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The Interactive Effects of Cerebral Perfusion and Depression on Cognitive Function in Older Adults with Heart Failure

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Abstract

Objectives—Depression is common among persons with heart failure (HF) and has been linked to cognitive impairment in this population. The mechanisms of this relationship are unclear, and the current study examined whether cerebral perfusion moderates the association between depressive symptomatology and cognitive impairment in patients with HF.

Methods—Persons with HF (N=89; 67.61 (SD = 11.78) years of age) completed neuropsychological testing and impedance cardiography. Depressive symptomatology was assessed using the Beck Depression Inventory-II and transcranial doppler was used to quantify cerebral perfusion.

Results—Depression was associated with reduced performance on tasks assessing attention/executive function ($r=-0.28$), language ($r=-0.30$) and motor function ($r=-.28$) in unadjusted models (p -values < 0.05). Global cerebral blood flow was correlated with memory performance ($r=0.22$, $p=.040$) but not to other tasks. A moderation analysis was performed using hierarchical regression models for attention/executive function, memory, language, and motor function. For each model, medical and demographic characteristics were entered into the initial blocks, and the final block consisted of an interaction term between global cerebral blood flow velocity (CBF-V) and the BDI-II. The interaction between greater depressive symptomatology and decreased global CBF-V was associated with greater deficits in attention/executive function ($\beta = .32$, $R^2 = .08$, $p = .003$).

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Conclusion—Depressive symptomatology and cerebral hypoperfusion interact to adversely affect cognitive performance in older adults with HF. Longitudinal studies are needed to clarify this relationship and elucidate subsequent neuropathology.

Keywords

Cognitive impairment; Cerebral Perfusion; Heart failure; Depression; Cardiovascular disease; Cerebral blood flow velocity

Introduction

The prevalence rate of heart failure (HF) within the United States is estimated to be nearly 6 million Americans (1) and is expected to increase 25% by the year 2030 (2). Along with being a significant source of economic hardship and the most common reason for re-hospitalization (3–5), HF is associated with increased risk for mortality (6,7), reduced ability to perform key self-care tasks (8,9), and diminished quality of life (10).

Rapidly growing evidence links HF with cognitive impairment with as many as 75% of patients with HF exhibiting cognitive deficits (11), particularly in memory, psychomotor speed, and executive function (12). HF patients are also at elevated risk for Alzheimer's disease (AD) (13) and vascular dementia (14), and frequently exhibit abnormalities on magnetic resonance imaging (MRI) scans (15). Not surprisingly, cognitive impairment in HF has been linked with adverse outcomes, including poor general health, decreased quality of life (16) and increased risk of mortality (17). Given such poor outcomes, research has focused on identifying potential risk factors of cognitive impairment in this population. Among the few established risk factors are older age, hyperglycemia, history of stroke, hypertension, and metabolic abnormalities (i.e., low serum albumin, anemia) (18).

The deficits in HF are not limited to cognitive performance and physical health, but extend into the realm of psychological well-being. As many as 42% of HF patients may have clinically meaningful levels of depression and depressive symptomatology increases as a function of HF severity (19,20). In addition to being associated with more frequent hospitalizations and cardiac events (20,21), depression is also a risk factor for cognitive impairment in patients with HF (22,23,24).

Despite evidence linking depression with cognitive dysfunction in patients with HF, modifiers of this relationship are unclear. Because cardiac dysfunction and vascular comorbidities accompany HF, it is plausible that reduced cerebral perfusion may exacerbate the diverse emotional and cognitive problems noted in persons with HF. Indeed, cerebral hypoperfusion is common in HF and has been proposed to influence cognitive impairment (25,26) and contribute to the development of depression in (27) HF populations. For instance, HF patients with Major Depressive Disorder (MDD) exhibit significant reductions in cerebral blood flow relative to both non-depressed HF patients and healthy controls (24). Other studies have demonstrated a link between depression and reduced cerebral perfusion independent of HF (28). Despite these findings, no study to date has examined whether reduced cerebral blood flow moderates the association between depression and cognitive function in older adults with HF. The current study did so and expected that reduced cerebral blood flow would exacerbate the adverse effects of depression on cognitive function in HF.

Methods

Participants

A sample of 89 consecutive persons with either systolic or diastolic HF were recruited from a large research study of neurocognitive impact of HF. Participants were members of Summa Health System in Akron, Ohio, and reflect the heart failure population receiving treatment at that facility. Data collection for this study has been ongoing since January 2009. The inclusion criteria were between ages of 50–85 years, English as a primary language, and a diagnosis of New York Heart Association (NYHA) class II or III at the time of enrollment. Potential participants were excluded for history of significant neurological disorder (e.g. dementia, stroke), head injury with >10 minutes loss of consciousness, severe psychiatric disorder (e.g. schizophrenia, bipolar disorder), substance use, and renal failure. Participants averaged 67.61 (SD = 11.78 years of age, 27.0% were women, and 92.1% were white. See Table 1 for demographic and medical information. Of the sample, 79 (88.8%) were classified as NYHA class II and 10 (11.2%) as NYHA class III. There were no significant between group differences on the BDI-II or any of the cognitive function composites ($p > .05$ for all). However, those in NYHA class III exhibited greater reductions CBF-V than those in NYHA class II ($t(87) = 2.18, p = .03$; $M (SD) = 106.22 (25.37)$ vs. $87.56 (27.15)$).

Measures

Depressive Symptomatology—Depression was assessed using the Beck Depression Inventory-II (BDI-II), a commonly used check-list of depressive symptoms that demonstrates good psychometric properties in persons with medical conditions (i.e., test-retest reliability of $r = .93$ to $r = .96$, and an internal consistency of $r = .94$) (29,30). The internal consistency of the BDI-II in the current sample is Cronbach's alpha = .93. The BDI-II is composed of affective and somatic subscales. The affective subscale consists of eight items that assesses pessimism, past failures, guilty feelings, punishment feelings, self-dislike, self-criticalness, suicidal thoughts, and worthlessness. The somatic subscale is comprised of thirteen items, including sadness, anhedonia, crying, agitation, loss of pleasure, indecisiveness, energy loss, sleep disturbances, irritability, appetite changes, concentration difficulties, fatigue, and loss of interest in sex. BDI-II total score is the summary composite of the affective and somatic subscales and scores range from 0–63. Higher scores are indicative of greater symptomatology.

Cerebral Blood Flow—Transcranial doppler (TCD) ultrasonography was employed to assess cerebral blood flow velocity (CBF-V), under an expanded STOP protocol (32). The protocol assesses blood flow velocity in the major brain arteries, including the Middle Cerebral Artery (MCA), and the Anterior Cerebral Artery (ACA), Posterior Cerebellar Artery (PCA), Intracranial Vertebral Arteries (IVA), Basilar Artery (BA), Terminal Internal Carotid Artery (TICA), Intracranial Internal Carotid Artery (ICA), and Ophthalmic Artery (OA). For each artery, the measurements provide several indices including mean flow velocity. For the current study, a global cerebral blood flow velocity (CBF-V) summary composite of the mean flow velocity of the ACA, MCA, and PCA was computed to represent the index of global cerebral perfusion.

Neuropsychological Measures—All neuropsychological tests used in the current study demonstrate strong psychometric properties including excellent reliability and discriminant and construct validity. The domains and neuropsychological tests administered are as follows:

Global Cognitive Function: The Modified Mini Mental State Examination (3MS) (32) was used to estimate global cognitive function. The 3MS is a brief cognitive screening

measure that taps into several cognitive domains, including attention, memory, language, and spatial abilities. Lower score on the 3MS reflects worse performance.

Attention and executive function: A series of measures were administered to assess attention/executive function, including the Trail Making Test A (33), Digit Symbol Coding (34), Trail Making Test B (35), Letter Number Sequencing (LNS) (36), and the Frontal Assessment Battery (FAB) (37). Within the current sample, performances on these tests were all significantly correlated ($r(87) = 0.35$ to $r(87) = 0.53$). Performances on these tests represent a range of attention/executive function abilities. Specifically, Trail Making Test A asks participants to connect a series of numbers as quickly as possible in sequential order. Completion time of this task is a reliable measure of visual scanning and psychomotor speed with longer time indicative of worse performance. Similarly, Trail Making Test B requires participants to alternately connect a series of letters and numbers in sequential order and poorer completion time of this task is indicative of reduced cognitive flexibility. Digit Symbol Coding is a reliable and valid measure of visuomotor speed and complex attention and this task asks individuals to identify shapes that correspond to numbers as quickly as possible; total number correct served as the dependent variable in the current study. Letter Number Sequencing is a measure of working memory that has participants verbally order numbers and letters that are presented in an unordered sequence. Fewer correct on this task represents decreased performance. Lastly, the FAB consists of six subtests that assess frontal lobe functioning, including abstract reasoning, inhibitory control, sensitivity to interference, higher ordered motor programming, and lexical fluency. Scores on this test range from 0–18 with lower scores representing poorer frontal systems functioning.

Memory: The California Verbal Learning Test-II (CVLT-II) short delay free recall, long delay free recall, and total hit indices were used to assess memory in this sample (38). Correlations among these indices were not performed given that they were all derived from the CVLT-II. The CVLT-II asks individuals to learn, recall, and recognize a 16-item word list. Total number correct for each index was used as the dependent variable.

Language: The Boston Naming Test (BNT) (39) and Animal Fluency (40) assessed language abilities in the current sample. Performances on the BNT and Animal Fluency demonstrated a significant correlation ($r(87) = 0.34$). The BNT has individuals name pictured objects ranging from high to low familiarity with fewer number correct reflective of worse language abilities. Animal fluency has individuals generate as many animal names as possible within a one-minute period and fewer number of animals named reflects reduced performance.

Motor Speed and Dexterity: Grooved Pegboard of the dominant and non-dominant hand (35,41,42) examined motor speed and dexterity. Correlations were also not necessary for this domain as performance indices were derived from the same test. The Grooved Pegboard has individuals orient grooved shaped pegs to fit into a series of holes with corresponding grooves as quickly as possible. Worse completion time reflects poorer motor speed and dexterity.

Demographic and Medical History—Demographic characteristics and medical history were collected through a review of the medical charts and self-report. Participants also completed brief self-report measures assessing history of HF risk factors, e.g., past history of cigarette smoking (Table 1).

HF Severity—Cardiac Output (CO) from a seated resting baseline was calculated for each patient to estimate preservation of cardiac function. Impedance cardiography signals were

recorded via a Hutcheson Impedance Cardiograph (Model HIC-3000, Bio-Impedance Technology, Chapel Hill, NC) using a tetrapolar band-electrode configuration. The electrocardiogram (ECG) was recorded from the Hutcheson Impedance Cardiograph using disposable ECG electrodes. The basal thoracic impedance (Z_0), the first derivative of the pulsatile impedance (dZ/dt), and the ECG waveforms were processed using specialized ensemble-averaging software (COP, BIT Inc., Chapel Hill, NC), which was used to derive stroke volume using the Kubicek equation (43,44). Following instrumentation, Impedance cardiographic signals were recorded for seven 40-second periods during a 10-minute resting baseline. Finally, all CO measurements were divided by body surface area (BSA), yielding cardiac index. In HF patients, cardiac index as quantified by impedance cardiography has been shown to be a reliable assessment of cardiac function and to correlate with cardiac indices obtained from echocardiography (e.g., ejection fraction; $r = .85$) (45).

Cardiovascular Endurance—The 2-minute step test (2MST) was also used to assess HF severity and further characterize the sample. The 2-minute step test is an assessment of cardiovascular endurance (46). The 2MST has been suggested to be an alternative to the 6-minute walk test, which has been linked with functional work capacity, maximal oxygen uptake, and poor prognosis in patients with HF (47,48). Past work has also shown that the 2MST is linked with poorer cognitive function among older adults with heart failure (49). The 2MST requires the patient to march in place for 2 minutes. The patient is asked to bring each knee up to a marked target set on the wall at the individual's own midpoint between the kneecap and crest of the iliac. The number of times the right knee met the marked target was counted. Increased step count within the 2-minutes was reflective of greater cardiovascular fitness. Average step count for women between the ages of 50–85 ranges from 71–115, while men for this age group range from 60–107 (46).

Procedures

The Institutional Review board (IRB) at Kent State University approved the study procedures and all participants provided written informed consent prior to study enrollment. Participants completed demographic, medical and psychosocial self-report measures, including the BDI-II. Individuals then completed impedance cardiography conducted by a trained research assistant followed by the administration of a brief neuropsychological test battery that was administered to all HF participants to assess cognitive functioning described above. Lastly, to quantify cerebral perfusion all participants underwent transcranial doppler upon enrollment that was conducted by a hospital-based technician.

Statistical Analyses

To facilitate clinical interpretation and to maintain directionality within scales, all raw scores of the neuropsychological measures assessing cognitive function were transformed to T-scores (a distribution with a mean of 50, and a standard deviation of 10) using existing normative data correcting for age (as well as gender, in the case of memory tasks). Composite scores for attention/executive function, memory, language, and motor function were means of the T-scores within each cognitive domain. The 3MS was used to characterize global cognitive status in the current sample (31) using normative data (50).

Initial partial correlation analysis adjusting for age, sex, cardiac index, 2MST, and history of diabetes and hypertension was conducted to examine the relationship between the BDI-II and CBF-V. Separate moderation analyses using a multiple linear hierarchical regression model were then performed for each cognitive domain. All continuous predictors were transformed to z-scores, gender was recoded as 1 for men and 0 for women, and medical history was recoded as 1 for a positive and 0 for negative history. For all analyses, demographic and medical variables including gender, education, cardiac index, 2MST, and

history of diabetes and hypertension were entered into the first block of the model. Age was not included as a covariate because all cognitive measures were adjusted for age using normative data. The BDI-II was entered into the second block of the model and global CBF-V entered in the third block. Finally, the cross product of the BDI-II and global CBF-V was entered into the final block of the model to determine incremental predictive validity of the interaction term.

Past work shows that affective and somatic symptoms of depression increase risk for cardiac events (51,52) and we sought to clarify the possible effects of affective and somatic depression on cognitive function. Specifically, follow-up partial correlation analyses controlling for the above medical and demographic factors examined the association between affective and somatic subscales from the BDI-II with each domain of cognitive function and CBF-V.

Results

Sample Characteristics

The current sample demonstrated a mean cardiac index ($M = 2.74$, $SD = 1.05$) that fell within normal rates of cardiac function. Compared to healthy individuals, other measures of cardiac function (e.g., stroke volume, cardiac output) also fell broadly within the normative range. In contrast, relative to healthy individuals of similar age and gender, men and women in the current sample exhibited low average and below average levels of cardiovascular endurance, respectively. Many participants also had a combination of comorbid medical and clinical conditions. Refer to Table 1 for clinical characteristics in the current sample.

Reported depressive symptomatology was prevalent in the current sample, as participants averaged 7.16 ± 8.32 on the BDI-II. On the basis of established BDI-II cut off scores (29), 75 (84.3%) of the participants exhibited minimal depressive symptomatology, 6 (6.7%) mild symptoms, 3 (3.4%) moderate symptoms, and 5 (5.6%) participants reported severe depressive symptomatology. There were no significant between BDI-II severity group differences for age ($t(87) = -1.46$, $p = .077$), education ($t(87) = -.77$, $p = .45$), 2MST ($t(87) = -.53$, $p = .60$), cardiac index ($t(87) = -.05$, $p = .96$), or history of hypertension ($\chi^2(1, N = 87) = 2.53$, $p = .11$), or diabetes ($\chi^2(1, N = 87) = .14$, $p = .71$). However, women reported greater depressive symptomatology than men ($\chi^2(1, N = 87) = 4.48$, $p = .034$; Mean (SD) = 10.50 (10.90) vs. 5.94 (6.63).

Depressive Symptomatology and CBF-V

Unadjusted bivariate correlations showed that increased scores on the BDI-II were associated with decreased CBF-V of the MCA ($r(88) = -.21$, $p = .049$). This pattern did not emerge for global CBF-V ($r(88) = -.12$, $p = .25$) or for CBF-V of the PCA ($r(88) = -.07$, $p = .55$) or ACA ($r(88) = -.03$, $p = .79$). In adjusted partial correlation analysis accounting for medical and demographic variables there was a trend for increased depressive symptomatology with decreased global CBF-V ($r(81) = -.19$, $p = .095$) and a significant association was noted for reduced CBF-V of the MCA ($r(81) = -.27$, $p = .013$). Cardiac index exhibited a significant association with CBF-V of the MCA ($r(88) = .22$, $p = .040$). Marginal significance emerged between cardiac index and the ACA ($r(88) = .21$, $p = .052$) and global CBF-V ($r(88) = .20$, $p = .058$).

Cognitive Function

When compared to healthy elderly of similar age and education, the current sample exhibited slightly reduced global cognitive status with a mean 3MS score of 93.80 ($SD = 4.65$). However, relative to normative data, many participants in this sample demonstrated

impaired performances on the 3MS. Specifically, 18.0% had a 3MS score less than 90, 38.2% had a 3MS score between 90 and 95, and 43.68% had a 3MS score greater than 95. See Table 2 for a summary of cognitive test performance in the current sample. Unadjusted correlations between CBF-V, cardiac function, and BDI-II with domains of cognitive function are also presented in Table 3.

Depressive Symptomatology and Cerebral Perfusion are Associated with Cognitive Function

Demographic and medical predictors of cognitive function were significantly associated with attention/executive function ($F(6, 82) = 2.62, R^2 = .16, p = .023$), language ($F(6, 82) = 3.38, R^2 = .20, p = .005$), and motor functioning ($F(6, 82) = 4.19, R^2 = .24, p = .001$). No such pattern emerged for memory ($F(6, 82) = 1.49, R^2 = .10, p = .19$). After controlling for sex, education, cardiac index, 2MST, and history of diabetes and hypertension, increased scores on the BDI-II was associated with poorer performance on tests of attention/executive function ($\beta = -.26, R^2 = .06, p = .016$), language ($\beta = -.26, R^2 = .06, p = .011$), and motor functioning ($\beta = -.34, R^2 = .11, p = .001$). There was no such pattern for memory ($\beta = -.03, R^2 = .00, p = .77$).

Decreased global CBF-V was also significantly associated with worse functioning in the domains of attention/executive function ($\beta = .21, R^2 = .04, p = .039$) and memory ($\beta = .25, R^2 = .06, p = .023$) even after controlling for medical and demographic characteristics and the BDI-II. Global CBF-V was not associated with language ($\beta = -.02, R^2 = .00, p = .87$) or motor functioning ($\beta = .08, R^2 = .01, p = .40$). See Table 4 for a summary of hierarchical regression analyses for blocks 1–3. Follow up partial correlation analyses adjusting for medical and demographic analyses showed that both affective and somatic subscales of the BDI-II were inversely associated with attention/executive function, language, motor function ($p < .05$ for all), but not CBF-V ($p > .05$).

Interaction between Depressive Symptomatology and Global CBF-V

The interaction between the BDI-II and global CBF-V demonstrated incremental predictive validity above and beyond medical and demographic factors, the BDI-II, and global CBF-V for attention/executive function ($\beta = .32, R^2 = .08, p = .003$). The interaction between greater depressive symptomatology and decreased global CBF-V was associated with greater deficits in this cognitive domain. Figure 1 demonstrates the significant interaction between the BDI-II and global CBF-V. The interaction term did not demonstrate significant associations with memory ($\beta = .11, R^2 = .01, p = .34$), motor function ($\beta = .17, R^2 = .02, p = .10$), or language ($\beta = .00, R^2 = .00, p = .98$).

Discussion

Consistent with past work, reported depressive symptomatology was prevalent and associated with reduced cognitive function in the current sample of HF patients. This study extends existing knowledge by showing that cerebral hypoperfusion—a commonly theorized contributor to cognitive dysfunction in HF—interacts with depressive symptomatology to exacerbate cognitive impairment in this population (24,25).

The current results suggest that greater depressive symptomatology interacts with cerebral hypoperfusion to exacerbate impairments in attention and executive function in persons with HF. It is also noted that among persons with high levels of cerebral blood flow velocity, the presence of depression symptoms alone were not sufficient to produce cognitive deficits (see Figure 1). Indeed, Figure 1 does not suggest that depression is protective against cognitive impairment in HF, rather in the presence of cerebral hypoperfusion, the adverse effects of

depressive symptomatology on cognitive function in HF are exacerbated. Reduced cerebral perfusion is well documented within HF patients and has been linked with cognitive impairment and depressive symptomatology within this population (24–27,53). Interestingly, past work shows HF patients with MDD symptoms exhibit greater deficits in cerebral blood flow than HF patients without MDD (24). These findings are noteworthy, as they suggest that HF patients with depression may be at greater risk for white matter hyperintensities (WMH). WMH refer to bright areas on magnetic resonance imaging of the brain that represent lesions in white matter regions (54). They are ischemic in nature and are believed to develop secondary to cerebral hypoperfusion and subsequent reductions in brain oxygenation (55,56). Indeed, reductions in cerebral perfusion has been linked to WMH in this population (57,58), and among persons with MDD but without HF (59). This pattern is concerning, as WMH have been shown to contribute to both cognitive impairment and greater depression in HF patients (15, 59). In-turn, the etiology of cognitive impairment and depression in HF patients may stem from cerebral hypoperfusion and subsequent WMH (60–62).

Depression in HF may also produce deficits in cognitive function through behavioral changes. For example, past work has shown otherwise healthy individuals with depression to exhibit deficits in attention and executive and motor function (63,64). These cognitive deficits among depressed individuals have been attributed to difficulties maintaining optimal effort, motivation, and potentially response bias (i.e., negative feedback within standardized testing) (65,66). Thus, the behavioral manifestations of depression and cerebral hypoperfusion associated with HF may interact to exacerbate cognitive impairment in cardiac populations. Moreover, it is also possible that both depression and cognitive dysfunction in HF are manifestations of physiological processes common in this population such as cerebral hypoperfusion, inflammation (67), reduced physical activity (68), or extensive medical comorbidities (18). Prospective studies are needed to validate our findings and to further elucidate underlying mechanisms associated with depression and cognitive impairment in HF.

The present findings corroborates past work demonstrating the inverse association between depressive symptomatology and cognitive function in HF (22,24). We also observed that both somatic and affective symptoms of depression were linked with reduced cognitive test performance. Past work shows that affective/somatic symptoms predict increased cardiac events (51,52), thus these symptoms may increase risk for poorer neurocognitive outcomes in HF through their association with heightened risk for vascular injury. Our findings may also have important implications regarding performance of key self-care behaviors. For instance, although cognitive impairment was generally mild in the current sample, reduced cognitive function among HF patients is associated with decreased ability to perform instrumental activities of daily living (i.e., medication management) (69) and is also associated with increased risk of mortality (17). Not surprisingly, depressive symptomatology among HF patients poses with additional risks, including poorer compliance to treatment recommendations and elevated risk for rehospitalization (70,71). Given the adverse outcomes associated with decreased treatment adherence (i.e., increased risk of mortality) (9) and the high prevalence of depression in this population, future work is needed to identify interventions targeting depressive symptomatology in HF, particularly as it relates to cognitive function.

Several limitations of the current study deserve mention. First, the current study is cross sectional, thus the directionality of the current findings remain unclear. While we argue that depressive symptomatology precedes cognitive impairment secondary to HF, it is possible that cognitive impairment may also enhance depression in this population. Similarly, greater depressive symptoms were associated with reduced cerebral blood flow indices and both

were linked to cognitive function. Thus, while the cross-sectional design of the current study precluded mediation analyses, future studies should examine whether cerebral hypoperfusion may mediate the link between depression and cognitive function in HF through the adverse effects of depression on factors that influence cerebral blood flow in HF (e.g., physical activity) (49,64,72,73). Case-controlled longitudinal studies among larger HF samples that use multiple neuroimaging indicators of disease severity (e.g., positron emission tomography (PET), arterial spin labeling (ASL)) would help clarify the exact role of cerebral perfusion in the association between depression and cognitive function in HF. Such studies should also explore whether varying HF etiologies influence the interaction between depressive symptomatology, perfusion, and cognition.

Moreover, the current study did not examine direct neuropathological changes associated with depression and cerebral perfusion. Future studies examining neuroimaging among depressed and non-depressed HF patients and healthy controls would provide key insight into the mechanisms of cognitive impairment in depressed HF patients, including whether cognitive impairment and depression are both manifestations of altered cerebral hemodynamics. Additionally, depressive symptomatology was assessed using a brief self-report instrument. Although the BDI-II is a well-validated measure (29,30), studies that administer structured assessments of psychopathology in the context of the aims of the current study would help validate our findings. Additionally, the current study operationalized cerebral blood flow using TCD. TCD is practical and noninvasive, reliably reflects changes in cerebral blood flow (74), and has been shown to demonstrate concordance validity with more direct measures of cerebral perfusion (e.g., ASL; 75). Despite these strengths, TCD assumes blood flow velocity is directly proportional to cerebral blood flow and that the area of the insonated arteries remains constant (76). In light of the prevalence of atherosclerosis and other conditions that negatively affect arterial diameter in cardiovascular disease populations, the validity of TCD may become compromised in this population. Future studies should directly assess cerebral blood flow (e.g., ASL or PET) to elucidate the relationship between cerebral perfusion and cognitive function in HF. Finally, impedance cardiography was used to assess cardiac function and describe disease severity of the current sample. While this is a valid, inexpensive, and non-invasive approach to quantify cardiac output, it should be noted that many confounding variables (e.g., hypertension, pleural effusion, sepsis) can compromise the quantitative accuracy of this technique (73). Indeed, future studies should use echocardiogram to examine the association among indices of cardiac function (e.g., ejection fraction, systolic and diastolic function) and other commonly used measures of HF severity with cognition, perfusion, and depression in HF patients.

In summary, the findings from the current study suggest that greater depressive symptomatology and cerebral hypoperfusion interact to exacerbate cognitive impairment in older adults with HF, particularly in attention and executive function. Future studies are needed to clarify the directionality of this relationship and elucidate the neuropathological effects produced by depression and cerebral hypoperfusion in HF.

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Acronyms

HF Heart Failure

CBF-V Cerebral blood flow velocity

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Figure 1.

Interaction Effect Between Depressive Symptomatology and Global Cerebral Perfusion on Attention/Executive Function. Lines reflect model specifics and not actual data. Higher scores on the x-axis are reflective of greater depressive symptomatology and higher scores on the y-axis represent better test performance. Cerebral blood flow velocity values are z-scores (distribution with a mean of 0 and a SD of 1) and high cerebral blood flow velocity is indicative of scores 1 SD above the mean and low cerebral blood flow velocity is reflective of scores 1 SD below the mean. Beck Depression Inventory-II scores on the x-axis are also within sample z-scores.

Table 1

Demographic and Clinical Characteristics of 89 Older Adults with Heart Failure.

Demographic Characteristics	
<i>N</i>	89
Age, mean years (SD)	67.61 (11.78)
Women, n (% women)	24 (27.0)
Race, white, n (%)	82 (92.1)
Education, mean (SD), y	13.45 (2.77)
Medical Characteristics	
Cardiac Index (L/min), mean (SD)	2.74 (1.05)
Cardiac Output (L/min), mean (SD)	5.57 (2.19)
Stroke Volume (mL), mean (SD)	85.48 (27.38)
NYHA Class II, N (%)	79 (88.8)
NYHA Class III, N (%)	10 (11.2)
Hypertension, N (%)	60 (67.4)
Diabetes, N (%)	28 (31.5)
Myocardial Infarction, N (%)	53 (59.6)
Sleep Apnea, N (%)	16 (18.0)
Total Elevated Cholesterol, N (%)	58 (65.2)
Past Smoking History, N (% yes)	60 (67.4)
MCA (cm/s), mean (SD)	40.80 (11.35)
ACA (cm/s), mean (SD)	35.29 (10.83)
PCA (cm/s), mean (SD)	28.03 (8.27)
Global CBF-V (cm/s), mean (SD)	104.12 (26.10)
Clinical Characteristics	
BDI-II, mean (SD)	7.16 (8.32)
2MST Overall Sample, mean (SD)	62.60 (24.34)
2MST Women, mean (SD)	61.46 (19.68)
2MST Men, mean (SD)	63.02 (25.98)

NYHA = New York Heart Association; BDI-II = Beck Depression Inventory-II; ACA = Cerebral Blood Flow Velocity in the Anterior Carotoid Artery; MCA = Cerebral Blood Flow Velocity in the Middle Cerebral Artery; PCA = Cerebral Blood Flow Velocity in the Posterior Cerebellar Artery; CBF-V = Cerebral Blood Flow Velocity; 2MST = 2-Minute Step Test

Table 2Descriptive Statistics of Cognitive Test Performance ($N = 89$)

	Raw Test Performance, mean (SD)	T-score, mean (SD)
<i>Global Cognitive Function</i>		
3MS	93.80 (4.65)	--
<i>Attention/executive Function</i>		
TMTA (seconds)	38.56 (14.23)	51.88 (8.90)
Digit Symbol Coding	51.36 (15.26)	49.02 (9.12)
TMTB (seconds)	116.04 (71.43)	46.59 (16.40)
LNS	9.20 (2.79)	52.26 (9.45)
FAB	16.01 (2.36)	44.08 (22.39)
<i>Memory</i>		
CVLT SDFR	7.48 (3.67)	47.70 (11.10)
CVLT LDFR	8.09 (3.82)	47.87 (10.97)
CVLT Recognition	13.44 (2.47)	44.89 (12.25)
<i>Language</i>		
Boston Naming Test	55.08 (3.85)	52.80 (9.27)
Animals	19.94 (5.14)	55.86 (11.61)
<i>Motor Functioning</i>		
Pegboard Dominant Hand (seconds)	102.38 (31.13)	36.29 (21.45)
Pegboard Non-dominant Hand (seconds)	107.34 (28.66)	39.62 (15.97)

3MS = Modified Mini Mental State Examination; TMTA = Trail Making Test A; TMTB = Trail Making Test B; LNS = Letter Number Sequencing; FAB = Frontal Assessment Battery; CVLT = California Verbal Learning Test; SDFR = Short Delay Free Recall; LDFR = Long Delay Free Recall

Table 3
Unadjusted Bivariate Correlation Matrix of CBF-V, Cardiac Function, BDI-II with the Cognitive Domains

	Medical Variables					
	Global CBF-V	MCA	ACA	PCA	BDI-II	CI
<i>Cognitive Domain</i>						
Global Cognition	.19	.17	.16	.14	-.03	-.05
Attention/Exec.	.23 *	.20	.18	.20	-.28 *	-.03
Memory	.22 *	.18	.18	.20	.00	-.12
Language	.04	.05	.00	.05	-.30 *	-.02
Motor	.12	.12	.10	.10	-.28 *	-.04

Note.

* $p < .05$;

Attention/Exec = Attention/Executive Function; CBF-V = Cerebral Blood Flow Velocity; ACA = Cerebral Blood Flow Velocity in the Anterior Carotid Artery; MCA = Cerebral Blood Flow Velocity in the Middle Cerebral Artery; PCA = Cerebral Blood Flow Velocity in the Posterior Cerebellar Artery; BDI-II = Beck Depression Inventory-II; CI = Cardiac Index; Global cognition was assessed using the Modified Mini Mental State Examination (3MS)

A Summary of Hierarchical Regressions Examining Predictors of Cognitive Function among Older Adults with Heart Failure ($N = 89$)

Table 4

Variable	Attention/Executive Function <i>b</i> (<i>SE b</i>)	Memory <i>b</i> (<i>SE b</i>)	Language <i>b</i> (<i>SE b</i>)	Motor <i>b</i> (<i>SE b</i>)
<i>Block 1</i>				
Gender	−2.32(2.30)	−3.29(2.32)	−1.09(.81)	−4.91(3.96)
Education	2.03(1.03)*	2.01(1.04)*	2.72(.85)**	.50(1.78)
Diabetes	−.82(2.29)	2.12(2.31)	.74(1.89)	−2.88(3.93)
Hypertension	−2.76(2.25)	2.63(2.27)	−.92(1.86)	−7.72(3.87)*
2MST	2.23(1.11)*	.58(1.12)	1.99(.92)*	6.32(1.91)**
CI	−.36(.98)	−.98(.99)	−.09(.81)	−1.25(1.69)
R^2	.16	.10	.20	.24
F	2.62*	1.49	3.38**	4.19**
<i>Block 2</i>				
BDI-II	−2.34(.95)*	−.30(1.00)	−2.03(.79)*	−5.68(1.58)**
R^2	.22	.10	.26	.34
F for R^2	6.03*	.09	6.71*	12.99**
<i>Block 3</i>				
CBF-V	2.16(1.03)*	2.49(1.07)*	−.14(.87)	1.48(1.75)
R^2	.19	.16	.26	.35
F for R^2	4.39*	5.37*	.03	.72
<i>Block 4</i>				
BDI-II X CBF-V	3.23(1.04)**	1.11(1.14)	−.02(.93)	3.04(1.83)
R^2	.27	.10	.26	.37
F for R^2	9.66**	.93	.00	2.77

Note.

* $p < .05$;

p<.01

Abbreviations: b – unstandardized regression coefficients, SE – standard error, CI = Cardiac index; BDI-II = Beck Depression Inventory-II; CBF-V = Cerebral Blood Flow Velocity