48, p = .23]; mMCA [F (3,96) = 0.44, p = .72]; pMCA [F (3,96) = 1.85, p = .14]; mPCA [F (3,96) = 1.52, p =.22].

Table 5. Full Model Results of Hierarchical Regression Analyses for Attention/Psychomotor.

Cerebrovascular Measure	B	SE	β	t	*p*
ACA - mean flow velocity					
mACA	0.90	0.97	0.10	0.93	.36
CO	<0.01	1.12	<0.01	<0.01	.99
mACA*CO	-1.03	1.21	-0.09	-0.85	.40
MCA - mean flow velocity					
mMCA	1.01	0.88	0.12	1.14	.26
CO	-0.16	1.10	-0.02	-0.15	.88
mMCA*CO	-0.05	1.29	<-0.01	-0.04	.97
PCA - mean flow velocity					
mPCA	2.08	1.07	0.20	1.94	.06
CO	-0.10	1.07	-0.01	-0.09	.93
mPCA*CO	-0.46	1.39	-0.03	-0.33	.74
ACA - pulsatility index					
pACA	-1.64	1.01	-0.17	-1.63	.11
CO	0.28	1.10	0.03	0.26	.80
pACA*CO	1.00	1.48	0.07	0.67	.50
MCA - pulsatility index					
pMCA	-3.89	1.81	-0.23	-2.15	.03
CO	0.19	1.07	0.02	0.17	.86
pMCA*CO	0.06	2.42	<0.01	0.03	.98
PCA - pulsatility index					
pPCA	-2.53	0.92	-0.28	-2.75	.01
CO	0.33	1.05	0.03	0.32	.75
pPCA*CO	0.70	1.25	0.06	0.57	.57

Language

Analyses indicated no significant full models for predicting language performance (see Table 6): mACA [F (3,96) = 0.13, p = .94]; pACA [F (3,96) = 0.77, p = .52]; mMCA [F (3,96) = 0.03, p =.99]; pMCA [F (3,96) = 0.09, p = .96]; mPCA [F (3,96) = 0.53, p = .66]; pPCA [F (3,96) = 0.27, p =.85].

Table 6. Full Model Results of Hierarchical Regression Analyses for Language.

Cerebrovascular Measure	B	SE	β	t	*p*
ACA - mean flow velocity					
mACA	-0.30	1.05	-0.03	-0.29	.77
CO	0.34	1.21	0.03	0.28	.78
mACA*CO	-0.70	1.30	-0.06	-0.54	.59
MCA - mean flow velocity					
mMCA	0.01	0.95	<0.01	0.01	.99
CO	0.17	1.18	0.02	0.15	.89
mMCA*CO	-0.39	1.39	-0.03	-0.28	.78
PCA - mean flow velocity					
mPCA	1.29	1.17	0.12	1.11	.27
CO	0.06	1.16	0.01	0.06	.96
mPCA*CO	-0.40	1.51	-0.03	-0.26	.80
ACA - pulsatility index					
pACA	-0.89	1.10	-0.09	-0.81	.42
CO	0.45	1.18	0.04	0.38	.71
pACA*CO	1.44	1.60	0.10	0.90	.37
MCA - pulsatility index					
pMCA	-0.55	2.00	-0.03	-0.28	.78
CO	0.23	1.18	0.02	0.20	.84
pMCA*CO	0.75	2.67	0.03	0.28	.78
PCA - pulsatility index					
pPCA	0.11	1.03	0.01	0.11	.91
CO	0.30	1.17	0.03	0.26	.80
pPCA*CO	1.22	1.39	0.09	0.88	.38

Note. ACA = anterior cerebral artery; MCA = middle cerebral artery; PCA = posterior cerebral artery; m = mean flow velocity; CO = cardiac output; p = pulsatility index.

Discussion

The current study examined the associations among cardiac output, cerebral blood flow, and cognition in older adults with HF, with focus on the potential moderating effect of cardiac output. Overall, a moderating effect of cardiac output was not observed, with the exception of memory and executive functioning. Several aspects of these findings warrant further discussion.

Cardiac output was found to moderate the association between the mean flow velocity of the ACA and memory and executive function performances. Given that previous research has identified memory and executive function as domains consistently affected by HF (Almeida & Flicker, 2001; Vogels, et al., 2007a; Vogels, Scheltens, Schroeder-Tanka, & Weinstein 2007; Bennett & Sauvé, 2003; Pressler et al., 2010) and that the ACA perfuses regions of the brain involved in mediating these tasks (Blumenfeld, 2002), such findings are not surprising. However, the moderating effect of cardiac output for each of these domains was inconsistent with the expectation that higher cardiac output and greater mean flow velocity of the ACA would be associated with better cognitive performance. Contrary to expectations, above average levels of cardiac output and increasing mean flow velocity of the ACA was associated with a *decrease* in executive function performance, and resulted in no substantial change in memory performance. Rather, better performance in both domains was found for below group average levels of cardiac output and increasing mean flow velocity of the ACA. Although previous work has suggested a link between systemic and cerebral perfusion in general forms of CVD (e.g., Jefferson, et al., 2007) and HF (e.g., Hoth, Poppas, Moser, Paul, Cohen, 2008), the current pattern of findings suggests a dissociation between systemic perfusion and cerebral perfusion. It is possible that the discrepancy may be the result of the measurement used to quantify systemic perfusion, as some work has found that cerebral blood flow in cardiac patients is not related to cardiac output (Eicke

et al., 2001); however, the use of a more precise measure of systemic perfusion (e.g., cardiac index which takes body surface area into account) in future work could reveal an association.

Alternatively, this pattern of findings could be a reflection of the compensatory mechanisms functioning to maintain adequate cardiac output negatively impacting vascular function within the brain. For example, endothelial dysfunction is common among individuals with HF and is implicated in the pathophysiology and adverse outcomes associated with the disease (Bauersachs & Widder, 2008; Fischer et al., 2005; Bank, Lee, & Kubo, 2000; Katz et al., 2005; de Berrazueta et al., 2010). In an effort to maintain adequate cardiac output in HF, compensatory mechanisms, including increased sympathetic nervous system activation, are recruited (Jackson, Gibbs, Davies, & Lip, 2000). However, increased sympathetic activation has been found to reduce endothelial function in healthy adults (Hijmering et al., 2002), which suggests even further dysfunction is likely among individuals with HF. Moreover, endothelial dysfunction may be implicated in brief episodes of hypoperfusion, as vascular endothelium work to maintain vascular homeostasis (Behrendt & Ganz, 2002), and this in turn may be associated with adverse brain changes.

Interestingly, cardiac output was not associated with memory or executive function performance. The current sample is comprised of individuals who are closely followed by their cardiologist and as a result their HF is likely currently well controlled. This is evidenced by mean resting cardiac output falling well within the normal range of 4-7 liters/minute at 5.11 liters/minute (Brownley, Hurwitz, & Schneiderman, 2000). However, while current cardiac function is intact, it is possible these individuals experienced reduced cardiac function in the past and structural brain damage was incurred at that time. For example, these individuals may already have sustained deep white matter damage, as such regions are susceptible to hypoperfusion (Brown & Thore, 2011). Future longitudinal work assessing individuals prior to the onset of HF

and other forms of CVD will be important in fully understanding the temporal relationship between cardiac dysfunction and pathophysiological brain changes.

A likely contributor to the current pattern of findings involves the relative intact cognitive function of the sample. Overall, the current sample represents a largely intact group of individuals with HF, with only 20% demonstrating some degree of impaired cognitive performance (i.e., $T < 35$) compared to the prevalence of impairment typically ranging from approximately 30-50% (Bennett & Sauvé, 2003). These findings may be a reflection of the current sample exhibiting above average premorbid intellectual functioning ($M = 111.28$) and being well educated ($M = 13.5$ years). In addition, cardiac function was largely intact and cerebral perfusion indices were grossly within normative ranges (e.g., Krejza, et al., 1999; Martin, Evans, & Naylor, 1994). If considered within the framework of systemic perfusion impacting cerebral perfusion, and ultimately cognitive function, this pattern of findings is not surprising as the majority of individuals are intact across these measures. Moreover, recent work from our group identified three distinct cognitive profiles that emerge in older adults with HF, including about 38% of persons with intact cognitive performance. Those who demonstrated intact cognitive performance had higher levels of estimated premorbid intelligence and more education, which suggests the possibility that cognitive reserve plays a role in preserving cognition among these individuals (Miller et al., 2012). Cognitive reserve models suggest that individual differences in cognition may be a function of the brain actively trying to cope with insult by relying on pre-existing factors, such as increased intellectual ability and educational attainment (Stern, 2009). While the underlying mechanisms linking cognitive reserve to cognition are not fully understood, cognitive reserve has been found to be a protective factor in various types of neurological conditions including in AD (Stern, 2009), frontotemporal dementia (Borroni et al., 2009), and traumatic brain injury (Kesler, Adams, Blasey, & Bigler, 2003). Moreover, cognitive reserve has been

found to impact cognition in diseases involving white matter such as stroke (Elkins et al., 2006) and multiple sclerosis (Benedict et al., 2010). These findings are particularly interesting given the increased incidence of infarcts and WMH among those with HF (Vogels, 2007c; Almeida et al., 2005) and their potential contribution to cognitive decline (Raz, Rodrigue, & Acker, 2003; Paul et al., 2005). Moreover, recent work has also demonstrated a moderating effect of cognitive reserve on the relationship between HF severity and cognitive function, with greater estimated premorbid IQ attenuating the negative effect of HF on cognitive performance in multiple domains (Alosco et al., 2012). It appears likely cognitive reserve and less severe HF are preserving cognitive performance among the majority of these individuals.

While the prevalence of cognitive impairment in the current sample is below the typical levels observed in the HF population, cognitive deficits are still present and are likely obscured by the majority of individuals demonstrating intact cognitive performance. The lack of such findings may be a function of range restriction or that fact that these individuals are closely followed by their health care providers. However, the pattern of findings for the moderating effect of cardiac output on memory and executive function suggest that the modifications that are made to compensate for functional insufficiencies of the heart may impact cognition as well, and differentially so for tasks involving frontal and temporal regions. As discussed above, the compensatory mechanisms to increase cardiac output may ultimately have a negative impact on vascular function in the brain. It is well established that vascular risk factors are associated with poor neurocognitive outcomes, including vascular dementia and Alzheimer's disease (Duron & Hanon, 2008). Vascular cognitive impairment (VCI) is a general term used to described the cognitive decline typically associated with vascular disease, and includes deficits in executive function, attention, and processing speed, (O'Brien, 2006)—primarily frontal and subcortical mediated tasks. Frontal-subcortical dysfunction is often worsened by small vessel damage which,

develops with increasing cardiovascular risk factors (Pugh & Lipsitz, 2002), and blood supply to deep white matter regions is derived from small vessels making these areas vulnerable to hypoperfusion and leukoaraiosis (Brown & Thore, 2011). While the above described impairments are commonly found, VCI is heterogeneous and deficits vary based on the regions of the brain affected and the extent of the damage (O'Brien, 2006; Moorhouse & Rockwood, 2008). Work by Vogels and colleagues (2007b) found impairments in the domains of memory and language (primarily temporally mediated tasks), along with VCI-consistent impairment, among individuals with HF. Moreover, as noted above, our work found that there are distinct groups of cognitively impaired individuals with HF. Within that study, a majority of individuals were found to exhibit memory deficits and a smaller subsample were impaired across multiple cognitive domains (Miller et al., 2012). The deficits seen in executive function and memory within the current sample suggest that most of these impaired individuals are exhibiting frontal and temporal patterns of decline. Reduced memory performance raises concern for mild cognitive impairment (MCI), a descriptive term for cognitive changes that occur prior to fully developing symptoms of dementia, and increase risk for Alzheimer's disease. (Petersen, 2007; Qiu, 2006).

The current findings are limited in several ways. The possible impact of disease duration cannot be examined due to the cross-sectional nature of the study. Prospective studies are necessary to determine the possibility of important disease by time interactions. In addition, future work should include additional measures of HF severity and cardiac function (e.g., ejection fraction, cardiac index), as well as measures of autonomic nervous system function. Similarly, while the use of TCD is a well accepted, non-invasive means of assessing cerebrovascular function, the use of more precise methodologies to quantify cerebral blood flow indices (e.g., arterial spin labeling from MRI) would be ideal, as would structural neuroimaging from MRI to correlate cognitive findings. However, many individuals with HF have contraindications that

prevent the utilization of such techniques. Lastly, there are multiple comorbid medical conditions associated with HF, including hypertension, diabetes mellitus, and sleep apnea (Metra et al., 2011), each of which are associated with adverse neurocognitive outcomes (Paglieri et al., 2008; Kodl & Seaquist; Aloia, Arndett, Davis, Riggs, & Byrd, 2004). Examining their individual and interactive effect on cognition, cardiac output, and cerebral perfusion in HF will be important.

In sum, while the current findings are suggestive for a moderating effect of cardiac output on the relationship between cognition and CBF in HF, additional work is needed to fully clarify the nature of these associations. The unexpected and limited findings of the current study are consistent with past work, confirming that the relationship between these variables is more complex than originally suspected. Larger scale longitudinal studies examining multiple measures of cardiac and cerebrovascular functioning are required to elucidate the ways in which these mechanisms interact to contribute to the cognitive performance seen in HF.

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