Cognitive Deficits in Chronic Heart Failure

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Abstract

Background: Patients with heart failure (HF) have been found to have cognitive deficits, but it
remains unclear whether these deficits are associated with HF or with aging or comorbid
conditions common in HF.

Objectives: To 1) determine the types, frequency, and severity of cognitive deficits among
patients with chronic HF compared to age- and education-matched healthy participants and
participants with major medical conditions other than HF; and 2) evaluate the relationships
between HF severity, age, and comorbidities and cognitive deficits.

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Methods: A sample of 414 participants completed the study (249 HF patients, 63 healthy and 102 medical participants). The HF patients completed measures of HF severity, comorbidity (multiple comorbidity, hypertension, depressive symptoms), and neuropsychological functioning. Blood pressure and oxygen saturation were assessed at interview; clinical variables were abstracted from records. Participants in the comparison groups completed the same measures as the HF patients except those specific to HF.

Results: Compared to the healthy and medical participants, HF patients had poorer memory, psychomotor speed, and executive function. Significantly more HF patients (24%) had deficits in three or more domains. Higher (worse) HF severity was associated with more cognitive deficits; HF severity interacted with age to explain deficits in executive function. Surprisingly, men with HF had poorer memory, psychomotor speed, and visuospatial recall ability than women. Multiple comorbidity, hypertension, depressive symptoms, and medications were not associated with cognitive deficits in this sample.

Discussion: Heart failure results in losses in memory, psychomotor speed, and executive function in almost one fourth of patients. Patients with more severe HF are at risk for cognitive deficits. Older patients with more severe HF may have more problems in executive function and men with HF may be at increased risk for cognitive deficits. Studies are urgently needed to identify the mechanisms for the cognitive deficits in HF and test innovative interventions to prevent cognitive loss and decline.

Heart failure (HF) remains a major public health problem, affecting more than 5.7 million Americans (Lloyd-Jones et al., 2009). The estimated direct and indirect costs of HF care in the United States in 2009 are estimated to be 37.2 billion dollars. Although the 12-month mortality rates for HF are high, 80 to 85% of patients survive longer than 12 months. Health-related quality of life is diminished by dyspnea, fatigue, and depressive symptoms (Bennett et al., 2003).

Patients have reported that cognitive deficits are another problem that diminishes their health-related quality of life (Bennett, Cordes, Westmoreland, Castro, & Donnelly, 2000). These deficits may compromise patients' reasoning and decision-making abilities, thereby limiting their ability to perform self-care. Among 1,583 elderly patients hospitalized with HF, cognitive impairment was associated with significantly higher mortality (Zuccala et al., 2003). Cognitive deficits in HF have been investigated, but the studies have yielded mixed results about the association between HF and cognitive deficits (Bennett & Sauve, 2003; Bennett, Sauve, & Shaw, 2005; Pressler, 2008; Pullicino et al., 2008; Vogels, Scheltens, Schroeder-Tanka, & Weinstein, 2007). Some investigators have found that HF and HF severity were associated with cognitive deficits, but others have not found significant associations between HF and cognitive deficits. Limitations of past studies may explain the equivocal results. First, investigators used global screening questionnaires to assess cognitive deficits. Screening questionnaires are clinically feasible but lack the sensitivity needed to detect subtle cognitive deficits and thoroughly evaluate the association between HF and types of cognitive deficits. Second, investigators conducted studies among small or select samples (e.g., transplant candidates) with few women and minority participants. Finally, investigators often did not include comparison groups or variables of age and comorbid conditions; these are needed to fully evaluate HF patients' cognitive deficits.

The conceptual framework guiding the study is presented in detail elsewhere (Bennett et al., 2005). Deficits in the cognitive domains of language, working memory, memory,

visuospatial ability, psychomotor speed, and executive function are hypothesized to occur in HF patients. More severe HF is proposed to be associated with more cognitive deficits. The mechanism for cognitive deficits in HF remains undetermined, but the most likely etiology is decreased cardiac output leading to inadequate cerebral perfusion and oxygenation (Vogels, Oosterman et al., 2007; Woo, Macey, Fonarow, Hamilton, & Harper, 2003). The brain, particularly the highly plastic areas, requires large amounts of oxygen to function adequately. As such, the hippocampus, amygdala, frontal lobes, and cerebellum are vulnerable to oxygen deprivation and may be selectively damaged during hypoxic episodes (Rains, 2002). Hippocampal damage is important because of its role in the acquisition of new information and generation of memory, which are essential for performing activities of daily living and HF self-care.

The brain changes associated with sudden or abrupt reductions in cerebral blood flow have been well characterized, but less is known about the effects of chronic reductions in cerebral blood flow (Vogels, Oosterman et al., 2007; Zipes, Libby, Bonow, & Braunwald, 2005). In an animal model, transient cerebral ischemia significantly decreased cells in the CA1 hippocampal region; longer periods of ischemia (5 and 10 minutes) produced increased cell loss and were associated with deficits in spatial learning (Briones & Therrien, 2000). In HF patients, structural brain changes consistent with decreased cerebral perfusion and oxygenation have been identified, including loss of gray matter volume in the frontal cortex and parahippocampal areas (Woo et al., 2003) and silent ischemic strokes (Siachos et al., 2005).

Two recent investigations using magnetic resonance imaging technologies found brain structural changes among HF patients. Kumar and colleagues (Kumar et al., 2009) documented significant decreases in the volumes of the right and left mammillary bodies and the cross-sectional areas of the fornix fibers of HF patients (n = 17) compared to age-matched healthy participants (n = 50). Kumar's study provides a structural basis for memory deficits in HF because the mammillary bodies and fornix fibers are linked to severe anterograde and spatial memory deficits in animal and human studies (Kumar et al., 2009). Woo and colleagues (Woo, Kumar, Macey, Fonarow, & Harper, 2009) identified injured areas in the hippocampus, the hippocampal output fibers that project to the septum and the anterior thalamus, the caudate nuclei, and the anterior midportions of the corpus callosum of 13 HF patients (mean age 54.6 years) when compared to 49 healthy control participants (mean age 50.6 years). All brain sites of the HF patients showed significantly more differences suggestive of brain damage compared to the control participants. The types of injuries identified by Woo and colleagues involve structures that support short-term memory, learning, and executive function.

However, variables of age, multiple comorbid conditions, and two specific comorbid conditions common in HF (i.e., hypertension and depressive symptoms) are alternative explanations for cognitive deficits in HF. In the present study, these factors were evaluated as variables that contribute to cognitive deficits in HF. Age-related cognitive decline occurs in some individuals and the incidence of HF increases with age. Multiple comorbid conditions are present because HF patients are older. Hypertension is a common condition in HF that is associated with cognitive deficits (Waldstein, 2003). Depression is common in HF, occurring in 21.5% of patients in a meta-analysis of 36 studies (Rutledge, Reis, Linke, Greenberg, & Mills, 2006). Depressive symptoms overlap with signs of cognitive deficits (e.g., decreased attention). In a population-based study, comorbidity (i.e., depression and anemia) attenuated cognitive impairment in HF (Pullicino et al., 2008). However, cognitive impairment was measured during a telephone interview using a brief questionnaire rather than a neuropsychological test battery.

Educational level, gender, and medications were evaluated as covariates in the current study because they may contribute to cognitive deficits noted in HF. Educational level was evaluated as a covariate because it is associated with neuropsychological test scores. Older women who received hormone replacement therapy were found to have an increased incidence of Alzheimer disease, although recent data have called this finding into question (Shumaker et al., 2003). Few studies have had sufficient numbers of women with HF to examine gender differences in cognitive deficits. In a retrospective study of patients awaiting cardiac transplant, women ($n = 158$) had significantly greater deficits in language and psychomotor speed than men ($n = 602$), but men had more deficits in verbal learning (Putzke et al., 1997). Medications with a known influence on cognition were included as a covariate because of their potential to contribute to cognitive deficits. No studies were found that evaluated medications in relationship to cognitive deficits in HF.

To address limitations of past studies and more fully evaluate cognitive deficits in HF, patients with a spectrum of HF severity were studied and their cognitive function was compared to the function of two samples: healthy individuals and individuals with major chronic medical conditions. The first aim was to determine the types, frequency, and severity of cognitive deficits (in domains of language, working memory, memory, visuospatial ability, psychomotor speed, and executive function) among patients with chronic HF. The second aim was to evaluate the relationships between HF severity, age, and medical comorbidities and cognitive deficits. We hypothesized that: 1) HF patients have significantly more cognitive deficits than age- and education-matched comparison participants; and 2) increased HF severity, age, and comorbidity are associated with more cognitive deficits in HF.

Methods

Procedures

This study used a comparative design to evaluate cognitive deficits among the three groups and an explanatory correlational design to evaluate the relationships between HF severity, age, and comorbidity and cognitive deficits among the HF patients (Bennett et al., 2005). Data were collected from September 2004 to May 2008. The HF patients were recruited by clinic staff from one general medicine practice and six HF clinics in a Midwestern metropolitan city. Potentially eligible participants were approached by clinic staff, and if interested in the study, their names and contact information were provided to members of the research team. Eighty patients declined participation for the following reasons: lack of interest (n = 43); lack of time (n = 12); too sick (n = 9); unknown (n = 5); family issues (n = 2); did not remember being approached about study (n = 1); moving out of state (n = 1); had too many doctors' appointments (n = 1); wanted to discuss with family (n = 1); wanted to take consent form home and be approached at another appointment (n = 1); and other (n = 4). The participants in the healthy and medical groups were recruited from one general medicine practice, family members of HF patients, and volunteers who responded to advertisements. The study was approved by the institutional review boards at the sites. All participants provided written informed consent prior to data collection.

Eligible participants completed face-to-face interviews at a location preferred by them (i.e., clinics where the patients received care, patients' homes, or the school of nursing). Two research team members completed each interview; one was responsible for collection of the data for sociodemographics, HF severity, and comorbidities and the second for collection of the neuropsychological data. The senior neuropsychologist investigator trained the testers according to guidelines for neuropsychological test administration and scoring procedures. Comparison group participants provided all data except HF-related variables. The length of time to obtain consent and administer the questionnaires and tests was 90 to 120 minutes.

All participants were asked to identify a family member who could provide an assessment of their cognitive status (Hachinski et al., 2006). Family members were interviewed by telephone using a structured questionnaire.

Sample

Eligibility criteria for the HF patients included a diagnosis of chronic HF documented by echocardiography, nuclear imaging, or cardiac catheterization within the past two years with findings of systolic HF and left ventricular ejection fraction less than or equal to 40% (Zipes et al., 2005). Eligibility criteria for the healthy participants included living independently and/or able to care for self and absence of any major medical conditions. Participants who had controlled cardiovascular risk factors (i.e., mild hypertension with blood pressure less than 140/90 or mild hyperlipidemia with total cholesterol less than 200 mg/dL) were eligible for the healthy group. Eligibility criteria for the medical participants included a current medical diagnosis of a major chronic disorder other than HF (e.g., diabetes, uncontrolled hypertension). Categorization of participants as healthy or medical group members was verified by two of the investigators. Persons were excluded from participation in all groups if they had conditions known to cause cognitive deficits (e.g., history of or current major alcohol or substance abuse, history of major psychiatric or neurological disorders, encephalopathy, renal failure requiring dialysis) or terminal illness.

Measures

Heart failure severity—Heart failure severity was measured by the New York Heart Association (NYHA) Class (New York Heart Association Criteria Committee, 1964) during the interview. Although other more invasive measures provide detailed information about HF severity, the NYHA Class was used as a measure of HF severity in this study because it is clinically feasible with low respondent burden and has documented validity and reliability in persons with cardiac disorders (Bennett, Riegel, Bittner, & Nichols, 2002). Oxygen saturation, assessed at the interview by pulse oximetry, was used as a severity indicator that would detect severe resting decompensation.

Comorbidity—The Charlson Comorbidity Index was used to measure multiple comorbidity (Charlson, Pompei, Ales, & MacKenzie, 1987). In this Index, participants are asked whether they have a history of medical problems in 12 areas with responses of "yes" or "no". The medical problems reported are weighted by severity with each rating being worth 1, 3, or 6 points. A summary score is obtained; higher scores represent more and/or more severe comorbid conditions. In other populations, the comorbidity categories of the Index predicted 1-year mortality and health care costs (Perkins et al., 2004).

Blood pressure—Blood pressure measurement was assessed during the interview. Hypertension was defined as blood pressure higher than 140/90 mm Hg for patients without diabetes mellitus and 130/80 mm Hg for patients with diabetes mellitus (National Heart, Lung, and Blood Institute, 2003).

Depressive symptoms—Depressive symptoms were measured using the Patient Health Questionnaire-8 (PHQ-8) (Kroenke & Spitzer, 2002). The PHQ-8 consists of the first 8 items of the PHQ-9, which was developed based on the 9 depression criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition. Item 9 requires that participants respond to whether they have had suicidal ideation; this item is not required when assessing nonpsychiatric populations (Kroenke & Spitzer, 2002). Psychometric properties of the PHQ-8 are similar to the properties of the PHQ-9. On the PHQ-8, possible scores range from 0 to 24. Scores of 1 to 4 indicate no depressive symptoms; 5 to 9 mild symptoms; 10 to 14 moderate symptoms, 15 to 19 moderately severe symptoms; and 20 to

24 severe depressive symptoms. Scores of 10 or higher indicate the need for possible treatment. Validity and reliability have been documented (Kroenke & Spitzer, 2002). Reliability estimates of the PHQ-9 were .89 and .86 among 3000 primary care and 3000 obstetrical and gynecological patients, respectively (Kroenke, Spitzer, Williams, 2001). The Cronbach's alpha in the current sample was .82.

Covariates—Educational level and gender were evaluated as covariates. Medications with known effects on cognitive function were evaluated for their relative contribution to cognitive deficits. Medications included were those with a primary central nervous system indication plus those with prominent central nervous system adverse effects: (a) major tranquilizers or anti-psychotic medications; (b) anti-depressants including lithium; (c) Alzheimer disease medications (cholinesterase inhibitors); (d) atropine and scopolamine; (e) steroid hormones including estrogens; (f) beta-adrenergic antagonists (especially propranolol); (g) narcotic analgesics; (h) anti-Parkinson's medications (e.g., L-dopa); (i) anti-epileptic medications (phenytoin; gabapentin); and (j) barbiturates (Hardman & Limbird, 2001). The medications were analyzed as dichotomous covariates and patients who were prescribed one or more of the medications from the above groups were considered as receiving a medication known to alter cognitive function while patients not prescribed the above medications were considered as not receiving a medication known to alter cognition.

Cognitive deficits—The neuropsychological test battery administered to all participants was designed to measure the cognitive domains most likely to be impaired in vascular cognitive disorders and commonly sampled in a neuropsychological examination for these disorders (Hachinski et al., 2006). The battery required approximately 60 minutes to administer. The tests have documented validity and reliability, including the ability to discriminate between persons with normal cognitive functioning, mild cognitive impairment, and dementia. Table 1 presents the cognitive domains evaluated, the neuropsychological tests administered, and brief descriptions of the tests.

Participants' family members completed a 24-item family interview questionnaire with responses of "yes" and "no" to support validation of the neuropsychological tests. This questionnaire measured family members' observations about whether their participants had changes in cognition or behavior in the past several years. It yields four subscale scores in memory difficulty (8 items), information recall (5 items), judgment (4 items), and behavior (7 items). Higher scores indicate more cognitive and/or behavioral problems.

Statistical analysis

Descriptive statistics were computed for study variables and compared among the HF, healthy, and medical participant groups using ANOVA, Chi-square, or Fisher' Exact tests. To achieve aim one, ANCOVA was first used to compare the raw scores of the neuropsychological tests among the three groups, adjusting for age, premorbid intellect, and education. Next, Z-scores of the neuropsychological tests were constructed and compared among the groups because local normative samples may better calibrate levels of deficits than published norms. For the healthy participant group, each test measure was regressed on age, premorbid intellect, and education. Recall of geometric figures (Figure Copy) and the Trail Making Test Part A scores were natural log transformed to achieve normality in the residuals. Predicted values for the HF, healthy, and medical participants were obtained from these regression models and Z-scores calculated. To compare the Z-scores between the HF patients and the healthy and medical participants, t-tests (equal or unequal variance as appropriate) were used for cognitive domains measured by a single neuropsychological test score (global cognitive function and language), and Hotelling's T^2 tests for domains measured by two or more test scores (working memory, memory, visuospatial ability,

psychomotor speed, and executive function). Tests were assessed at the .05 level of significance for single score domains and by Bonferroni correction for multiple score domains when the Hotelling's T^2 test was significant at the .05 level.

Cognitive impairment cutoff scores were defined from the healthy participants' Z-scores using the 7th percentile. Patients who performed at or below the 7th percentile cutoff were regarded as being cognitively impaired in that domain (Peterson et al., 1995). Chi-square or Fisher's Exact test as appropriate were used to compare the percent of HF patients with cognitive impairment to the percent of healthy and medical participants with cognitive impairment, using Bonferroni corrections for multiple measures. Family-reported changes in cognition were compared using Kruskal-Wallis for overall differences and Wilcoxon-Rank sum tests for pairwise comparisons.

To accomplish aim two, a series of multiple linear regression analyses were conducted using the data from the HF patients. Each neuropsychological variable was entered as the dependent variable in separate regression equations. Independent variables were NYHA Class, oxygen saturation, age, and comorbidity (Charlson Comorbidity Index, hypertension, and depressive symptoms); interactions between NYHA Class and age and comorbidity were examined at a more stringent .01 significance level to control for multiple testing. Covariates were premorbid intellect, education, gender, and medications with an influence on cognitive function.

Results

A total of 414 participants completed the study, including 249 HF patients, 63 healthy participants, and 102 medical participants. Sample characteristics are presented in Table 2. The demographic characteristics were balanced among the groups with the exceptions that the healthy participants were younger than the HF and medical participants and the HF group had more men and more were married. Some participants were unable to complete the full neuropsychological test battery due to sensory or health problems; sample size varies slightly across analyses.

Comparisons among the groups of oxygen saturation, comorbidity, blood pressure, and depressive symptoms are presented in Table 3. Compared to participants in the other two groups, the HF patients had significantly more or more severe comorbid conditions, more or more severe depressive symptoms, and lower diastolic blood pressure. Compared to the medical participants, the HF patients had significantly lower systolic blood pressure.

The neuropsychological test scores of the HF patients were compared to the healthy and medical participants. Raw score comparisons are presented in Table 3. The HF patients had worse scores than the healthy and medical participants in total recall memory and than the medical participants in delayed recall memory. The HF patients had slower psychomotor speed than the healthy and medical participants. The HF patients had worse scores in executive function.

The Z-score means and standard deviations of the neuropsychological test results among the groups are presented in Table 4. Compared to the medical participants, the HF patients had poorer performance in memory, slower psychomotor speed, and poorer executive function.

Using the 7th percentile Z-score as a cutoff, significantly more HF patients had memory impairment (total recall) compared to healthy and medical participants (Table 5). Among the groups, 23% of the HF patients had impaired total recall memory compared to 8% of the healthy and 9% of the medical participants. In psychomotor speed, 19% of the HF patients were impaired compared to 8% and 6% of the healthy and medical participants, respectively.

On executive function measures, 19% and 16% of the HF patients performed as impaired, compared to 8% of the healthy and 10% and 7% of the medical participants. Twenty-four percent of the HF patients were impaired in three or more cognitive domains, compared to 14% of the healthy and 12% of the medical participants. *Post hoc* analysis indicated HF patients had more impairment than medical participants.

Family members of the HF patients (n = 230) reported that the patients had more cognitive changes than family members of healthy (n = 53) and medical (n = 89) participants. Differences were found in memory difficulty (Chi-square = 22.03, p < .0001), information recall (Chi-square = 12.27, p = .002), judgment (Chi-square = 7.06, p = .029), and behavior (Chi-square = 15.43, p = .0004). In *post hoc* analyses using Wilcoxon-Rank sum with Bonferroni adjustment to alpha = .0167, more changes were reported by family members of HF patients than family members of healthy and medical participants in memory difficulty (p < .0001) and than healthy participants in information recall (p = .002) and behavior (p = . 0004).

In the regression models, HF severity (NYHA Class) was significantly associated with memory (Hopkins total recall), visuospatial ability (Figure Memory recall), psychomotor speed (Digit Symbol), and executive function (Trail Making Test Part B and Controlled Oral Word Association). Patients with NYHA Class I and II HF had higher Z-scores overall, indicating better cognitive function. Heart failure severity (NYHA Class) and age significantly interacted to explain executive function (Trail Making Test B and Controlled Oral Word Association) (Tables 6 and 7). Older age was associated with better executive function scores (Trail Making Test B) for NYHA Class II and with worse executive function scores (Controlled Oral Word Association) for NYHA Class IV.

In the regression models, men had significantly poorer total and delayed recall memory (t = 4.7 and 25.2, respectively, p < .0001 in both cases), psychomotor speed (Digit Symbol; t = 12.2, p = .0006), and visuospatial ability (Figure Memory recall; t = 2.0, p = .046) than women. There were no significant mean differences between men and women in age, premorbid intellect, education, LVEF, oxygen saturation, multiple comorbidity, or depressive symptoms. Women were more likely to have NYHA Class III and IV than men (59% vs. 46%, Chi-square = 4.38, p = .04).

Multiple comorbidity, depressive symptoms, and hypertension were not significant explanatory variables for cognitive deficits. Medications with a known influence on cognitive function were entered into the equations but were not significant explanatory variables for cognitive deficits.

Discussion

Three important results emerged from this study. First, the 249 HF patients had poorer memory, psychomotor speed, and executive function than the 63 healthy and 102 medical participants and 24% of the HF patients had cognitive deficits in three or more domains. Second, patients with more severe HF had poorer total recall memory, visuospatial recall ability, psychomotor speed, and executive functioning. Older patients with more severe HF had poorer executive functioning. Third, men with HF had poorer memory, psychomotor speed, and visuospatial recall ability than women.

Consistent with past studies, HF patients had poorer performance compared to healthy and medical participants in memory, psychomotor speed, and executive functioning (Bennett & Sauve, 2003; Vogels, Scheltens et al., 2007; Pressler, 2008; Vogels, Oosterman et al., 2007). Some inconsistencies remain about the relationship between HF severity and cognitive deficits. In the current study, more severe HF was associated with poorer total recall

memory, poorer visuospatial recall ability, psychomotor slowing, and poorer executive function, although not across all tests. Heart failure severity (NYHA classes II and IV) and age interacted to explain executive function. It is possible that the trajectory of chronic HF, with episodic decompensations interspersed with periods of stability, contributes to the varying extent of deficits in individual patients. The multiple anatomic defects in the brain described by Kumar et al. (2009) and Woo et al. (2009) lend credence to cerebral events being part of the constellation of systemic damage in chronic HF.

No significant differences were found in the cognitive domains of language, working memory, and visuospatial ability among the HF patients when compared to the healthy and medical participants. It is possible that the measures used to assess these domains were not sensitive or challenging enough to detect differences among the groups given that the groups were matched on education and premorbid intellect. However, the measures (Boston Naming Test, Digit Span, and Figure Copy and Memory) have discriminated between healthy and cognitively impaired individuals in other studies and are recommended for use when evaluating vascular cognitive disorders (Hachinski et al., 2006). An attempt was made to minimize environmental distractions during testing, which may have facilitated the attention of patients. Although not tested in this study, it is possible that the brain structures responsible for language and working memory are less sensitive to cerebral hypoperfusion than the areas responsible for memory, psychomotor speed, and executive function.

The ability to detect the relationship between HF severity and cognitive deficits may have been limited by measurement factors. The NYHA Class is valid, reliable, and clinically feasible, but more invasive methods are required to fully evaluate HF severity. Selection bias may have prevented demonstrating a systematic relationship between HF severity and cognitive deficits across all tests because only those NYHA Class IV patients who were well enough completed the interviews; others were too sick to participate.

Multiple comorbidity, hypertension, and depressive symptoms were not associated with the cognitive deficits in this sample of HF patients. These results are in contrast to a study that reported that depression and anemia predicted cognitive impairment in HF (Pullicino et al., 2008). Participants in that study were categorized as probably having HF based on symptoms of dyspnea and orthopnea and cognitive impairment and depression were measured using 6- and 4-item questionnaires, respectively, that were administered by telephone interviews. These differences between the two studies in the validation of the HF diagnosis, measures for cognitive deficits, and administration methods, may explain the differences in the results. In the current study, patients had a definitive HF diagnosis and cognitive deficits were measured during face-to-face interviews using valid objective neuropsychological tests. Depressive symptoms were measured as a subjective phenomenon using the valid and reliable PHQ-8 that is sensitive to depression.

The finding that men with HF had poorer memory, psychomotor speed, and visuospatial recall ability than women with HF was unexpected. This was the first controlled study found to report this result. Interestingly, there were no differences between men and women in age, premorbid intellect, education, LVEF, oxygen saturation, multiple comorbidity, or depressive symptoms. The HF group had 63% men and 37% women; the higher percentage of men in the sample may have contributed to the finding of more cognitive deficits in men than women. In one of the few studies reporting gender differences, Putzke (Putzke et al., 1997) did find that men had more deficits in verbal learning. It is intriguing to speculate that sex hormones may play a role in the fewer deficits of women but other factors such as duration of HF, thromboembolic risk, incidence of diabetes, smoking, and concomitant medications may also have been contributory to the deficits. One potential factor, severity of HF, does not seem as likely of an explanation of the gender differences since NYHA Class

III and IV HF was more prevalent in women yet men had more profound cognitive deficits. The type and extent of cognitive deficits related to gender need to be confirmed in an adequately powered prospective study that controls for demographic, biological, clinical, and social variables that may differ between men and women.

Strengths of the current study include a carefully characterized sample of HF patients with representative numbers of women and minority (African-American) participants; comparison groups matched on premorbid intellect and education; use of valid objective neuropsychological tests to measure cognitive deficits; and evaluation of comorbid conditions that could contribute to cognitive deficits. The HF patients were recruited from seven sites; this increases the representative of the sample. A limitation of the study was that the healthy participants were younger than the HF patients and this difference cannot be excluded as a reason for the differences observed in cognitive deficits. Despite efforts to enroll age-matched healthy elders without major medical conditions, most participants over age 60 had at least one medical condition. This is expected; 74% of Americans age 65 years and older have one or more chronic health conditions (National Institute on Aging, 2007). The finding that the HF patients had more deficits than the medical participants who were age-matched lends support to HF as the cause of the deficits. The results are not generalizable to the entire HF population because only patients with documented systolic dysfunction and without obvious reasons for cognitive deficits were included.

In conclusion, cognitive deficits are a common problem that affects nearly one fourth of patients with chronic systolic HF. Memory deficits are most common, followed by psychomotor slowing and decreased executive function. Patients with more severe HF had more cognitive deficits, and older patients with more severe HF had more deficits in executive function. Men with HF had poorer memory, psychomotor speed, and visuospatial recall ability than women. Future studies are needed to determine the etiology of the cognitive deficits in order to prevent them and to test novel interventions targeted at preventing and delaying cognitive loss and decline.

The finding that many patients with HF have cognitive deficits has important clinical implications. Patients need to be carefully evaluated for cognitive deficits and whether these deficits alter their ability to perform activities of daily living and comply with HF self-care behaviors. Older patients with more severe HF may be most at risk for deficits and diminished decision-making abilities. These patients require assistance from family caregivers and would likely benefit from disease management and transitional care programs.

Acknowledgments

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Table 1

Cognitive Domain, Neuropsychological Tests, and Tests Descriptions

Cognitive domain	Neuropsychological tests[a]	Brief description
Global cognitive function	Mini-mental State Examination[b]	Participants complete a 30-point screening questionnaire to evaluate general mental status. Higher scores indicate better mental status.
Premorbid intellect	Wechsler Test of Adult Reading[c]	Participants asked to pronounce a list of phonologically irregular words aloud. Measure of analysis was a standard score with mean = 100 and standard deviation = 15.
Language	Boston Naming Test[d]	Participants name line drawings of common objects. Possible raw scores range from 0 to 60, with higher scores indicating better ability.
Working memory	Digit Span[e]	Participants repeat series of numbers forward and backward. The raw forward and backward spans were analyzed separately (possible forward score 0 to 16; possible backward score 0 to 14) and the total score was transformed to a scaled score (mean = 10 and standard deviation = 3) as derived from the WAIS-3.
Verbal memory	Hopkins Verbal Learning Test[f]	Participants asked to learn orally presented 12-word list over three rehearsal trials, with recall after each list presentation. After a 20-minute delay, they are asked to recall as many of the 12 words as they can. The variables analyzed were total learning over the three trials (possible score 0 to 36 for summed recall of trials 1 through 3) and delayed recall (possible score 0 to 12). Higher scores indicate better performance.
Visuospatial ability	Figure Copy and Figure Memory recall[g]	Participants are shown five figures that increase in complexity (circle, diamond, intersection, rectangle, and cube) and are asked to draw a copy of each figure. After a 20-minute delay, they are asked to recall and draw the figures again. The variables analyzed were total (possible scores range from 0 to 11) and recall (possible scores range from 0 to 14) with higher scores indicating better performance.
Psychomotor speed	Digit Symbol[e]	Participants required to match a series of numbers with symbols using a key that shows the unique pairing of the numbers with the symbols. The measure of analysis was the scaled score derived from the WAIS-3 standardization sample (mean = 10; standard deviation = 3).
	Trail Making Test, Part A[h]	Participants use a pencil to draw a line that connects numbered circles arrayed on a page as fast as possible. The measure of analysis was the number of seconds to complete the task, with higher scores (longer time) indicating slower psychomotor speed.
Executive function	Trail Making Test, Part B[h]	Participants use a pencil to connect numbered and lettered circles sequentially as fast as possible, but in alternate alpha-numeric order (i.e., number-letter-number-letter). The measure of analysis is the number of seconds to complete the task, with higher scores (longer time) indicating poorer shifting between numbers and letters.
	Controlled Oral Word Association[i]	Participants given a letter of the alphabet and asked to name as many words as possible that begin with that letter. The test measures the speed with which participants can search and retrieve a word from their mental lexicon using a phonemic stem. The measure of analysis was the number of words produced in 90 seconds for each of the letters C, F, and L, with higher scores indicating better performance.

[a] Although the tests were used to sample a specific domain, each test actually samples multiple domains.

[b] Folstein, Folstein, & McHugh, 1975

[c] The Psychological Corporation. *Wechsler[R] Test of Adult Reading Manual.* San Antonio: The Psychological Corporation; 2001.

[d] Kaplan, Goodglass, & Weintraub, 2001

[e] Wechsler, 1997

^{f}Brandt & Benedict, 2001

^{g}Welsh et al., 1994

^{h}Reitan, 1992

^{i}Benton & Hamsher, 1978

Table 2

Sample Characteristics by Group (n = 414)

Characteristic	Heart failure[a] (n = 249)	Healthy (n = 63)	Medical (n = 102)	Chi-square, F-statistic, or Fisher's	p-value[b]	Pair-wise differences[c]
Age, mean ± standard deviation (SD[d])	62.9 ± 14.6	53.3 ± 17.2	63.0 ± 11.9	F = 12.07	<.0001	HF, Medical > Healthy
Sex, n (%)				χ^2 = 50.3	<.0001	HF different than Medical and Healthy
Men	158 (63)	18 (29)	28 (27)			
Women	91 (37)	45 (71)	74 (73)			
Race, n (%)				Fisher's	.43	
African American	79 (32)	19 (30)	30 (29)	Exact Test		
Asian	2 (1)	0	0			
White	167 (67)	43 (68)	69 (68)			
American Indian or Alaskan	1 (<1)	0 (0)	1 (1)			
Other	0 (0)	1 (2)	2 (2)			
Ethnicity, n (%)				Fisher's	.28	
Hispanic	0	0	1 (1)	Exact Test		
Non-Hispanic	248 (100)	62 (98)	101 (99)			
Missing/Not Reported	1 (<1)	1 (2)	0 (0)			
Marital status, n (%)				χ^2 = 11.5	.003	HF different than Medical and Healthy
Married	140 (56)	22 (35)	44 (43)			
Not married	109 (44)	41 (65)	58 (57)			
Economic, n (%)				Fisher's	.56	
Comfortable	123 (49)	34 (54)	56 (56)	Exact Test		
Just enough to make ends meet	81 (33)	22 (35)	28 (27)			
Not enough to make ends meet	44 (18)	7 (11)	16 (16)			
Missing/Refused	1 (<1)	0 (0)	2 (2)			
Education, years, mean ± SD	12.9 ± 2.8	13.7 ± 2.5	12.9 ± 2.4	F = 2.7	.07	
Premorbid intellect, mean ± SD[e]	94.3 ± 17.0	98.6 ± 15.8	96.2 ± 16.7	F = 1.7	.18	
HF Stage, n (%)						

Characteristic	Heart failure[a] (*n* = 249)	Healthy (*n* = 63)	Medical (*n* = 102)	Chi-square, *F*-statistic, or Fisher's	*p*-value[b]	Pair-wise differences[c]
B	8/169 (5)					
C	146/169 (86)					
D	15/169 (9)					
NYHA[f] Class n (%)						
I	38 (15)					
II	85 (34)					
III	97 (39)					
IV	29 (12)					
Ejection fraction, mean ± SD	28.2 ± 10.3					
Implantable defibrillator, n (%)	101 (41)					
Bi-ventricular pacemaker, n (%)	54 (22)					
Duration of HF, years, mean ± SD	7.5 ± 7.5					

[a]Heart failure = HF

[b]p-values for univariate analysis of variance F, Chi-square, or Fisher's Exact test.

[c]p < .05, unadjusted.

[d]Standard deviation = SD

[e]Wechsler Test of Adult Reading, standard score; nationally standardized sample (mean = 100, SD ± 15)

[f]New York Heart Association = NYHA

Table 3

Comparison of Means and Standard Deviations of Variables by Group (n = 414)

Variable	Heart Failure[a] (n = 249) Mean ± SD[b]	Healthy (n = 63) Mean ± SD	Medical (n = 102) Mean ± SD	F value	p-value[c]	Pair-wise Differences[d]
Oxygen saturation	95.7 ± 1.9	96.1 ± 1.2	95.7 ± 1.3	1.5	.22	
Comorbidity (Charlson)	3.1 ± 1.8	0.1 ± 0.4	1.0 ± 1.4	124.7	< .0001	HF > Healthy, Medical; Medical > Healthy
Depressive symptoms (PHQ-8)	6.5 ± 5.5	2.6 ± 3	3.7 ± 3.4	23.1	< .0001	HF > Healthy, Medical
Systolic blood pressure	116.9 ± 18.2	118.5 ± 14.1	133.1 ± 19	30.1	< .0001	HF, Healthy < Medical
Diastolic blood pressure	68.6 ± 11.6	75.3 ± 7.7	75.5 ± 12	18.4	< .0001	HF < Healthy, Medical
Mini-mental State Examination	27.6 ± 2.2	28.3 ± 1.5	28.0 ± 1.6	1.5	.23	
Language (Boston Naming Test # correct)	52.0 ± 7.4	52.4 ± 7.4	52.4 ± 7.5	1.6	.21	
Working memory (Digit Span)						
Forward	6.2 ± 1.3	6.6 ± 1.5	6.3 ± 1.4	.1	.93	
Backward	4.3 ± 1.1	4.5 ± 1.3	4.6 ± 1.2	2.2	.12	
Scaled	9.7 ± 2.9	10.0 ± 2.8	10.1 ± 3.1	.4	.70	
Memory (Hopkins Verbal Learning Test; raw scores)						
Total recall	20.0 ± 5.8	23.9 ± 5.2	23.0 ± 5.2	12.0	< .0001	HF < Healthy, Medical
Delayed recall	6.8 ± 2.8	8.3 ± 2.8	8.1 ± 2.8	6.2	.002	HF < Medical
Visuospatial (Figure Copy, Memory; raw)						
Total	8.7 ± 1.5	9.0 ± 1.3	8.9 ± 1.3	0.4	.70	
Recall	7.5 ± 2.7	8.3 ± 2.3	7.8 ± 2.5	0.3	.77	
Psychomotor speed						
Digit Symbol, scaled	8.5 ± 2.9	9.9 ± 2.7	10.0 ± 3.0	10.1	< .0001	HF < Healthy, Medical
Trail Making Test A (time in seconds)	48.8 ± 24.1	39.8 ± 29.2	40.5 ± 14.5	4.4	.01	HF > Medical
Executive function						

Variable	Heart Failure[a] (n = 249) Mean ± SD[b]	Healthy (n = 63) Mean ± SD	Medical (n = 102) Mean ± SD	F value	p-value[c]	Pair-wise Differences[d]
Trail Making Test B (time in seconds) Controlled Oral Word	133.4 ± 69.8	96.2 ± 53.9	106.2 ± 53.2	7.6	.0006	HF > Medical
Association (raw scores)	30.1 ± 11.9	36.2 ± 11.6	33.4 ± 11.5	3.1	.05	NS[e]

[a] Heart failure = HF

[b] Standard deviation = SD

[c] p-values for univariate ANOVA for non-neuropsychological data and ANCOVA for neuropsychological data adjusting for age, premorbid intellect and education.

[d] p < .05 after Tukey-Kramer adjustment.

[e] No significant pair-wise differences.

Table 4

Comparison of Means and Standard Deviations of Z-scores for Neuropsychological Tests by Group (n = 414); Healthy Group Mean Scores = 0 as Reference Group[a]

Variable	Heart Failure[b] (n = 249) Z-score Mean ± SD[c]	t-test or Hotelling's T²	Heart Failure and Healthy Overall p-value and significant pair-wise differences	Medical (n = 102) Z-score Mean ± SD	t-test or Hotelling's T²	Heart Failure and Medical Overall p-value and significant pair-wise differences
Global Cognition (Mini-mental State Examination)	−.1 ± 1.3	t = 0.9	.39	.1 ± 1.0	t = 1.7	.09
Language (Boston Naming Test)	.4 ± 1.2	t = 2.2	.03	.3 ± 1.1	t = .5	.64
Working memory (Digit Span)[d]		T² = 3.0	.40		T² = 3.1	.39
Forward	−.02 ± .9			−.1 ± 1.0		
Backward	.2 ± .8			.3 ± .9		
Scaled	.1 ± .9			.2 ± 1.1		
Memory (Hopkins Verbal Learning Test)[e]		T² = 6.8	.04		T² = 20.0	<.0001
Total recall	−.4 ± 1.3		HF < Healthy	.2 ± 1.2		HF < Medical
Delayed recall	−.2 ± 1.1			.3 ± 1.2		HF < Medical
Visuospatial (Figure Copy and Figure Memory)[e-f]		T² = 1.2	.54		T² = 0.4	.81
Total	.1 + 1.1			.1 ± 1.0		
Recall	−.2 ± 1.9			−.1 ± 2.1		
Psychomotor speed[e]		T² = 5.3	.07		T² = 19.2	<.0001
Digit Symbol, scaled	−.3 ± 1.0			.2 ± 1.1		HF < Medical
Trail Making Test A (time in seconds)[f]	−.1 ± 1.0			.2 ± .8		HF < Medical
Executive function[e]		T² = 6.1	.049		T² = 17.4	.0002
Trail Making Test B (time in seconds)	−.4 ± 1.4		HF < Healthy	.3 ± 1.2		HF < Medical
Controlled Oral Word Association	−.3 ± 1.0			−.03 ± 1.0		

[a] Using t-test and p-value for cognitive domains with one measure (global cognition and language) and Hotelling's T² test for cognitive domains with more than one measure (working memory, memory, constructional praxis, psychomotor speed, and executive function)

[b] Heart failure = HF

[c] Standard deviation = SD

[d] Bonferroni adjustment, $p < .017$ for working memory with three scores from Digit Span

[e] Bonferroni adjustment, $p < .025$ for memory, visuospatial ability, psychomotor speed, and executive function, each with two measures

[f] Variable log-transformed prior to creation of Z-scores due to lack of normality

Table 5

Comparisons of Percent of Participants who Performed at or below the 7th Z-score Percentile

Neuropsychological tests	Heart Failure (%)	Healthy (%)	Medical (%)	Chi-square/Fisher's Heart Failure/ Healthy	Heart Failure and Healthy p-value[a]	Chi-square/Fisher's Heart Failure/ Medical	Heart Failure and Medical p-value[a]
Global (Mini-mental State Examination)	14	8	6	$\chi^2 = 1.6$	.20	$\chi^2 = 4.3$	.04*
Language (Boston Naming Test)	8	8	7	Fisher's Exact Test	1.00	$\chi^2 = 0.1$	.79
Working memory (Digit Span)							
Forward	4	8	3	Fisher's Exact Test	.18	Fisher's Exact Test	1.00
Backward	1	8	0	Fisher's Exact Test	.01***	Fisher's Exact Test	.56
Scaled score[b]	1	8	3	Fisher's Exact Test	.01***	Fisher's Exact Test	.36
Memory (Hopkins Verbal Learning Test)							
Total recall	23	8	9	$\chi^2 = 6.9$	.009**	$\chi^2 = 9.0$	.003**
Delayed recall	14	8	8	$\chi^2 = 1.4$	.23	$\chi^2 = 2.0$	.15
Visuospatial (Figure Copy)							
Total	6	8	7	Fisher's Exact Test	.56	$\chi^2 = 0.2$	.68
Recall	12	8	11	$\chi^2 = 0.9$	.35	$\chi^2 = 0.1$	.77
Psychomotor speed							
Digit Symbol, Scaled	19	8	6	$\chi^2 = 4.0$	.047	$\chi^2 = 7.8$	.005**
Trail Making Test A (time in seconds)[c]	13	8	5	$\chi^2 = 1.1$	.29	$\chi^2 = 4.1$	.04
Executive function							
Trail Making Test B (time in seconds)	19	8	10	$\chi^2 = 4.7$	.03	$\chi^2 = 4.7$	.03
Controlled Oral Word Association	16	8	7	$\chi^2 = 2.6$	.11	$\chi^2 = 4.9$	.03

[a] p-values for Chi-square or Fisher's Exact Test as appropriate

[b] Nationally standardized mean of 10, standard deviation = 3

[c] Variable log-transformed prior to creation of Z-scores due to lack of normality

* Significant at p < .05 for 1 item domain

** Significant at p < .025 with Bonferroni adjustment for domains with two measures (memory, visuospatial ability, psychomotor speed, executive function)

*** Significant at p < .017 with Bonferroni adjustment for domain with three scores (working memory)

Table 6

Multiple Linear Regression Model Explaining Executive Function (Trail Making Test B) (n = 229)

Variables	b[a]	SE[a]	t (F)[b]	p[c]	sr²[d]	bivariate r or point biserial
Cognitive medications[e]	.13	.19	.68	.50	.003	.05
Gender (women)[e]	−.15	.19	−.77	.45	.001	−.03
Education (years)[e]	−.09	.04	−1.99	.05	.008	.08
Premorbid intellect[e]	.03	.01	5.03	<.0001	.010	.30
Oxygen saturation[e]	−.001	.05	−.02	.98	<.001	−.03
Age	.01	.02	.85	.40	<.001	.06
Multiple comorbidity	−.02	.05	−.30	.77	.003	−.07
Hypertension	−.15	.25	−.61	.54	.001	−.06
Depressive symptoms	−.02	.02	−.86	.39	.002	−.07
NYHA[f] Class			(3.33)	(.02)		
(Reference level: Class I)						
Class II	−.49	1.16	−.42	.67	.002	--
Class III	1.80	1.17	1.54	.13	.006	--
Class IV	3.74	1.90	1.97	.05	<.001	--
Age * NYHA[g]			(4.00)	(.009)		
Age * Class II	.01	.02	.39	.70	.03	--
Age * Class III	−.03	.02	−1.81	.07	.004	--
Age * Class IV	−.06	.03	−2.00	.047	.02	--

$R^2 = .17$; adjusted $R^2 = .11$

[a] beta coefficient and standard error.

[b] *t* reported for individual variables, *F* also reported for overall NYHA effects.

[c] p-value reported for testing individual variables equal to 0, and also overall for NYHA effects only.

[d] squared semi-partial correlation coefficient (Type I).

[e] Covariates.

[f] New York Heart Association = NYHA.

[g]When estimating the overall effect of age on executive function for each level of NYHA, the only significant effect was for NYHA Class II, where the estimate for age was .02 (SE = 0.01, t = 2.01, p-value = 0.045).

Table 7

Multiple Linear Regression Model Explaining Executive Function (Controlled Oral Word Association) (n = 237)

Variables	b[a]	SE[a]	t (F)[b]	p[c]	sr²[d]	bivariate r or point biserial
Cognitive medications[e]	−.13	.14	−.96	.34	<.001	−.04
Gender (women)[e]	.26	.14	1.93	.06	.01	.12
Education (years)[e]	.05	.03	1.69	.09	.01	.06
Premorbid intellect[e]	−.01	.00	−1.56	.12	.02	−.08
Oxygen saturation[e]	.01	.04	.25	.80	<.001	.03
Age	.00	.01	−.02	.98	.004	−.08
Multiple comorbidity	−.001	.04	−.03	.98	<.001	.00
Hypertension	.17	.18	.93	.35	.004	.09
Depressive symptoms	−.01	.01	−.63	.53	.003	−.02
NYHA[f] Class			(4.41)	(.005)		
(Reference level: Class I)						
Class II	.14	.84	.19	.85	<.001	--
Class III	−.01	.85	−.01	.99	.004	--
Class IV	4.45	1.37	3.23	.001	.002	--
Age * NYHA[g]			(5.13)	(.002)		
Age * Class II	−.00	.01	−.17	.86	<.001	--
Age * Class III	.00	.01	.15	.88	.01	--
Age * Class IV	−.07	.02	−3.42	<.001	.05	--

$R^2 = .12$; adjusted $R^2 = .06$

[a] beta coefficient and standard error.

[b] *t* reported for individual variables, *F* also reported for overall NYHA effects.

[c] p-value reported for testing individual variables equal to 0, and also overall for NYHA effects only.

[d] squared semi-partial correlation coefficient (Type I).

[e] Covariates.

[f] New York Heart Association = NYHA

[g]When estimating the overall effect of age on executive function for each level of NYHA, the only significant effect was for NYHA Class II, where the estimate for age was −0.07 (SE = 0.02, t = −4.02, p-value = <.0001).