AUTONOMIC NERVOUS SYSTEM DYSREGULATION AND COGNITIVE FUNCTIONING IN PATIENTS WITH CONGESTIVE HEART FAILURE

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TABLE OF CONTENTS

LIST OF TABLES ................................................................................................................. iv
INTRODUCTION .................................................................................................................. 1
METHOD ............................................................................................................................ 17
RESULTS ............................................................................................................................ 24
DISCUSSION ....................................................................................................................... 35
REFERENCES ..................................................................................................................... 45
List of Tables

Table 1. Demographic and Cognitive Characteristics of Participants..........................25

Table 2. Pearson correlations between cognitive domains and demographic and clinical covariates ...........................................................................................................26

Table 3. Mean Values (SD) of Cardiovascular Measures.............................................26

Table 4. Multiple Hierarchical Regression Results Using Pre-Ejection Period to Predict Cognitive Performance .................................................................28

Table 5. Multiple Hierarchical Regression Results Using Low Frequency Heart Rate Variability to Predict Cognitive Performance ........................................30

Table 6. Multiple Hierarchical Regression Results Using High Frequency Heart Rate Variability to Predict Cognitive Performance ........................................32

Table 7. Multiple Hierarchical Regression Results Using the LF/HF Ratio to Predict Cognitive Performance.................................................................34
Introduction

Over five million U.S. adults suffer from heart failure (HF) and 670,000 new cases are diagnosed each year (American Heart Association [AHA], 2012). Estimates predict a 25% increase in prevalence resulting in an additional three million individuals developing HF by 2030 (AHA, 2012). In addition to high incidence and prevalence, HF mortality remains high. Fifty percent of HF patients die within five years of diagnosis (Levy et al., 2002; Roger et al., 2004). Given the high morbidity and mortality, HF carries significant economic and social burdens. For example, HF costs are expected reach 97 billion U.S. dollars by 2030 (AHA, 2012).

Despite advances in treatment, complex disease self-management accompanies HF and often leads to poor self-care. Inadequate adherence to complicated self-management regimens results from multiple factors including the complexity of the regimen itself, high medication costs (Dunlay, Eveleth, Shah, McNallan, & Roger, 2011), depression (Morgan et al., 2006) and cognitive dysfunction (Pressler, 2008; Vogels, Scheltens, Schroeder-Tanka, & Weinstein, 2007; Zuccalá, Cattel, Manes-Gravina, Di Niro, Cocchi, & Bernabei, 1997).
Cognitive Functioning in Heart Failure

Thirty-five to 50 percent of HF patients demonstrate cognitive impairment (Almeida & Flicker, 2001; Zuccalá et al., 2005). Moreover, individuals with HF have 4 times greater risk of cognitive impairment compared with matched controls without HF (Sauve, Lewis, Blankenbiller, Rickabaugh, & Pressler, 2009). Cognitive impairment in HF spans multiple domains of cognitive functioning including attention, working memory, executive function, memory, and language (Almeida & Flicker, 2001; Schmidt, Fazekas, Offenbacher, Dusleag, & Lechner, 1991; Gorkin et al., 1993; Trojano et al., 2003). Additionally, cognitive impairment predicts poor medication adherence (Hawkins, Kilian, Firek, Kashner, Firek, & Silvet, 2012), as well as disability and mortality in HF (Konstam, 2000; Zuccalá et al., 2003; Pressler, Kim, Riley, Ronis, & Gradus-Pizlo, 2010).

In addition to influencing disease self-management, cognitive impairment is linked to the pathophysiology of HF. Although structural brain changes (Schmidt, Fazekas, Offenbacher, Dusleag, & Lechner, 1991; Vogels et al., 2007a; Woo, Macey, Fonarow, Hamilton, & Harper, 2003) and reduced cerebral blood flow (Alves, et al., 2005; Roman, 2004) have been implicated as mechanisms underlying cognitive impairment in HF, autonomic nervous system (ANS) dysfunction may also contribute to diminished cognitive performance. Substantial research has found ANS disruption in HF patients, such as elevated catecholamine levels (Cohn et al., 1984). ANS function has been related to cognitive performance in healthy samples and individuals with cardiovascular disease (Epstein et al., 2013; Keary et al., 2007; Gunstad et al., 2009). No
studies have examined ANS dysfunction and cognitive performance in a sample of HF patients.

**Autonomic Nervous System**

The autonomic nervous system (ANS) is the branch of the peripheral nervous system that regulates the body’s internal environment by affecting heart rate, blood pressure, respiratory rate, digestion, body temperature, and sexual arousal in order to adapt to changes in the external environment. The ANS is traditionally conceptualized as having two divisions that can operate independently, reciprocally, or coactively (Berntson, Cacioppo, & Quigley, 1991; 1993): the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS). Both branches contribute to regulation of the cardiovascular system (Levy & Pappano, 2007) and seek to maintain homeostatic balance in response to internal and external demands (Akselrod et al., 1981; Porges, 1995). Typically, the sympathetic branch controls functions related to arousal and energy expenditure. Sympathetic activation contributes to increased heart rate, cardiac contractility, and vascular tone. Conversely, the parasympathetic branch exerts a calming or stabilizing effect. The ANS is considered healthy when both the sympathetic and parasympathetic branches respond to external demands in a balanced manner that promotes optimal mobilization and conservation of physiological resources, whereas an imbalanced system cannot respond appropriately.

In HF, the sympathetic nervous system becomes overactive to compensate for the heart’s decreasing ability to efficiently pump blood throughout the body, whereas the
parasympathetic nervous system becomes hypoactive. As such, the parasympathetic and sympathetic branches of the ANS may differentially relate to cognitive functioning. Increased understanding of the potential pathophysiological connection between cognitive functioning and ANS activity may increase understanding of the development of cognitive impairment in HF.

**ANS: Sympathetic Activity and Heart Failure**

The heart is primarily innervated by the sympathetic nervous system (Randall, Randall, & Ardell, 1991). Although increases in heart rate reflect a widely known correlate of sympathetic activation, increases in heart rate do not provide a specific measure of sympathetic changes as heart rate may not directly relate to changes in sympathetic influence on the heart. Similarly, plasma norepinephrine fails to provide a clear index of sympathetic activation because it cannot account for differences in norepinephrine release resulting from stress as well as the rate which norepinephrine is removed from circulation (Esler et al., 1988).

**Pre-ejection period.** Pre-ejection period (PEP) represents a noninvasive index of sympathetic activity and has been the focus of much psychophysiological research (e.g., Allen, Obrist, Sherwood, Crowell, & Grange, 1987; Cacioppo, Unchino, & Bernston, 1994; Sherwood, Allen, Obrist, & Langer, 1986). PEP represents the time interval from the beginning of electrical stimulation of the ventricles to the opening of the aortic value when blood begins ejection from the heart. Sympathetic activation of the heart results in shortenings in the PEP time interval (Cacioppo et al., 1994; Schächinger, Weinbacher,
Kiss, Ritz, & Langewitz, 2001). Resting HR is not strongly correlated with PEP (McCubbin, Richardson, Langer, Kizer, & Obrist, 1983). Adrenergic-induced increases in heart rate lead to shortened PEP, whereas increased heart rate resulting from vagal blockage or atrial pacing does not affect PEP (Harris, Schoenfeld, & Weissler, 1967). Therefore, PEP provides a measure of sympathetic activity independent of heart rate. Also, PEP is lengthened by elevated mean and diastolic blood pressure (Weissler, Harris, & Schoenfeld, 1968).

**Low-frequency heart rate variability.** Heart rate variability (HRV), specifically the low frequency (LF: 0.04-0.15 Hz) component, has also been used to assess sympathetic activity. HRV is a non-invasive measure of variability in the beat-to-beat intervals of heart rate. Lower resting levels of total HRV are understood to reflect decreased ability to physiologically and behaviorally adapt to changing environmental demands. HRV is influenced by a number of factors including age, genetic factors, diet, and depression (Mozaffarian, Stein, Prineas, & Siscovick, 2008; Nahshoni et al., 2004; Tulppo, Mäkikallio, Seppänen, Laukkanen, & Huikuri, 1998). Additionally, multiple conditions, including hypertension, acute myocardial infarction, chronic obstructive pulmonary disease, diabetes, and HF are related to variations in HRV (Chandra, Yeates, & Wong, 2003). The LF component of HRV is generally thought to reflect both sympathetic and parasympathetic influence (Cacioppo et al., 1994). However, LF-HRV is primary sympathetically-driven. In HF, a decrease in LF-HRV (i.e., decreased sympathetic activity) has been associated with increased mortality risk (Chandra et al., 2003).
Evidence from experimental psychophysiology supports a connection between various indices of sympathetic activity, including PEP and LF-HRV, and cognitive performance. McCubbin and colleagues (1983) reported a reduction in PEP (i.e., increased sympathetic activity) following a stressful cognitive task designed to assess reasoning ability (Raven matrices) in male undergraduate students. McCubbin et al. also noted that shorter PEP (indicating greater sympathetic activity) was associated with higher plasma norepinephrine (indicating greater sympathetic activity) following the cognitive tasks, supporting the use of PEP as a marker of sympathetic cardiac activation in response to acute psychological stress. Similarly, Esler and colleagues (1999) examined plasma norepinephrine release in response to a forced mental arithmetic challenge in 12 participants with untreated essential hypertension. Results indicated an increase in norepinephrine spillover (the release from sympathetic nerve terminals) from the heart and plasma arterial norepinephrine. Although the authors did not report results of cognitive performance, these findings support a relationship between expending cognitive effort and sympathetic activation.

A more recent study found that sympathetic activation, as measured by R-wave to pulse interval (RPI) decreased (indicating sympathetic stimulation) during a letter cancellation test of attention in 60 healthy college students (Duschek, Muckenthaler, Werner, & Reyes del Paso, 2009). Furthermore, lower values of RPI were related to increased attentional performance (Duschek et al., 2009). Thus, it seems that enhanced sympathetic activity contributes to cardiovascular reactivity that can lead to improved attentional performance.
Additionally, some research has investigated sympathetic influences on memory, suggesting that sympathetic activation, signifying increased effort, leads to better memory performance (Cahill & Alkire, 2003; Shah et al., 2011; Frewen et al., 2013). For example, Frewen and colleagues (2013) reported that higher LF-HRV was associated with better scores on the Montreal Cognitive Assessment (MoCA) in a cross-sectional population study of over 4,000 aging adults. Analysis of sub-domains revealed memory recall primarily accounted for the observed relationship between LF-HRV and MoCA performance. Additionally, controlling for familial and genetic influence, Shah and colleagues (2011) found an association between higher 24-hour ambulatory LF-HRV and better verbal, but not visual, memory performance in 416 middle-aged male twins without posttraumatic stress disorder (PTSD) from the Vietnam Era Twin Registry. However, the authors note that the verbal selective reminding task also tapped executive function. Still, the influence of sympathetic activity on memory is worth consideration in HF. Many patients with HF are prescribed beta-blockers for hypertension, which likely contributes to the lengthened PEP seen in HF. Sympathetic blockade has been shown to lead to memory impairment (Cahill, Prins, Weber, & McGaugh, 1994; Maheu, Joober, Beaulieu, & Lupien., 2004). Maheu et al., reported that propranolol impaired short- and long-term declarative memory for emotionally arousing, but not neutral, material. Similarly, it has been reported that elderly adults with chronic beta-blocker use did not demonstrate normative memory enhancement following muscle-tension-induced arousal (Nielson & Jensen, 1994). As beta-blocker use reduces
sympathetic activation and can impair memory, HF patients taking beta-blockers may experience memory impairment resulting from sympathetic dampening.

Cardiovascular parameters influenced by ANS function, such as heart rate recovery and blood pressure variability, have also been associated with cognitive functioning in older adults with cardiovascular disease (Epstein et al., 2013; Keary et al., 2007; Gunstad et al., 2009; Okonkwo et al, 2011). Gunstad et al. (2009) reported greater blood pressure variability was related to better cognitive performance in nearly 99 older adults with cardiovascular disease. Domains of language, visual-spatial, memory, and executive-attention-psychomotor function were assessed, noting that the strongest relationships emerged between blood pressure variability and memory and language ability. The authors attribute these findings to ANS disruption present in cardiovascular disease or possible white matter disease causes by BP variability. Similarly, Okonkwo et al. (2011) reported that lower cardiac output, reduced systolic blood pressure variability and increased diastolic blood pressure variability predicted 3-year decline in attention-executive-psychomotor function in older adults with cardiovascular disease. Additional research is lacking on the relationship between sympathetic indices, such as PEP and LF-HRV, and cognitive functioning in HF. Although sympathetic activation is typically related to increased cognitive or physical effort and better performance, the chronically elevated sympathetic nervous system in HF is detrimental to the vascular system and may also negatively impact cognitive function. Thus, in HF, elevated sympathetic functioning may be related to poorer cognitive performance.
ANS: Parasympathetic Activity and Heart Failure

**High-frequency heart rate variability.** HRV is also a commonly used index of parasympathetic activity. Both time and frequency domain measures of HRV have been used to assess parasympathetic activity. In the time domain, commonly used indices of HRV include the standard deviation of the interbeat intervals (IBI), standard deviation of R to R intervals (SDNN), the root mean square successive differences (RMSSD), and measures of baroreflex sensitivity. Unlike the frequency domain measures, parasympathetic and sympathetic control cannot be distinguished in time domain indices (Achen & Jeukendrup, 2003). However, sympathetic influence minimally contributes to the high frequency spectral power component (HF-HRV: 0.15-0.40 Hz). Thus, the high frequency component of HRV provides a reliable indicator of parasympathetic function (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [Task Force], 1996).

HF-HRV, similar to and commonly referred to as respiratory sinus arrhythmia (RSA), reflects periodic normal variations in heart rate that fluctuate according to respiratory cycles. HF-HRV accelerates during inspiration and decelerates during expiration (Frazier, Strauss, & Steinhauer, 2004). HF patients exhibit reduced HF-HRV relative to healthy adults (Casolo, Balli, Taddei, Amuhasi, & Gori, 1989) signifying reduced parasympathetic reactivity. In addition to altered parasympathetic functioning in HF, reduced HRV is also associated with risk factors for cognitive impairment including...
hypertension (Singh et al., 1998), diabetes mellitus (Carnethon, Golden, Folsom, Haskell, & Liao, 2003), high cholesterol (Christensen, Toft, Christensen, & Schmidt, 1999), and elevated cortisol (Karlamangla, Singer, Chodosh, McEwen, & Seeman, 2005).

Evidence suggests that parasympathetic function is related to cognitive performance. Multiple studies report higher resting HF-HRV is associated with better cognitive performance in healthy individuals (Hansen, Johnson, Thayer, 2003; Hansen, Johnson, Sollers, et al., 2004). HF-HRV is also reduced during cognitive tasks (Althaus, Mulder, Mulder, Roon, & Minderaa, 1998; Duschek et al., 2009). For example, Duschek et al., (2009) reported that parasympathetic activation, as measured by RSA decreased during a letter cancellation test of attention in 60 healthy college students. Higher levels of baseline RSA were correlated with greater declines during task performance (Duschek et al., 2009). Furthermore, RSA was negatively related to attentional performance during task performance. Although greater reductions in parasympathetic activity during cognitive tasks in healthy individuals signal flexible response to cognitive stress, chronically reduced parasympathetic activity seen in HF is unlikely to be beneficial. Reduced parasympathetic activity during cognitive tasks reflects greater adaptability, whereas chronically reduced parasympathetic activity reflects a system incapable of appropriate responses to stress.

In a sample of fifty-three male military personnel, Hansen, Johnsen, and Thayer (2003) found that individuals in the high HRV group (based on median split of RMSSD) demonstrated greater accuracy on both the working memory task and sustained attention.
task, as well as faster reactions times on the sustained attention task. Sub-analyses indicated that differences between groups emerged only for components of the continuous performance task involving executive function. However, performance on a simple reaction time task did not differ between individuals with high and low HRV.

Consistent with HF-HRV reductions evidenced during cognitive tasks, Hansen et al. (2003), also noted that HRV during task performance was suppressed compared to HRV during recovery. In a similar study, Hansen, Johnsen, and Thayer (2009) explored the relationship between resting HF-HRV and cognitive performance on a continuous performance task and a working memory task during threat of shock in sixty-five male military personnel. Hansen et al. (2009) reported that HF-HRV was positively associated with cognitive tasks reflecting executive function, but was not associated with non-executive tasks. Participants in the high HRV group (based on a median split of HF-HRV) demonstrated better performance during cognitive tasks than individuals in the low HRV group regardless of presence of threat of shock. Thus, individuals with higher HF-HRV demonstrate increased physiological flexibility in the face of environmental challenges, including cognitive demands. Conversely, HF patient who exhibit reduced resting HF-HRV are less likely to demonstrate adequate physiological adaption in response to cognitive stress.

Community samples reveal conflicting findings. Kim and colleagues (2006) garnered further support for a relationship between ANS function and cognitive performance. Reduced time (RMSSD and NN50) and frequency (HF power) domain HRV was independently associated with 6.7 times greater odds of cognitive impairment
defined as a MMSE score less than 24 in 300 older physically disabled, community-dwelling women, controlling for clinical variables including cardiovascular disease (Kim et al., 2006). Conversely, although Frewen et al. (2013), reported a relationship between reduced LF-HRV and lower MoCA score, HF-HRV was not related to performance in predominately healthy older adults. Similarly, the Whitehall II cohort study indicated no cross-sectional, prospective, or longitudinal relationship between time domain (SDNN) nor frequency domain (LF and HF) HRV and cognitive impairment in 5,375 middle-aged men and women. Cognitive functioning was assessed with a battery comprised of five tasks including a test of short-term verbal memory, verbal and mathematical reasoning tests of inductive reasoning, a test of verbal meaning and word comprehension, and two tests of verbal fluency (phonemic and semantic). However, stronger effects were found in a sub-group of the sample with angina or myocardial infarction (Britton et al., 2008). Thus, Britton et al.’s findings may have been limited by examining a middle-aged, relatively disease-free sample. A larger sample of individuals with reduced HF-HRV secondary to cardiovascular disease may exhibit a stronger relationship between HF-HRV and cognitive performance. No additional studies have examined these relationships in patients within cardiovascular disease.

**ANS: Parasympathetic and Sympathetic Influence**

**LF/HF ratio.** The ratio of LF to HF power (LF/HF ratio) has also been examined and commonly reported to reflect sympathovagal balance (Pagani et al., 1986), with ratios greater than one indicating reduced cardiac parasympathetic tone and increased cardiac sympathetic dominance. However, the understanding of the LF/HF ratio has
recently been challenged (Billman, 2013). Billman argues that the understanding of the LF/HF ratio as a reflection of “sympathetic dominance” versus “parasympathetic dominance” is an oversimplification of the non-linear and often non-reciprocal relationship of the sympathetic and parasympathetic nervous systems. For example, although the LF component of HRV is largely thought to be driven by sympathetic influence, parasympathetic activity also modulates the LF component. Currently, there is no consensus regarding the accurate interpretation of the LF/HF ratio. Additionally, no clear picture emerges from the available evidence regarding the relationship between LF/HF ratio and cognitive function.

Two studies have supported a relationship between cognitive performance and the LF/HF ratio. Assessing both time and frequency domain indices, Luft, Takase, and Darby (2009) suggested that tasks requiring increased attentional demand were associated with attenuated HRV. Frequency domain (LF/HF ratio), but not time domain (SDNNs, rMSSDs), analysis of HRV was consistent with previous research indicating that performance on tests of executive function leads to increased HRV using a computerized battery of executive and non-executive tasks of cognitive performance. However, Luft (2009) also reported that frequency and time domain measures of HRV were not well-correlated in the sample, unlike previous research. However, Luft’s sample consisted of 30 highly trained athletes. Given the importance of physical fitness in HRV (Tulppo et al., 1998), Luft’s findings, suggesting increased parasympathetic and sympathetic activation, may have been influenced by the high fitness level of participants. In addition to LF-HRV, Frewen et al., (2013) also noted a relationship
between lower LF/HF ratio and poorer MoCA performance in healthy older adults. Consistent with Billman (2013), the authors suggested that the LF/HF ratio requires more complex interpretation than being understood to reflect sympathovagal. Instead, Frewen et al. (2013) suggested the LF/HF ratio reflects autonomic modulation so that reduced cardiac autonomic modulation is associated with poor cognitive performance. According to traditional interpretations, it may be expected that HF patients would demonstrate sympathetic dominance, signified by ratios greater than one. Given the pathophysiological ANS disruption in HF, it may also be expected that lower LF/HF ratio would be associated with reduced cognitive performance. However, without a clear understanding of the LF/HF ratio, hypotheses must remain tentative.

**Potential Mechanisms**

Despite the connection between ANS performance and cognitive functioning, the mechanisms explaining the relationship between cognitive and ANS function are not well understood. Disruption in other cardiac processes associated with ANS dysfunction, such as impaired endothelial function (Hijmering, 2002), may partially account for the relationship. Alternatively, the relationship between the ANS and cognition may be a marker of the functioning of the prefrontal cortical network. Thayer and Lane (2000) proposed a neurovisceral integration model linking cognitive, affective, and autonomic neural networks. This model suggests that cognitive functions associated with the prefrontal cortex are linked to markers of ANS activity such as heart rate variability. According to the model, an underlying central autonomic network (CAN) exists so that
autonomic function and executive function are both regulated by the prefrontal cortex, and that heart rate variability likely represents a marker of both. Thus, domains of cognitive functioning associated with the prefrontal cortex, such as executive function, selective attention, and affective responses (Thayer & Lane, 2000; Thayer, Hansen, Saus-Rose, & Johnsen, 2009), may be those most affected by heart rate variability (Luft, 2009).

Although empirically supported in a variety of healthy samples, this model has not been studied in cardiovascular populations. Applied to HF patients, the neurovisceral integration model may support the notion that cognitive function in HF is linked to autonomic function, and that the pathophysiologival autonomic dysfunction characteristic of HF may then contribute to poorer cognitive functioning.

**Summary**

Underlying mechanisms that explain the etiology of cognitive impairment in HF are still being explored. Structural brain changes and reduced cerebral blood flow have been implicated. The ANS imbalance presents another possible contributor given the connection between ANS indices and cognitive performance in healthy samples and the prevalence of ANS dysfunction in HF. In healthy samples, evidence suggests that sympathetic activation, indicative of increased effort, is associated with better cognitive performance. Similarly, higher resting parasympathetic activity is associated with greater adaptability to psychological stressors and better performance on cognitive tasks. HF is characterized by ANS imbalance as a hyperactive sympathetic nervous system
attempts to compensate for the weakening heart unable to efficiently pump blood throughout the body. However, the ANS-cognition relationship has not been studied in HF patients.

**Present Study**

Previous research examining cognitive performance and ANS function have been inconsistent and none has been conducted in a sample of HF patients. The present study sought to evaluate the associations between HRV, PEP, and cognitive functioning in HF patients. The hypotheses were as follows:

1. Higher resting sympathetic activity, evidenced by shorter PEP and higher LF-HRV, would predict poorer cognitive performance.
2. Reduced parasympathetic activity, measured by HF-HRV, would predict poorer cognitive performance, particularly on tasks of executive function.
3. Higher LF/HF ratio would be associated with better cognitive performance. However, this hypothesis is tentative given the lack of consensus regarding the interpretation of the LF/HF ratio.
Method

Participants
The sample consisted of 104 older adults with HF enrolled in a longitudinal study examining cognitive performance in older adults with HF following completion of cardiac rehabilitation. HF patients from outpatient cardiology clinics were recruited if they were between 50-85 years of age, English-speaking, and diagnosed as New York Heart Association (NYHA) class II, III, or IV. Individuals were ineligible if they had a history of neurological disorder or injury (e.g., stroke), moderate or severe head injury, past or current history of severe psychiatric illness (e.g., schizophrenia), history of alcohol or drug abuse, history of learning disorder or developmental disability, untreated sleep apnea, or renal failure requiring dialysis. See Table 1 for demographic, medical, and cognitive characteristics.

Measures
Cardiac and ANS function. Participants underwent a laboratory protocol that quantified cardiac and ANS function using impedance cardiography with a standard electrocardiogram (ECG). Impedance cardiography is considered a safe, noninvasive technique for measuring systolic time intervals. A Hutcheson Impedance Cardiograph (Model HIC-2500, Bio-Impedance Technology, Chapel Hill, NC) with a tetrapolar band-electrode configuration was used to quantify impedance. Impedance signals were
sampled continuously at 500 Hz using four impedance cardiograph electrode bands placed circumferentially around the neck and chest, and the thorax following established guidelines (Sherwood et al., 1990). The ECG was recorded from the Hutcheson Impedance Cardiograph. Heart rate was measured with an automated oscillometric blood pressure device (Accutor Plus Oscillometric BP Monitor, Datascope Corp, Mahwah, NH).

A trained research staff member placed disposable electrodes on the neck and chest of participants to assess impedance changes in the thorax. A minimum of one ECG recording was measured to ensure optimal placement of the electrodes. Participants were seated in a comfortable chair at standard room temperature and monitored for a 10 minute resting baseline period. Cardiovascular measures were recorded for seven 40 second periods during each portion of the protocol. A minimum of 3 ECG recordings were required to be included in final analyses. The following indices were quantified:

**Pre-Ejection Period (PEP):** PEP was measured to evaluate changes in sympathetic activity. PEP measurements were derived from the ECG output. Ensemble-averaging software was used to process the basal thoracic impedance ($Z_0$), the first derivative of the pulsatile impedance ($dZ/dt$) and the ECG waveforms. A trained member of the research team inspected the ECG and $dZ/dt$ signals on a beat-by-beat basis. Incorrect R peaks were corrected manually and $dZ/dt$ artifacts were eliminated by deleting the corresponding R peak. PEP was defined as the interval between the onset of
the ECG Q wave and the onset of left ventricular ejection time (LVET) in milliseconds (ms).

*Heart Rate Variability (HRV):* HRV was measured to assess changes in cardiac control by deriving the interbeat interval in milliseconds from the ECG. R-R interval data were generated and imported into Kubios version 2.1 for analysis (Biosignal Analysis and Medical Imaging Group, Kupio, Finland). A trained member of the research team manually reviewed and edited data for electrical interference and artifact by applying a filter prior to analysis. Kubios generated the frequency domain (LF n.u., HF n.u., LF ms², HF ms², and LF/HF) HRV indices. Spectral analysis was used to determine frequency domain HRV by means of the Fast Fourier Transformation. For the present study, the following HRV variables were included in analyses: the low frequency component of HRV (LF-HRV), the high frequency component of HRV (HF-HRV), and the ratio of LF-HRV to HF-HRV (LF/HF).

**Neuropsychological test battery.** Participants completed a series of neuropsychological measures designed to assess multiple domains of cognitive functioning including attention, executive function, language, and memory (See Table 1). Raw test scores were converted into T-scores using normative data based on age, and gender when possible (Memory only), prior to analysis in order to simplify interpretation. Composite scores were created for each domain by averaging the standardized scores of the subtests of each domain. The battery included the following measures:
Global Cognitive Functioning

Modified Mini-Mental Status Examination (3MS; Teng & Chui, 1987). The 3MS is a brief screening measure of global cognitive performance. The 3MS represents an expansion to the Mini-Mental Status Examination (Folstein, Folstein, & McHugh, 1975) and includes aspects of attention, memory, language, and spatial abilities.

Estimated Premorbid Intelligence

North American Adult Reading Test (NAART; Blair & Spreen, 1989). The NAART is a measure that reliably estimates IQ in medical populations. Participants are asked to read a list of irregularly pronounced words.

Attention

Trail Making Test A (TMT-A; Reitan, 1958). TMT-A evaluates psychomotor speed and complex visual attention by asking individuals to draw lines to connect 25 numbered circles in ascending order as quickly as possible. Estimated test-retest reliability is r = 0.79.

Letter Number Sequencing (LNS; Wechsler, 1997). LNS assesses working memory by asking participants to verbally reorganize numbers and letters that are presented in an unordered sequence. Test-retest reliability is estimated to be r = 0.75.

Stroop Word and Color subtests (Golden, 1978). This task assesses selective attention, cognitive flexibility, and processing speed through the first two of three tasks. In the first task, individuals say the names of colors printed in black ink. In the second task, the participant must state the color of the ink regardless of the written word.
**Executive Function**

*Frontal Assessment Battery* (FAB; Dubois, Slachevsky, Litvan, & Pillon, 2000). The FAB briefly assesses executive functioning through six subtests designed to measure abilities related to conceptualization, mental flexibility, motor programming, sensitivity to interference, inhibitory control, and environmental autonomy.

*Stroop Color* Word subtest (Golden, 1978). This task assesses selective attention, cognitive flexibility, and processing speed through the final of three tasks. Participants are asked to read a list with written color names that differ from the word color ink they are printed in.

*Trail Making Test B* (TMT-B; Reitan, 1958). TMT-B measures executive dysfunction by instructing participants to draw lines to connect circled numbers and letters in ascending order, alternating between numbers and letters. Estimated test-retest reliability is $r = 0.89$.

**Language**

*Animal Naming* (Eslinger, Damasio, & Benton, 1984). This task measures language abilities by asking participants to name as many animals as possible in 60 seconds.

*Boston Naming Test* (Kaplan, Goodglass, & Weintraub, 1983). This task assesses language skills by having individuals name objects depicted in 60 illustrations.

**Memory**

*California Verbal Learning Test-Second Edition* (CVLT; Delis, Kramer, Kaplan, & Ober, 2000). The CVLT assesses verbal memory by asking participants to learn (Sum
of Trials 1-5, recall (Short Delay Free Recall & Long Delay Free Recall), and recognize (Recognition) a 16-item word list. The Short and Long Delay Free Recall and Recognition subtests were included in the current analyses.

Procedure

The Institutional Review Boards (IRBs) of Summa Health System and Kent State University approved the following study protocol. Research activities were conducted at Summa Health System in Akron, OH. All participants provided informed written consent prior to enrollment. Following consent, participants completed self-report measures of demographic, psychosocial, and medical history information. A medical chart review was conducted to verify inclusion criteria provided through self-report. Participants then underwent assessment of cardiac function followed by the brief, neuropsychological test battery. Total assessment time was approximately 4 hours. Participants were provided with $100.00 in compensation.

Preliminary statistical analyses. The data were first examined for group differences in mean HRV and PEP between participants with and without a pacemaker, implantable cardiac device, or a combination of the two. Results of a series of one-way ANOVAs revealed no significant difference in HR, PEP, LF-HRV, HF-HRV or the LF/HF ratio between groups (all p values > .05). However, as having a pacemaker or implantable cardiac device could be expected to affect heart rate and heart rate variability, pacemaker/ICD status was controlled for in HRV analyses.
Prior to testing study hypotheses, the data was also examined for violations of the assumptions of hierarchical multiple linear regression. Both the LF- and HF-HRV indices were log transformed to ensure that the data were normally distributed (skewness < 3 and kurtosis < 10). No other violations of assumptions were evident and no additional transformations were performed. The criterion for statistical significance was set at $p < .05$ for all analyses.

**Analytic Strategy**

Statistical analyses were performed using SPSS, version 20. Pearson correlation analysis was used to assess the relationship between demographic variables, LF-HRV, HF-HRV, LF/HF ratio, PEP, and cognitive functioning in order to assess for potential confounds. Hierarchical multiple regression was used to examine the relationship between each ANS variable and individuals domains of cognitive performance. Four analyses were conducted for each cognitive domain to examine the relationships between cognitive performance and ANS dysfunction with LF-HRV, HF-HRV, LF/HF ratio, and PEP. The composite cognitive performance score was the dependent variable in each analysis. Block 1 included pacemaker/ICD status and covariates known to be associated with cognitive function including age, gender, education, left ventricular ejection fraction, depressive symptoms, and self-reported hypertension and diabetes. Block 2 included the ANS variable to assess its incremental predictive validity. All missing data was excluded listwise.
Results

The sample consisted of 104 (67.9% male) predominately Caucasian (84.4%) HF patients (68.70 ± 9.01 years) and had class II HF (87.5%). Participants demonstrated largely average performance across cognitive domains. Twenty-five (22.7%) participants exhibited global cognitive impairment using < 90 as a 3MS cutoff to determine cognitive impairment, a less conservative cutoff than < 78 used to screen for dementia (n = 1; 0.01%). Additional demographic, medical, and cognitive characteristics are presented in Table 1. Relationships between ANS indices and demographic and medical variables including sex, race, body mass index, beta-blocker use, depression, anxiety, smoking status, alcohol use were examined. Both LF-HRV and HF-HRV were significantly correlated with BDI-II score (LF: \( r = -.28, p < .01 \); HF: \( r = -.20, p < .05 \)) and diabetes mellitus (LF: \( r = -.22, p < .05 \); HF: \( r = -.19, p < .05 \)). Sex was correlated with LF/HF ratio (\( r = -.19, p < .05 \)). Correlations between demographic and clinical variables and cognitive domains are presented in Table 2. Mean values of cardiovascular measures are presented in Table 3.
Table 1. Demographic and Cognitive Characteristics of Participants \((n = 104)\).

<table>
<thead>
<tr>
<th>Demographic and Medical Factors</th>
<th>M(SD) or n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>69.02 (8.83)</td>
</tr>
<tr>
<td>Male</td>
<td>70 (67.3)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>87 (83.7)</td>
</tr>
<tr>
<td>Education (years)</td>
<td>13.40 (2.64)</td>
</tr>
<tr>
<td>Married</td>
<td>75 (72.1)</td>
</tr>
<tr>
<td>Lives alone</td>
<td>29 (27.9)</td>
</tr>
<tr>
<td>Depression (BDI-II)</td>
<td>7.82 (8.25)</td>
</tr>
<tr>
<td>NYHA</td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Class II</td>
<td>91 (87.5)</td>
</tr>
<tr>
<td>Class III</td>
<td>12 (11.5)</td>
</tr>
<tr>
<td>Class IV</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Beta-Blocker use</td>
<td></td>
</tr>
<tr>
<td>Device</td>
<td></td>
</tr>
<tr>
<td>Pacemaker</td>
<td>11 (10.6)</td>
</tr>
<tr>
<td>ICD</td>
<td>6 (5.8)</td>
</tr>
<tr>
<td>Combo</td>
<td>7 (6.7)</td>
</tr>
<tr>
<td>None</td>
<td>80 (76.9)</td>
</tr>
<tr>
<td>Cognitive Factors</td>
<td></td>
</tr>
<tr>
<td>Estimated IQ</td>
<td>110.18 (14.47)</td>
</tr>
<tr>
<td>3MS</td>
<td>92.69 (5.55)</td>
</tr>
<tr>
<td>Attention*</td>
<td>46.05 (7.05)</td>
</tr>
<tr>
<td>Executive Function*</td>
<td>42.76 (14.20)</td>
</tr>
<tr>
<td>Memory*</td>
<td>46.46 (9.87)</td>
</tr>
<tr>
<td>Language*</td>
<td>52.60 (10.93)</td>
</tr>
</tbody>
</table>

Notes. NYHA = New York Heart Association. ICD = Implantable Cardioverter Defibrillator. 3MS = Modified Mini-mental Status Exam. Means and standard deviations are presented for continuous variables. Sample size and percentages are presented for categorical variables. *Domain composite score created as an average of T-scores of domain-specific tests.
Table 2. Pearson correlations between cognitive domains and demographic and clinical covariates.

<table>
<thead>
<tr>
<th></th>
<th>Gender</th>
<th>Education</th>
<th>LVEF</th>
<th>Depressive Symptoms</th>
<th>Hypertension (no = 0; yes = 1)</th>
<th>Diabetes (no = 0; yes = 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention</td>
<td>-.07</td>
<td>.40***</td>
<td>.05</td>
<td>-.23*</td>
<td>-.16</td>
<td>-.26**</td>
</tr>
<tr>
<td>Executive Function</td>
<td>-.06</td>
<td>.35***</td>
<td>-.04</td>
<td>-.37***</td>
<td>-.17</td>
<td>-.21*</td>
</tr>
<tr>
<td>Language</td>
<td>-.12</td>
<td>.31*</td>
<td>.08</td>
<td>-.20*</td>
<td>-.13</td>
<td>-.14</td>
</tr>
<tr>
<td>Memory</td>
<td>.02</td>
<td>.22*</td>
<td>-.01</td>
<td>-.06</td>
<td>.07</td>
<td>-.06</td>
</tr>
</tbody>
</table>

* p < .05, ** p < .01, *** p < .001. Note. LVEF = Left ventricular ejection fraction.

Table 3. Mean Values (SD) of Cardiovascular Measures.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>62.51 (13.46)</td>
</tr>
<tr>
<td>PEP</td>
<td>138.11 (25.72)</td>
</tr>
<tr>
<td>LF-HRV (ln)</td>
<td>4.83 (1.82)</td>
</tr>
<tr>
<td>HF-HRV (ln)</td>
<td>4.90 (2.03)</td>
</tr>
<tr>
<td>LF/HF ratio</td>
<td>1.63 (2.17)</td>
</tr>
</tbody>
</table>

Notes. HR results presented here are based on analyses of interbeat interval (IBI). PEP = pre-ejection period; LF-HRV = low frequency heart rate variability; HF-HRV = high frequency heart rate variability.
**PEP**

*Attention.* Hierarchical multiple linear regression was performed to examine the relationship between PEP and attention. In the first step, the linear combination of demographic and medical control variables accounted for 25.3% of the variability in attention, $F(7, 96) = 4.65, p < .001$. Specifically, more education ($\beta = .34, p < .001$) was associated with better attention, whereas depressive symptoms ($\beta = .19, p < .05$) and having positive history of diabetes ($\beta = -.22, p < .05$) was associated with poorer attention. In the second step, adding PEP did not improve model fit, $\Delta F(1, 96) = .00, p = .96$.

*Executive Function.* Hierarchical multiple linear regression was performed to examine the relationship between PEP and executive function. In the first step, the linear combination of demographic and medical control variables accounted for 27.4% of the variability in executive function, $F(7, 96) = 6.22, p < .001$. Specifically, more education ($\beta = .31, p < .01$) was associated with better executive function, whereas depressive symptoms ($\beta = -.35, p < .001$) were associated with poorer executive function. In the second step, adding PEP did not improve model fit, $\Delta F(1, 96) = .39, p = .53$.

*Language.* Hierarchical multiple linear regression was performed to examine the relationship between PEP and language. In the first step, the linear combination of demographic and medical control variables accounted for 14.6% of the variability in attention, $F(7, 96) = 2.92, p < .05$. Specifically, more education ($\beta = .26, p < .01$) was
associated with better language ability. In the second step, adding PEP did not improve model fit, $\Delta F(1, 96) = .23, p = .64$.

*Memory.* Hierarchical multiple linear regression was performed to examine the relationship between PEP and memory. In the first step, the linear combination of demographic and medical control variables did not explain variability in memory, $F(7, 96) = 1.46, p = .20$. In the second step, adding PEP did not improve model fit, $\Delta F(1, 96) = .58, p = .45$. See Table 4.

Table 4. Multiple Hierarchical Regression Results Using Pre-Ejection Period to Predict Cognitive Performance.

<table>
<thead>
<tr>
<th></th>
<th>Attention</th>
<th>Executive Function</th>
<th>Language</th>
<th>Memory</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>β(SE b)</strong></td>
<td>β(SE b)</td>
<td>β(SE b)</td>
<td>β(SE b)</td>
<td>β(SE b)</td>
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<tr>
<td><strong>PEP</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Block 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>.07(1.45)</td>
<td>.14(2.85)</td>
<td>-.02(2.39)</td>
<td>.09 (2.23)</td>
</tr>
<tr>
<td>Education</td>
<td>.34(.25)***</td>
<td>.31(.49)**</td>
<td>.26(.41)**</td>
<td>.27 (.39)</td>
</tr>
<tr>
<td>EF</td>
<td>.10(.05)</td>
<td>-.01(.09)</td>
<td>.11(.07)</td>
<td>-.04(.07)*</td>
</tr>
<tr>
<td>BDI-II</td>
<td>-.19(.08)*</td>
<td>-.35(.16)***</td>
<td>-.16(.13)</td>
<td>-.06(.12)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>-.07(1.43)</td>
<td>-.03(2.80)</td>
<td>-.02(2.31)</td>
<td>.15(2.19)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>-.22(1.38)*</td>
<td>-.17(2.71)</td>
<td>-.13(2.22)</td>
<td>-.07(2.10)</td>
</tr>
<tr>
<td>$R^2$</td>
<td>.25</td>
<td>.27</td>
<td>.15</td>
<td>.08</td>
</tr>
<tr>
<td>$F$</td>
<td>5.48***</td>
<td>6.23***</td>
<td>2.92*</td>
<td>1.46</td>
</tr>
<tr>
<td>Block 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEP</td>
<td>.01(.03)</td>
<td>-.06(.05)</td>
<td>-.05(.04)</td>
<td>.08 (.04)</td>
</tr>
<tr>
<td>$R^2$</td>
<td>.25</td>
<td>.28</td>
<td>.15</td>
<td>.08</td>
</tr>
<tr>
<td>$F$ for $\Delta R^2$</td>
<td>.003</td>
<td>.39</td>
<td>.23</td>
<td>.58</td>
</tr>
</tbody>
</table>

* $p < .05$, ** $p < .01$, *** $p < .001$. Note. EF = ejection fraction. BDI-II = Beck Depression Inventory. Hypertension: no = 0; yes = 1. Diabetes: 0 = no; yes = 1.
**LF-HRV**

*Attention.* Hierarchical multiple linear regression was performed to examine the relationship between ANS indices and attention. In the first step, the linear combination of pacer/ICD status and demographic/medical control variables accounted for 25.8% of the variability in attention, $F(8, 95) = 4.77, p < .001$. Specifically, more years of education ($\beta = .33, p < .01$) was associated with better attention, whereas having positive history of diabetes ($\beta = -.22, p < .05$) was associated with poorer attention. In the second step, adding LF-HRV did not improve model fit, $\Delta F(1, 95) = 2.47, p = .12$.

*Executive Function.* Hierarchical multiple linear regression was performed to examine the relationship between LF-HRV and executive function. In the first step, the linear combination of pacer/ICD status and demographic/medical control variables accounted for 27.5% of the variability in executive function, $F(8, 95) = 5.32, p < .001$. Specifically, more education ($\beta = .30, p < .01$) was associated with better executive function, whereas depressive symptoms ($\beta = -.35, p < .001$) were associated with poorer executive function. In the second step, adding LF-HRV did not improve model fit, $\Delta F(1, 95) = .05, p = .83$.

*Language.* Hierarchical multiple linear regression was performed to examine the relationship between LF-HRV and language ability. In the first step, the linear combination of pacer/ICD status and demographic/medical control variables accounted for 14.8% of the variability in language, $F(8, 95) = 2.52, p < .05$. Specifically, more
education ($\beta = .27, p < .01$) was associated with better language ability. In the second step, adding LF-HRV did not improve model fit, $\Delta F(1, 95) = .00, p = .95$.

**Memory.** Hierarchical multiple linear regression was performed to examine the relationship between LF-HRV and memory. In the first step, the linear combination of pacer/ICD status and demographic/medical control variables did not explain variability in memory, $F(8, 95) = 1.61, p = .14$. In the second step, adding LF-HRV did not improve model fit, $\Delta F(1, 95) = .11, p = .74$. See Table 5.

Table 5. Multiple Hierarchical Regression Results Using Low Frequency Heart Rate Variability to Predict Cognitive Performance.

<table>
<thead>
<tr>
<th></th>
<th>Attention</th>
<th>Executive Function</th>
<th>Language</th>
<th>Memory</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\beta(\text{SE } b)$</td>
<td>$\beta(\text{SE } b)$</td>
<td>$\beta(\text{SE } b)$</td>
<td>$\beta(\text{SE } b)$</td>
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<tr>
<td><strong>LF-HRV (ln)</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Block 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>.07(.45)</td>
<td>.14(.26)</td>
<td>-.02(.24)</td>
<td>.09(.24)</td>
</tr>
<tr>
<td>Education</td>
<td>.33(.25)**</td>
<td>.30(.30)**</td>
<td>.27(.41)**</td>
<td>.25(.39)*</td>
</tr>
<tr>
<td>EF</td>
<td>.08(.05)</td>
<td>-.02(.09)</td>
<td>.12(.08)</td>
<td>-.08(.07)</td>
</tr>
<tr>
<td>BDI-II</td>
<td>-.18(.08)</td>
<td>-.35(.16)**</td>
<td>-.16(.13)</td>
<td>-.04(.12)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>-.08(.145)</td>
<td>-.04(.24)</td>
<td>-.01(.235)</td>
<td>.13(.20)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>-.22(.39)*</td>
<td>-.17(.22)</td>
<td>-.13(.23)</td>
<td>-.07(.20)</td>
</tr>
<tr>
<td>Pacer status</td>
<td>-.07(.75)</td>
<td>-.04(.17)</td>
<td>.05(.125)</td>
<td>-.16(.17)</td>
</tr>
<tr>
<td>$R^2$</td>
<td>.26</td>
<td>.28</td>
<td>.15</td>
<td>.10</td>
</tr>
<tr>
<td>$F$</td>
<td>4.77***</td>
<td>5.32***</td>
<td>2.52*</td>
<td>1.61</td>
</tr>
<tr>
<td>Block 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LF-HRV(ln)</td>
<td>.15(.37)</td>
<td>-.02(.74)</td>
<td>.01(.59)</td>
<td>-.03(.55)</td>
</tr>
<tr>
<td>$R^2$</td>
<td>.28</td>
<td>.28</td>
<td>.15</td>
<td>.10</td>
</tr>
<tr>
<td>$F$ for $\Delta R^2$</td>
<td>2.47</td>
<td>.05</td>
<td>.00</td>
<td>.11</td>
</tr>
</tbody>
</table>

* $p < .05$, ** $p < .01$, *** $p < .001$. Note. EF = ejection fraction. BDI-II = Beck Depression Inventory. Hypertension: no = 0; yes = 1. Diabetes: 0 = no; yes = 1.
**HF-HRV**

*Attention.* Hierarchical multiple linear regression was performed to examine the relationship between HF-HRV and attention. In the first step, of pacer/ICD status and demographic/medical control variables accounted for 25.8% of the variability in attention, $F(8, 95) = 4.77, p < .001$. Specifically, more education ($\beta = .33, p < .01$) was associated with better attention, whereas having positive history of diabetes ($\beta = -.22, p < .05$) was associated with poorer attention. In the second step, adding LF-HRV did not improve model fit, $\Delta F(1, 95) = .46, p = .50$.

*Executive Function.* Hierarchical multiple linear regression was performed to examine the relationship between HF-HRV and executive function. In the first step, of pacer/ICD status and demographic/medical control variables accounted for 27.5% of the variability in executive function, $F(8, 95) = 5.32, p < .001$. Specifically, more education ($\beta = .30, p < .01$) was associated with better executive function, whereas depressive symptoms ($\beta = -.35, p < .001$) were associated with poorer executive function. In the second step, adding HF-HRV did not improve model fit, $\Delta F(1, 95) = .81, p = .37$.

*Language.* Hierarchical multiple linear regression was performed to examine the relationship between HF-HRV and language ability. In the first step, of pacer/ICD status and demographic/medical control variables accounted for 14.8% of the variability in language, $F(8, 95) = 2.52, p < .05$. Specifically, more education ($\beta = .27, p < .01$) was associated with better language ability. In the second step, adding HF-HRV did not improve model fit, $\Delta F(1, 95) = .47, p = .50$. 
Memory. Hierarchical multiple linear regression was performed to examine the relationship between HF-HRV and memory. In the first step, the linear combination of pacer/ICD status and demographic/medical control variables did not explain variability in memory, $F(8, 95) = 1.61, p = .14$. In the second step, adding HF-HRV did not improve model fit, $\Delta F(1, 95) = .04, p = .83$. See Table 6.

Table 6. Multiple Hierarchical Regression Results Using High Frequency Heart Rate Variability to Predict Cognitive Performance.

<table>
<thead>
<tr>
<th></th>
<th>Attention</th>
<th>Executive Function</th>
<th>Language</th>
<th>Memory</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HF-HRV (ln)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Block 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>.07(1.45)</td>
<td>.14(2.86)</td>
<td>-.02(2.40)</td>
<td>.09(2.24)</td>
</tr>
<tr>
<td>Education</td>
<td>.33(.25)**</td>
<td>.30(.50)**</td>
<td>.27(.41)**</td>
<td>.25(.39)*</td>
</tr>
<tr>
<td>EF</td>
<td>.08(.05)</td>
<td>-.02(.09)</td>
<td>.12(.08)</td>
<td>-.08(.07)</td>
</tr>
<tr>
<td>BDI-II</td>
<td>-.18(.08)</td>
<td>-.35(.16)**</td>
<td>-.16(.13)</td>
<td>-.04(.12)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>-.08(1.45)</td>
<td>-.04(2.84)</td>
<td>-.01(2.35)</td>
<td>.13(2.20)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>-.22(1.39)*</td>
<td>-.17(2.72)</td>
<td>-.13(2.23)</td>
<td>-.07(2.08)</td>
</tr>
<tr>
<td>Pacer status</td>
<td>-.07(.75)</td>
<td>-.04(1.48)</td>
<td>.05(1.25)</td>
<td>-.16(1.17)</td>
</tr>
<tr>
<td>$R^2$</td>
<td>.26</td>
<td>.28</td>
<td>.15</td>
<td>.10</td>
</tr>
<tr>
<td>$F$</td>
<td>4.77***</td>
<td>5.32***</td>
<td>2.52*</td>
<td>1.61</td>
</tr>
<tr>
<td>Block 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HF-HRV(ln)</td>
<td>.06(.33)</td>
<td>-.08(.65)</td>
<td>-.07(.55)</td>
<td>-.02(.51)</td>
</tr>
<tr>
<td>$R^2$</td>
<td>.26</td>
<td>.28</td>
<td>.15</td>
<td>.10</td>
</tr>
<tr>
<td>$F$ for $\Delta R^2$</td>
<td>.46</td>
<td>.81</td>
<td>.47</td>
<td>.04</td>
</tr>
</tbody>
</table>

* $p < .05$, ** $p < .01$, *** $p < .001$. Note. EF = ejection fraction. BDI-II = Beck Depression Inventory. Hypertension: no = 0; yes = 1. Diabetes: 0 = no; yes = 1.
**LF/HF HRV**

*Attention*. Hierarchical multiple linear regression was performed to examine the relationship between the LF/HF ratio and attention. In the first step, the linear combination of pacer/ICD status and demographic/medical control variables accounted for 25.8% of the variability in attention, $F(8, 95) = 4.77, p < .001$. Specifically, more education ($\beta = .33, p < .01$) was associated with better attention, whereas having positive history of diabetes ($\beta = -.22, p < .05$) was associated with poorer attention. In the second step, adding the LF/HF ratio did not improve model fit, $\Delta F(1, 95) = 2.37, p = .13$.

*Executive Function*. Hierarchical multiple linear regression was performed to examine the relationship between the LF/HF ratio and executive function. In the first step, the linear combination of pacer/ICD status and demographic/medical control variables accounted for 27.4% of the variability in executive function, $F(8, 95) = 5.32, p < .001$. Specifically, more education ($\beta = .30, p < .01$) was associated with better executive function, whereas depressive symptoms ($\beta = -.35, p < .001$) were associated with poorer executive function. In the second step, adding the LF/HF ratio improved model fit, $\Delta F(1, 95) = 3.94, p = .05$. Marginal significance emerged for the increased predictive ability of executive function beyond demographic and medical variables and pacemaker/ICD status ($\beta = .18, p = .05$).

*Language*. Hierarchical multiple linear regression was performed to examine the relationship between the LF/HF ratio and language ability. In the first step, the linear
combination of pacer/ICD status and demographic/medical control variables accounted for 16.1% of the variability in language, $F(8, 95) = 2.52, p < .05$. Specifically, more education ($\beta = .27, p < .01$) was associated with better language ability. In the second step, adding the LF/HF ratio did not improve model fit, $\Delta F(1, 95) = 1.54, p = .22$.

Memory. Hierarchical multiple linear regression was performed to examine the relationship between the LF/HF ratio and memory. In the first step, the linear combination of pacer/ICD status and demographic/medical control variables did not explain variability in memory, $F(8, 95) = 1.61, p = .14$. In the second step, adding the LF/HF ratio did not improve model fit, $\Delta F(1, 95) = .42, p = .52$. See Table 7.

<table>
<thead>
<tr>
<th>Block 1</th>
<th>Attention</th>
<th>Executive Function</th>
<th>Language</th>
<th>Memory</th>
</tr>
</thead>
<tbody>
<tr>
<td>LF/HF ratio</td>
<td>$\beta(\text{SE} \ b)$</td>
<td>$\beta(\text{SE} \ b)$</td>
<td>$\beta(\text{SE} \ b)$</td>
<td>$\beta(\text{SE} \ b)$</td>
</tr>
<tr>
<td>Sex</td>
<td>.07(1.45)</td>
<td>.14(2.86)</td>
<td>-02(2.40)</td>
<td>.09(2.24)</td>
</tr>
<tr>
<td>Education</td>
<td>.33(.25)**</td>
<td>.30(.50)**</td>
<td>.27(.41)**</td>
<td>.25(.39)*</td>
</tr>
<tr>
<td>EF</td>
<td>.08(.05)</td>
<td>-02(.09)</td>
<td>.12(.08)</td>
<td>-.08(.07)</td>
</tr>
<tr>
<td>BDI-II</td>
<td>-.18(.08)</td>
<td>-.35(.16)***</td>
<td>-.16(.13)</td>
<td>-.04(.12)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>-.08(1.45)</td>
<td>-.04(2.84)</td>
<td>-.01(2.35)</td>
<td>.13(2.20)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>-.22(1.39)*</td>
<td>-.17(2.72)</td>
<td>-.13(2.23)</td>
<td>-.07(2.08)</td>
</tr>
<tr>
<td>Pacer status</td>
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<td>-.04(1.48)</td>
<td>.05(1.25)</td>
<td>-.16(1.17)</td>
</tr>
<tr>
<td>$R^2$</td>
<td>.26</td>
<td>.28</td>
<td>.15</td>
<td>.10</td>
</tr>
<tr>
<td>$F$</td>
<td>4.77***</td>
<td>5.32***</td>
<td>2.52*</td>
<td>1.61</td>
</tr>
<tr>
<td>Block 2</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>LF/HF ratio</td>
<td>.14(.30)</td>
<td>.18(.58)**</td>
<td>.12(.49)</td>
<td>-.06(.46)</td>
</tr>
<tr>
<td>$R^2$</td>
<td>.28</td>
<td>.30</td>
<td>.16</td>
<td>.10</td>
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<tr>
<td>$F$ for $\Delta R^2$</td>
<td>2.37</td>
<td>3.94**</td>
<td>1.54</td>
<td>.42</td>
</tr>
</tbody>
</table>

$^\dagger p = .05, * p < .05, ** p < .01, *** p < .001$. Note. EF = ejection fraction. BDI-II = Beck Depression Inventory. Hypertension: no = 0; yes = 1. Diabetes: 0 = no; yes = 1.
Discussion

The current study examined potential associations between ANS functioning and cognitive performance in a sample of well-characterized HF patients. Indices of sympathetic (PEP and LF-HRV) and parasympathetic (HF-HRV) activity were included, as well as a measure reflecting an ANS-influenced cardiovascular parameter (LF/HF ratio). It was hypothesized that PEP and LF-HRV would be negatively associated with cognitive performance, so that shorter PEP and higher LF-HRV (i.e., increased sympathetic activation) would predict poorer performance. It was also hypothesized that lower HF-HRV would predicted poorer cognitive performance on tasks of executive function. Furthermore, it was expected that HF-HRV would not be associated with other domains of cognitive function, including attention, language ability, and memory. Exploration of the predictive ability of an ANS-influenced parameter was also included, assessing the relationship between the LF/HF ratio and cognitive performance across multiple cognitive domains. Results indicated that higher LF/HF ratio was marginally associated with better executive performance. No other significant relationships emerged.

The LF/HF ratio was marginally associated with executive function. According to traditional interpretations of the LF/HF ratio characterizing sympathovagal balance, mean LF/HF ratio (M = 1.62, SD = 2.14) suggested reduced parasympathetic tone and increased cardiac sympathetic dominance. This is consistent with the known pattern of
ANS imbalance characteristic of HF. Prior research also demonstrated an association between the LF/HF ratio and executive function (Luft et al., 2009). However, Luft and colleagues reported the opposite relationship. In Luft’s sample, lower LF/HF ratios (i.e., increased parasympathetic) emerged during performance of executive-related tasks in highly trained athletes and mean LF/HF ratios were below 1.0 during all cognitive tasks. As such, it is possible that the LF/HF ratio may relate to cognitive performance, although the relative dominance of each ANS branch may vary across healthy versus cardiac samples.

Other domains of cognitive functioning were not associated with the LF/HF ratio. Frewen and colleagues (2013) reported a relationship between LF/HF power, but not HF-HRV and global cognitive performance. Like the current sample, Frewen’s sample consisted of primarily older adults (mean age 61.7 ± 8.3 years). However, like Luft’s sample, mean LF/HF ratio was less than 1.0 in both paced and spontaneous breathing conditions. Only a small percentage of participants had a cardiovascular disease diagnosis. For example, only 35 out of over 4,000 participants reported having HF. Thus, again, the current results may be influenced by differences caused by the pathology of HF itself. However, until greater understanding of the LF/HF ratio develops, inferences must remain tentative.

PEP was also not associated with cognitive performance. The current findings are not consistent with prior reports of associations between sympathetic activity and cognitive performance (McCubbin et al., 1983; Duschek et al., 2009). However,
Duscheck et al. assessed sympathetic activation using the RPI, which is not considered to be a pure measure of sympathetic activity. Although ample evidence supports the use of PEP as a marker of sympathetic activation, others note that PEP assesses peripheral sympathetic activation rather than central sympathetic activation (Schächinger et al., 2001). HF is accompanied by many peripheral changes in the skeletal muscle including reduced muscle mass partially resulting from reduced blood flow, alterations in muscle structure, metabolism, and normal function (Jackson, Gibbs, Davies, & Lip, 2000). Central sympathetic activation, however, may be more strongly related to cognitive and emotional processes (Schächinger et al., 2001). Prior studies estimating central SNS activity using BP variability (i.e., Gunstad et al., 2009; Okonkwo et al., 2011) found support for a connection between blood pressure variability and cognitive performance. However, BP variability is not correlated with PEP (Schächinger et al., 2001). Thus, it is possible that assessment of central sympathetic activity may provide different results.

Perhaps more importantly, prior studies demonstrating a relationship between sympathetic nervous system function and cognitive performance were comprised of young, healthy samples unlikely to have experienced significant ANS dysfunction. Despite chronically elevated sympathetic activation in HF, PEP is prolonged in HF patients compared with PEP in healthy individuals. Prolonged PEP is also associated with elevated peripheral resistance, decreased cardiac output and reduced stroke volume (Chen & Gibson, 1979; Weissler, Harris, & Schoenfeld, 1968). PEP is increased by beta-blockers (i.e., propranolol) in patients with and without heart disease through a
different mechanism than heart disease itself (Chen & Gibson, 1979; Harris et al., 1967; Hunt, Sloman, Clark, & Hoffmann, 1970). It seems likely that the lengthening of PEP by beta-blocker treatment reflects reduced contraction velocity. In individuals with left ventricular dysfunction not receiving beta-blocker treatment, prolonged PEP is correlated with asynchronous left ventricular wall movement during isovolumic contraction (Chen & Gibson, 1979). Thus, the lengthening of PEP in individuals with HF likely results from a combination of treatment with beta-blocking drugs as well as asynchronous onset of contraction (Chen & Gibson, 1979).

The prolongation of PEP in HF represents the opposite pattern of sympathetic activation observed in individuals with normal left ventricular function (Qureshi et al., 1978; Thomas & Marks, 1978). Similarly, Thomas and Marks (1978) found that elevated plasma norepinephrine was correlated with prolonged PEP in HF patients. This is also opposite of the relationship demonstrated in patients with normal ventricular function. Moreover, left ventricular ejection time appears shortened in response to sympathetic activation in individuals with HF (Thomas & Marks, 1978). These opposite patterns seem to counteract the activation of the sympathetic nervous system. Although sympathetic activation initially acts to maintain blood pressure, over time, such alterations in ANS functioning lead to increased myocardial oxygen consumption, adverse cardiac remodeling, and increased risk of ventricular arrhythmia (Frenneaux, 2004). As a result, a similar relationship between sympathetic nervous system activity
and cognitive performance may not be present in HF patients with underlying ANS dysregulation.

Additionally, LF-HRV was not associated with cognitive performance. Shah et al. (2011) found an association between LF-HRV and a selective reminding task in males without PTSD; however, the effects were not found in males with PTSD, a disorder also characterized by ANS dysfunction. These findings also suggest a different relationship between cognitive and ANS function in healthy individuals without cause for ANS dysfunction compared with individuals experiencing pathophysiological imbalance. Given the severe decompensation in HF, the relationships observed in individuals with normal ventricular function may not be present given the alterations to ANS function. One study found that oxygen therapy stabilized sympathetic nervous system activity, but not cognitive function, in HF patients with obstructive sleep apnea (Staniforth, Kinnear, Starling, Hetmanski, & Cowley, 1998). Thus, the prolonged activation of the sympathetic nervous system in HF may obscure evidence of a relationship between sympathetic nervous system functioning and cognitive performance.

Contrary to hypotheses, HF-HRV did not predict executive function in the present sample of HF patients. HF-HRV was also unrelated to attention, language, and memory. This is inconsistent with prior research demonstrating an association between reduced HF-HRV and poorer cognitive performance (Hansen et al. 2003; 2009; Kim et al., 2006) and the stronger effects found in a subset of individuals with cardiovascular disease in the Whitehall II Cohort study (Britton et al., 2008). Much previous psychophysiological
research was limited by small samples (n < 50). Furthermore, the previous observed relationships were assessed in primarily younger, healthy samples without evidence of underlying ANS dysfunction. Britton et al. reported generally no consistent relationship between HRV and cognitive performance in a middle-aged sample without underlying cause for ANS dysfunction.

Also, previous research has dichotomized HRV into a high and low group (Hansen et al., 2003) or defined reduced HRV as the lowest quartile (Kim et al., 2007). Britton used logistic regression to model the relationship between HRV and the lowest quintile of performance on each cognitive task. In the current study, both HRV and cognitive performance were analyzed continuously. However, a non-linear relationship may exist so that a relationship between HRV and cognitive impairment emerges only for individuals with the most severe impairments.

The cognitive profile of the current sample may also have impacted detection of a relationship between HF-HRV and cognitive performance. The current sample demonstrated generally intact cognitive functioning. HF is a known risk factor for vascular dementia and Alzheimer’s disease (Duron & Hanon, 2008). Previous work has shown that the pattern of cognitive impairment seen in HF is typical of vascular cognitive impairment (VCI) and is characterized by deficits in executive function, attention, processing speed, and, less often, memory and language (O’Brien, 2006; Vogels et al., 2007a). Although no studies have examined autonomic dysfunction in VCI specifically, some research has examined autonomic dysfunction in vascular dementia (Wantanbe,
Niimi, Koike, & Sugiyama, 2000; Allan et al., 2005; 2007). However, conflicting findings exist. Watanabe et al. (2000) found that HF-HRV was reduced in patients with Binswanger’s encephalopathy, a form of small vessel vascular dementia, compared with healthy controls. No difference emerged in HF power between mild and severe cases of Binswanger’s encephalopathy. Conversely, Allan et al., (2005) found that HRV does not appear to be abnormal in individuals with vascular dementia and that although autonomic dysfunction is prominent in other types of dementia, including Parkinson’s disease dementia and dementia with Lewy bodies, little evidence emerged for prominent autonomic dysfunction in individuals with vascular dementia (Allan et al., 2007). Thus, perhaps the vascular cognitive impairment typically present in HF is not highly influenced by parasympathetic dysfunction as seems to be the case in other forms of dementia. Moreover, perhaps early reductions in parasympathetic functioning are overshadowed by the development of chronic sympathetic activation.

The current study provides the first examination of the potential of ANS dysregulation to serve as a mechanism for underlying cognitive impairment in HF. Although the current data generally do not support a relationship between ANS functioning and cognitive performance in HF patients, continued investigation of these relationships is warranted to increase understanding of the mechanistic contributors to cognitive impairment in HF.
Limitations and Future Directions

Limitations of the current study should be noted. As the current findings are based on cross-sectional design, conclusions regarding the mechanistic relationship between ANS indices and cognitive functioning cannot be made based on the current data. Furthermore, the current study did not address the temporal relationship between the development of ANS changes and cognitive decline. Longitudinal research is needed to understand whether impaired ANS function precedes the development of cognitive impairment in HF. Additionally, although comorbid conditions with known cognitive effects were accounted for, the impact of disease duration of these comorbid conditions in addition to the duration of HF was not included. Factors such as disease duration and age may contribute to both cognitive and ANS decline. Future studies should account for disease duration and include additional indices of disease severity. Finally, although beta-blocker use was not associated with any cognitive domains, medication adherence was not assessed and should be accounted for in future research in order to better estimate the potential influence of beta-blocker use on these relationships.

Future studies should consider alternative measures of ANS function. Some have derived HRV measures from comparisons of paced and spontaneous breathing protocols to allow for adjustment of respiration (Frewen et al., 2013). Moreover, paced breathing presents superiority reliability compared with spontaneous breathing protocols (Pinna, Maestri, La Rovere, Gobbi, & Fanfulla, 2006; Sandercock et al., 2008). Frewen et al. (2013) noted greater HF and LF-HRV during spontaneous breathing, but greater LF/HF
ratio during paced breathing. For example, they reported that lower HF-HRV was associated with lower MoCA score during paced breathing, but not during spontaneous breathing. However, adjustment for medical covariates attenuated this relationship. However, lower LF and LF/HF ratio HRV were significantly related to lower MoCA score even after adjustment for covariates. Ambulatory measures of HRV more strongly predict mortality in HF (Task Force, 1996) and may more accurate assessment of ANS functioning. Additionally, the selection of PEP as an index of sympathetic functioning presents an important limitation. Future studies may wish to include markers of central sympathetic function.

**Conclusions**

In sum, ANS functioning largely did not appear to be related to cognitive functioning in HF patients with the exception of the LF/HF ratio and executive function. However, the LF/HF ratio accounted for a small amount of variability in executive function and the interpretation of the LF/HF ratio is not well-accepted. The pathophysiology of HF may prevent detection of a relationship between cognitive performance and non-invasive, indirect measures of ANS functioning. Alternatively, other mechanisms may better explain the relationship between cognitive functioning and HF, such as structural brain changes and reduced cerebral blood flow. Given the additive burden of cognitive impairment above and beyond the disease burden itself, increased
understanding of the pathophysiological causes of cognitive impairment in HF is warranted.
References


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