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Congestive heart failure and its associations with cognition and cerebral blood flow

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Abstract:

BACKGROUND: Congestive heart failure (CHF) has been linked to dementia but for reasons not well understood. Our retrospective cohort study aims to determine if specific measures of CHF severity are associated with cognitive performance or cerebral blood flow velocity (CBFV) among decompensated CHF outpatients.

MATERIALS AND METHODS: One hundred and thirty-eight patients with transthoracic echocardiogram ≤1-year preceding consent were included. Forty-nine patients had concurrent transcranial Doppler ultrasonography administered by a trained technician assessing anterior cerebral artery, middle cerebral artery, and internal carotid artery (ICA) CBFV. CHF characteristics considered were NYHA classification, CHF type (heart failure with preserved ejection fraction vs. heart failure with mildly reduced/reduced ejection fraction), and left ventricular ejection fraction (LVEF; continuous [per 5%] or categorized [≤40%, 40%–55%, and ≥55%]). A trained psychometrist administered a standardized cognitive battery including Rey Auditory Verbal Learning Test, Rey Complex Figure Copy and Immediate Recall test, Letter-Number Sequencing (LNS) test, and Trail Making Tests. Adjusted multivariable linear regression models determined the association between CHF characteristics and standardized cognitive tests as well as between CHF characteristics and standardized CBFV, in distinct models.

RESULTS: On average, NYHA Class 1–2 patients had better LNS scores than NYHA Class 3–4 patients (β: 0.47; 95% CI: 0.09, 0.84). Patients with LVEF 40%–55% had higher ICA CBFVs than those with LVEF ≤40% (β: 13.7; 95% CI: 1.01, 26.39). No associations between other CHF characteristics and either cognitive performance or CBFV were found.

CONCLUSION: Blood flow may be an important mechanism behind CHF-related cognitive decline, but studies with larger sample sizes and a control group without CHF are needed.

Keywords:

Cardiovascular disease, cerebral blood flow velocity, cognition, cognitive performance, heart failure

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Introduction

Cognitive impairment commonly co-occurs with heart failure, with up to 74% of patients with heart failure having mild cognitive impairment.[1] Cognitive impairment impacts patients' ability to manage their conditions and provide self-care: in a study of ninety-three patients with congestive heart failure (CHF), patients with mild cognitive impairment had lower self-care management and self-confidence.[2] Cognitive impairment among CHF patients has also been found to increase patient mortality and hospital readmission rates.[3] The severity of heart failure has been suggested to be associated with the severity of cognitive dysfunction; however, other work has not suggested that specific characteristics of the heart failure state contribute to cognition.[3-7] These conflicting results may be due to

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differing study designs and study-specific limitations, which include using a dementia screener as a measure of cognitive function and not including comorbidities that affect cognition in analyses.[3-7] Thus, clarification is still needed as to which characteristics, if any, of heart failure may have an impact on which cognitive domains.

There are several hypothesized methods by which CHF might impact cognition, including the induction of a systemic inflammatory state, silent infarction, and hypoperfusion.[8,9] In particular, hypoperfusion due to decreased cerebral blood flow is widely considered to be a principal mechanism, as the brain is highly sensitive to oxygen deprivation. Nuclear, magnetic resonance, or sonographic imaging methods have been used to measure cerebral blood flow velocity (CBFV), which is widely used as a surrogate measure of cerebral blood flow.[10,11] Transcranial Doppler (TCD) ultrasonography offers a low risk, cost-effective, and information-rich alternative method to evaluate CBFV, with a sensitivity of 93%–96% when compared to magnetic resonance imaging (MRI).[12-16] Overall, the association between CBFV and characteristics of the heart failure has not been well studied but could be clinically meaningful when considering potential therapy options.

The objective of this study, therefore, is to determine if characteristics of heart failure are associated with cognitive performance among a tertiary care, outpatient cohort of patients with decompensated CHF undergoing diuretic therapy, controlling for vascular risk factors. In addition, we aim to determine if characteristics of heart failure are associated with decreased CBFV as assessed by TCD. We hypothesize that patients with markers of more severe heart failure will have worse cognitive performance compared to those with less severe heart failure characteristics. We also hypothesize that heart failure characteristics that reflect worse disease will also be associated with decreased CBFV.

Materials and Methods

Study design

This study was a prospective cohort study. No clinical trials were involved.

Study population

This prospective cohort study took place from August 2013 to June 2019 at a single medical institution. At this institution, heart failure patients frequently present at its diuresis clinic, which provides outpatient IV diuretics to treat CHF. Inclusion criteria for this study included patients older than 18 years old being treated at the diuresis clinic with an admitting diagnosis of heart failure.

Patients were not eligible for enrollment if they were pregnant at the time of therapy and had any of the following laboratory abnormalities: creatinine >2.5 mg/dL; potassium <3.0 mEq/L or >5.5 mEq/L; sodium <128 mEq/L; or had any of the following vital signs: temperature >101°F; systolic blood pressure <90 mmHg or >180 mmHg; diastolic blood pressure <50 mmHg or >100 mmHg; heart rate <50 beats/min or >120 beats/min. Additional exclusion criteria for this study included an EKG with new ST changes, new left bundle branch block, new-onset atrial fibrillation/flutter, or rapid ventricular response; active chest pain; pro-brain natriuretic peptide <200 pg/mL; presence of rales more than halfway up lung fields; presence of urinary obstruction; oxygen saturation <90% on room air (or home oxygen); history of dementia; non-English speaking; a transthoracic echocardiogram (TTE) outside a 1-year window of their neurocognitive assessment; and missingness of any heart failure characteristics and covariates used for the study [Figure 1]. Exclusion criteria for analysis of CBFV measures also included a lack of at least one CBFV recording for each cerebral artery.

The research team approached eligible patients about the study. If interested, consent was obtained, and basic demographic information was collected prior to performing cognitive testing procedures.

Characteristics of heart failure (independent variable)

Heart failure characteristics considered in this study were NYHA Functional Classification, left ventricular ejection fraction (LVEF, continuous and categorized), and heart failure with preserved ejection fraction (HFpEF) vs. heart failure with reduced ejection fraction (HFrEF) or heart failure with mildly reduced ejection fraction (HFmrEF). Left atrial diameter was considered in a secondary analysis, as left atrial diameter may contribute to cognitive function and enlarged left atrial diameter has been associated with both clinical and subclinical infarction as well as cognitive decline.[17,18] Characteristics were collected from medical records and TTEs performed at maximum 1 year before their neurocognitive assessment.

Stage of heart failure was classified according to the NYHA Functional Classification system at the time of the visit to the diuresis clinic by a heart failure nurse who saw and evaluated all patients throughout the study duration. This system groups CHF patients into one of four classes based on their symptoms at rest and during physical activity.[19] NYHA Functional Classification was grouped as NYHA Class 1–2 (less severe heart failure) and NYHA Class 3–4 (more severe heart failure) for all analyses in this study.

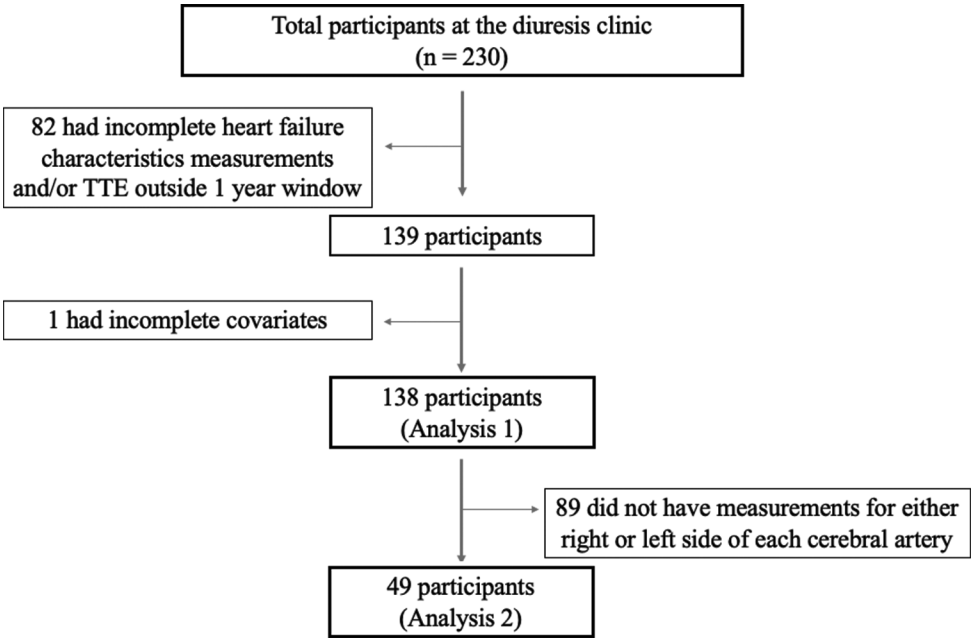

Figure 1: Flow diagram of study participants demonstrating reasons for study exclusion. TTE = Transthoracic Echocardiogram

TTE was performed, as clinically indicated, prior to the time of cognitive testing. The sequential segmental approach was used to observe anatomical and hemodynamic abnormalities. Standard views were used, which included parasternal long-axis and short-axis views of the ventricles, parasternal view of the right ventricular inflow tract, and apical four-chamber views. All TTEs were performed by accredited technicians and read by echocardiography board certified cardiologists. Data from TTEs performed at no more than 1 year before their neurocognitive assessment were collected, and if multiple TTEs had been performed, the most recent TTE, but prior to the time of cognitive testing, was used.

LVEF was considered continuously (%) and categorically: (1) ≤40%, (2) 40%–55%, and (3) ≥55%. LVEF was also used to categorize patients into (1) those with HFpEF (LVEF ≥50%) and (2) those with HFrEF (LVEF ≤40%) or HFmrEF (LVEF 40%–50%) as per the standard American College of Cardiology and American Heart Association guidelines.[20]

Measures of cognition (dependent variable)

Patients underwent several standardized neurocognitive assessments as a part of a cognitive battery to determine overall cognition, executive functioning, memory, visuospatial perception, processing speed, attention, and, finally, current mood. The cognitive assessment battery was administered in-person in a quiet, adjacent outpatient clinic exam room by a trained psychometrist.

The cognitive measures assessed include (1) Rey Auditory Verbal Learning Test (RAVLT), which assesses learning and memory, determining immediate recall as well as delayed recall. The score on each trial is different per trial, but a higher raw score indicates better cognition; (2) Rey Complex Figure Test (RCF) Copy and Immediate Recall, which assess visuospatial perception, as well as visuospatial memory. Each one is scored 0–36, with higher numbers indicating better cognition; (3) Letter-Number Sequencing (LNS), which asks patients to repeat a group of letters and numbers with the numbers in order of increasing value, and the letters alphabetically. It assesses processing speed, and attention. It is scored 0–21, with a higher number indicating better cognition; and (4) Trail Making Tests A and B, which is a pair of tests administered to test motor speed/processing speed as well as executive functioning and attention. It is measured by time to complete the task in seconds, with higher numbers indicating worse cognition. During administration, the Trail Making A test was truncated at a maximum of 150 s and Trail Making B test at 240 s.

Cranial blood flow velocity (dependent variable)

TCD ultrasonography was performed according to standard practice by a trained ultrasound technician 1–2 h after the start of diuresis therapy and admission to the diuresis clinic.[21] The blood flow velocity of proximal anterior cerebral arteries (ACA), proximal middle cerebral arteries (MCA), and internal carotid arteries (ICA) were collected through the transtemporal acoustic window. Right and left recordings of each CBFV measurement were averaged to determine one value if both were available.

Covariates

Patient demographics and comorbidities were self-reported by patients and collected during the

clinic visit. The following covariates were collected from medical records and used in analysis to adjust for vascular health and vascular risk: age, sex, race, education (years), Charlson Comorbidity Index (CCI), and current smoking status.

CCI predicts the 10-year survival of adults with multiple comorbidities, including CHF, myocardial infarction, hypertension, peripheral vascular disease/bypass, cerebrovascular accident/transient ischemic attacks, hemiplegia, dementia/Alzheimer's, depression, pulmonary disease/asthma, diabetes mellitus, diabetes mellitus with end-organ damage, mild liver disease, severe liver disease, renal disease, gastric or peptic ulcer, rheumatic or connective tissue disease, skin ulcers/cellulitis, cancer (lymphoma, leukemia, and solid tumor), metastatic solid tumor, HIV/AIDS, and/or use of warfarin.[22]

Statistical analysis

Prior research found that patients with HFrEF had a significantly lower Montreal Cognitive Assessment Test score (mean 22, SD 2.31) compared to those with HFpEF (mean 24.8, SD 2.76).[12] Assuming a similar difference in our study and given our sample size of 138 patients with heart failure as well as a ratio of 1.42 of HFpEF vs. HFrEF/HFmrEF, we had >99.9% power to detect a difference in our study.

To determine the association between the scores for each cognitive test (dependent variable) and heart failure characteristic (independent variable), adjusted multivariable linear regression models were used. For each cognitive test, *z*-scores were derived using the study population's means and standard deviations to compare results across tests. *Z*-scores of the LNS, RAVLT immediate recall, and RAVLT delayed recall tests were summed to create a study-defined global cognitive score to assess the three main cognitive domains: processing speed, learning, and memory, respectively. These tests were chosen a priori as they assessed cognitive domains relevant in heart failure patients.[8,23] Adjustment Model 1 adjusted for participant age, sex, race (black vs. other), and education (years). Model 2 further adjusted for CCI and smoking status.

To determine the association between each CBFV measurement (dependent variable) and heart failure characteristics (independent variable), multivariable linear regression models were also used. The covariates used in the adjustment models were the same as that of the cognitive test models, except education, which was excluded in the CBFV models.

Heart failure characteristics considered in both models as independent variables were NYHA Functional Classification, LVEF (continuous and categorized), and HFpEF vs. HFrEF/HFmrEF status. Standard assumptions of linear regression were checked by looking at the Residual-Fitted plot for each model. Statistical significance was defined as $P \leq 0.05$. All statistical analyses were conducted using R Statistical Software (v4.3.1; R Core Team 2023). (2023-06-16) R version 12.[24]

Results

Cohort characteristics

One hundred and thirty-eight participants met inclusion criteria for this study, of whom 49 had all TCD measurements recorded. Our overall cohort was 49.3% female, 32.6% were of Black race, and median age was 65 years [Table 1]. The median time of TTE was 90 (25.75 8–205.5) days prior to the time of consent. The median (IQR) LVEF was 52.5% (36.3%–62.5%), and 82 (59%) participants had HFpEF [Table 1]. One (0.7%) had NYHA Class 1, 39 (28.1%) had NYHA Class 2, 93 (66.9%) had NYHA Class 3, and 6 (4.3%) had NYHA Class 4 [Table 1]. Of the 49 with available TCD measurements for all cerebral arteries of interest, the median (IQR) proximal MCA CBFV (cm/s) was 60.5 (49–66), proximal ACA was 52.5 (36.5–61), and ICA was 46.5 (40.5–55.5) [Table 1].

Heart failure characteristics and cognitive function

When considering NYHA classification as a measure of heart failure severity, we found that NYHA Class 1–2 patients had on average a better LNS score when compared to NYHA Class 3–4 patients, which remained significant after adjusting for covariates (β: 0.47; 95% CI: 0.09, 0.84). We did not find a significant association between NYHA and any other cognitive tests.

When considering heart failure severity in terms of LVEF, we did not find a significant association between percent increase in LVEF and performance on any of our cognitive measures, including our global cognitive score, composed of the LNS, RAVLT immediate recall, and RAVLT delayed recall tests (β: −0.004; 95% CI: −0.16, 0.15). This did not change when adding vascular comorbidities to our adjustment model (β: −0.03; 95% CI: −0.17, 0.11), or when we categorized LVEF. Specifically, there was no difference in the association between measures of memory, attention, processing speed or executive functioning when considering patients who had an LVEF of ≤40%, versus those between 40% and 55%, or ≥55% [Table 2].

When considering heart failure severity in terms of either reduced or preserved ejection fraction, there was again no evidence of a significant association between each specific cognitive test for patients with HFpEF (vs.

Table 1: Participant demographics (*N* = 138)

Characteristic	Continuous variables: median (IQR). Categorical variables: *N* (%)
Age (years)	65 (57.3–74)
Female sex	68 (49.3)
Nonhispanic black	45 (32.6)
Education (years)	12 (12–14)
Current smoker	19 (13.8)
Diabetes[a]	67 (48.6)
Hypertension	123 (89.1)
AF	69 (50)
Anticoagulation medication use	58 (42)
CCI[b]	5.5 (4–7)
LVEF (%)	52.5 (35.6–62.5)
HFpEF	81 (58.7)
HFmrEF	47 (34.1)
HFrEF	10 (7.2)
NYHA Class 1	1 (0.7)
NYHA Class 2	39 (28.1)
NYHA Class 3	92 (66.7)
NYHA Class 4	6 (4.3)
Left atrial diameter (cm)	4.6 (4.1–5.2)
Proximal middle cerebral artery velocity (cm/s)[c]	60.5 (49–66)
Proximal anterior cerebral artery velocity (cm/s)[c]	52.5 (36.5–61)
ICA velocity (cm/s)[c]	46.5 (40.5–55.5)

*Diabetes is defined as diagnosis of diabetes mellitus with or without end-organ damage. Hypertension is defined as diagnosis of hypertension, †CCI predicts the 10-year survival of adults with multiple comorbidities, including CHF, myocardial infarction, hypertension, peripheral vascular disease/bypass, cerebrovascular accident/transient ischemic attacks, hemiplegia, dementia/Alzheimer's, depression, pulmonary disease/asthma, diabetes mellitus, diabetes mellitus with end-organ damage, mild liver disease, severe liver disease, renal disease, gastric or peptic ulcer, rheumatic or connective tissue disease, skin ulcers/cellulitis, cancer (lymphoma, leukemia, and solid tumor), metastatic solid tumor, HIV/AIDS, and/or use of warfarin, ‡The blood flow velocity of proximal middle cerebral artery, proximal anterior cerebral artery, and ICA were collected through TCD ultrasonography. Right and left recordings of each cerebral artery measurement were averaged if both were available. Continuous variables show median (IQR); categorical variables show *n* (%) (*n*=138). NYHA: New York Heart Association, IQR: Interquartile range, LVEF: Left ventricular ejection fraction, CHF: Congestive heart failure, ICA: Internal carotid artery, TCD: Transcranial Doppler, HfrEF: Heart failure with reduced ejection fraction, HFpEF: Heart failure with preserved ejection fraction, HFmrEF: Heart failure with mildly reduced ejection fraction, CCI: Charlson Comorbidity Index, AF: Atrial fibrillation

HFrEF/HFmrEF), including the LNS (β: −0.01; 95% CI: −0.43, 0.4), with minimal change in effect estimate with adjustment (β: −0.01; 95% CI: −0.37, 0.35).

We also found no significant association between left atrial diameter and any measure of cognitive function [Supplementary Table 1].

Heart failure characteristics and cerebral blood flow velocities

Our mean ACA CBFV was 52.7 cm/s, MCA CBFV was 61.02 cm/s, and ICA CBFV was 53.2 cm/s. When considering LVEF as a measure of heart failure severity, we found that patients with an LVEF of 40%–55% had on average a higher ICA CBFV when compared to those with an LVEF ≤40% (β: 13.7; 95% CI: 1.01, 26.39). We did not find any significant associations between categorized LVEF and all other CBFVs [Table 3]. This did not change when adding vascular comorbidities to our adjustment model or when we considered LVEF as a continuous variable.

When considering heart failure severity in terms of either reduced or preserved ejection fraction, there was no evidence of significant association between any CBFV measure for patients with HFpEF (vs. HFrEF/HFmrEF), including ICA CBFV, even after adjustment for vascular comorbidities (β: 4.63; 95% CI: −6.11,15.37) [Table 3]. We also found no significant association between NYHA and any of our CBFV measures, including ICA CBFV (β: 6.45, 95% CI: −18.91, 6). This did not change when adding vascular comorbidities to our adjustment model (β: 3.36; 95% CI: −15.19, 8.47) [Table 3].

Discussion

In this study of patients with decompensated CHF undergoing diuresis therapy, overall, we did not find associations between specific measure of heart failure severity and performance on cognitive tests across memory, attention, processing speed, or executive functioning domains. In addition, it does not appear in our cohort that TTE measures of heart function in the preceding 1 year are indicative of cognitive performance. We did find that patients with NYHA Class 1–2 had on average a better LNS score when compared to NYHA Class 3–4 patients, even after adjusting for demographic and vascular risk factor confounders. This would support our initial hypothesis that those with poorer cardiac function would have lower cognitive performance, but we recognize that this result was not found consistently and should not be overinterpreted.

Studies have suggested that measures of heart failure severity that may contribute to cognitive impairment include stage of heart failure and echocardiographic measures of systolic function such as LVEF.[3,4,6,7] Zuccalà *et al*. found that patients with LVEF <30% had worse performance than patients with higher LVEF on the Mini Mental State Exam.[4] NYHA class was found to be associated with memory, visuospatial ability, psychomotor speed, and executive function.[6,7] However, other studies have suggested that characteristics of heart failure do not make a difference in cognition.[2,4-6] Van den Hurk *et al*. found no association between LVEF and cognitive performance, specifically assessing processing speed, memory, and executive functioning.[2,5] Hanon *et al*. did not find a significant association between NYHA class and performance on the delayed-recall Memory Impairment Screen. Our study was consistent

Table 2: Multivariable linear regression models demonstrating the association between measures of heart failure severity and cognitive performance among congestive heart failure patients

	HFpEF (vs. HFrEF/HFmrEF), β (95% CI) (*n*=139)		NYHA heart failure Class 1/2 (vs. Class 3/4), β (95% CI) (*n*=139)		LVEF, β (95% CI) (*n*=139)		LVEF 40%–55% (*n*=40) versus LVEF ≤40% (base category) (*n*=49), β (95% CI)		LVEF ≥55% (*n*=50) versus LVEF ≤40% (base category) (*n*=49), β (95% CI)	
	Model A	Model B	Model A	Model B	Model A	Model B	Model A	Model B	Model A	Model B
Letter number sequence (*n*=99)	−0.01 (−0.43–0.4)	−0.01 (−0.37–0.35)	0.57 (0.13–0.95)	0.47 (0.09–0.84)	0.02 (−0.04–0.08)	0.01 (−0.05–0.06)	−0.18 (−0.73–0.16)	−0.29 (−0.73–0.16)	0.24 (−0.21–0.6)	0.2 (−0.21–0.6)
Trail making A (*n*=125)	−0.09 (−0.36–0.18)	−0.11 (−0.38–0.16)	−0.24 (−0.54–0.06)	−0.24 (−0.54–0.06)	−0.03 (−0.07–0.01)	−0.03 (−0.07–0.01)	0.08 (−0.27–0.38)	0.06 (−0.27–0.38)	−0.22 (−0.54–0.08)	−0.23 (−0.54–0.08)
Trail making B (*n*=114)	0.22 (−0.13–0.57)	0.15 (−0.18–0.48)	−0.29 (−0.67–0.1)	−0.27 (−0.64–0.1)	0.001 (−0.05–0.06)	−0.002 (−0.05–0.05)	0.4 (−0.03–0.76)	0.36 (−0.03–0.76)	−0.01 (−0.42–0.36)	−0.03 (−0.42–0.36)
RCF copy (*n*=127)	−0.12 (−0.45–0.21)	−0.07 (−0.39–0.25)	0.29 (−0.07–0.64)	0.27 (−0.08–0.61)	0.01 (−0.04–0.06)	0.01 (−0.04–0.06)	−0.2 (−0.57–0.2)	−0.19 (−0.57–0.2)	0.05 (−0.31–0.44)	0.06 (−0.31–0.44)
RCF immediate recall (*n*=126)	−0.19 (−0.54–0.15)	−0.16 (−0.5–0.18)	0.28 (−0.09–0.65)	0.27 (−0.1–0.63)	−0.01 (−0.06–0.05)	−0.01 (−0.06–0.04)	−0.3 (−0.69–0.12)	−0.29 (−0.69–0.12)	−0.14 (−0.55–0.24)	−0.16 (−0.55–0.24)
RAVLT immediate recall (*n*=137)	−0.25 (−0.58–0.08)	−0.24 (−0.56–0.09)	0.21 (−0.16–0.57)	0.21 (−0.15–0.57)	−0.02 (−0.08–0.03)	−0.03 (−0.08–0.02)	−0.13 (−0.49–0.3)	−0.1 (−0.49–0.3)	−0.18 (−0.58–0.19)	−0.2 (−0.58–0.19)
RAVLT delayed recall (*n*=137)	−0.03 (−0.38–0.32)	−0.02 (−0.37–0.33)	−0.12 (−0.5–0.27)	−0.13 (−0.51–0.26)	0.01 (−0.05–0.06)	0.01 (−0.05–0.06)	0.16 (−0.24–0.62)	0.19 (−0.24–0.62)	0.01 (−0.4–0.43)	0.01 (−0.4–0.43)
Global cognitive score* (*n*=98)	−0.43 (−1.44–0.58)	−0.41 (−1.34–0.51)	0.94 (−0.15–2.03)	0.76 (−0.24–1.75)	−0.004 (−0.16–0.15)	−0.03 (−0.17–0.11)	−0.31 (−1.68–0.65)	−0.51 (−1.68–0.65)	0.02 (−1.13–1.01)	−0.06 (−1.13–1.01)

**Z*-scores of the LNS, RAVLT immediate recall, and RAVLT delayed recall tests were summed to create a global cognitive score to assess multiple cognitive domains. Model A adjusted for age, sex, race, and education. Model B adjusted for Model A + CCI and smoking status. Bolded values indicate statistical significance ($P<0.05$). Italicized rows indicate that the direction of association is reversed, with higher scores on this cognitive test indicating worse performance. LVEF: Left ventricular ejection fraction, HFpEF: Heart failure with preserved ejection fraction, HFrEF: Heart failure with reduced ejection fraction, HFmrEF: Heart failure with mildly reduced ejection fraction, NYHA: New York Heart Association, RAVLT: Rey Auditory Verbal Learning Test, RCF: Rey Complex Figure, CI: Confidence interval

Table 3: Multivariable linear regression models demonstrating the association between measures of heart failure severity and cerebral blood flow velocity among congestive heart failure patients

	HFpEF (vs. HFrEF/HFmrEF), β (95% CI) (*n*=49)		NYHA heart failure Class 1/2 (vs. Class 3/4), β (95% CI) (*n*=49)		LVEF, β (95% CI) (*n*=49)		LVEF 40%–55% (*n*=16) versus LVEF ≤40% (base category) (*n*=18), β (95% CI)		LVEF ≥55% (*n*=15) versus LVEF ≤40% (base category) (*n*=18), β (95% CI)	
	Model A	Model B	Model A	Model B	Model A	Model B	Model A	Model B	Model A	Model B
Proximal MCA (cm/s)	−2.61 (−13.62–8.39)	−1.01 (−12.01–9.98)	2.52 (−9.46–14.51)	0.44 (−11.61–12.49)	−0.2 (−1.79–1.38)	0.23 (−1.41–1.87)	2.66 (−10.92–16.23)	3.81 (−9.71–17.32)	−4.9 (−18.2–8.39)	−2.1 (−15.67–11.48)
Proximal ACA (cm/s)	0.21 (−12.26–12.68)	1.92 (−10.55–14.39)	−1.07 (−14.65–12.51)	−3.53 (−17.16–10.11)	0.14 (−1.65–1.93)	0.7 (−1.15–2.55)	7.49 (−7.67–22.66)	8.87 (−6.23–23.98)	−4.13 (−18.98–10.72)	−1.03 (−16.2–14.14)
ICA (cm/s)	1.9 (−9.66–13.47)	4.63 (−6.11–15.37)	6.45 (−18.91–6)	3.36 (−15.19–8.47)	0.46 (−1.2–2.12)	1.18 (−0.39–2.76)	11.84 (−1.95–25.64)	**13.7 (1.01–26.39)**	−0.94 (−14.45–12.58)	3.82 (−8.92–16.56)

Model A adjusted for age, sex, and race. Model B adjusted for Model A+CCI and smoking status. Bolded values indicate statistical significance (P<0.05). ACA: Anterior cerebral artery, HFpEF: Heart failure with preserved ejection fraction, HFrEF: Heart failure with reduced ejection fraction, HFmrEF: Heart failure with mildly reduced ejection fraction, ICA: Internal carotid artery, MCA: Middle cerebral artery, NYHA: New York Heart Association, CI: Confidence interval

with these prior findings that suggest that characteristics of heart failure do not make a difference with regards to cognitive performance. We emphasize that in our study, we were comparing incremental changes in certain characteristics of heart failure among a whole cohort of patients with decompensated heart failure, rather than comparing those with heart failure to those without heart failure. Thus, in our analyses, the true comparator is other heart failure patients with differing degrees of heart failure, as measured by different heart failure characteristics. Our lack of association may also be due to our cohort having decompensated heart failure, thereby warranting diuretic therapy, rather than stable CHF. In addition, though we included important comorbidities, and covariates in our analyses, we did not include pre-morbid intellect, which was included in the analyses of those studies that did report an association.

Although we did not perform an interventional study, identifying characteristics of heart failure that are associated with cognitive impairment, and which cognitive domains are impacted, could inform potential therapeutic targets to prevent or reduce cognitive impairment. Currently, there are no guideline-directed cognitive screening recommendations for heart failure patients.[25] Patients could undergo more frequent screening of cognitive domains impacted by heart failure, which would allow for more proactive modification of medical management to address signs of cognitive decline. Other therapies, like guideline-directed medical therapy regimens, could be modified to optimize hemodynamic parameters (blood pressure, cardiac output) and thereby potentially improve functional outcomes.[9] Diuretics, for example, can lower blood pressure, and there is ongoing research in our study to assess how diuresis could affect the cognitive performance of heart failure patients pre-and post-treatment.

In this study, we also uniquely provided measurements of CBFV, as a surrogate measure for cerebral blood flow, which was collected concurrently at the time of cognitive testing via TCD ultrasonography, a lower risk, cost-effective, and information-rich method that reliably evaluates CBFV. Literature suggests reductions in CBFV as a potential mechanism for cognitive impairment in CHF patients.[10] Studies evaluating specific characteristics of heart failure severity associated with CBFV have had varying results due to differing study designs and patient cohorts. Choi *et al*. found that global CBFV was significantly associated with NYHA class among a cohort of patients with CHF.[26] Babayiğit *et al*. found that LVEF positively correlated with TCD CBFV among a cohort of patients with HFrEF and demonstrated that HFrEF patients with permanent atrial fibrillation had lower mean CBFV than those with sinus rhythm.[12] We found that patients with an LVEF

of 40%–55% had on average a higher ICA CBFV when compared to those with an LVEF ≤40%, after adjustment for demographic and vascular risk factor confounders, which would support our hypothesis that blood flow may differ based on heart failure measures. The small sample size for TCD measurements may have limited our ability to find meaningful comparisons, particularly in the context of potential anatomical changes in cerebral arteries among patients, but the work of others does lend credence to our findings.

Reduced cerebral perfusion is one mechanism widely considered to cause cognitive impairment in heart failure patients. In addition to hypoperfusion, other potential mechanisms including a systemic inflammatory state, ischemic white matter disease, and atrial fibrillation (AF) may be related to cognitive decline in heart failure. Increased inflammatory cytokines are seen in heart failure, and these cytokines can cross the blood brain barrier, activating microglia. Levels of inflammatory cytokines are also associated with severity of heart failure and neuronal degeneration.[8,27] In patients with heart failure, MRI white matter lesions and other silent infarctions have been associated with cognitive decline.[28,29] It is suspected that white matter hyperintensities contribute to cognitive slowing, executive dysfunction, and visuospatial impairment, among other impaired cognitive domains, as myelin and axonal damage could slow neuronal signaling across the brain.[28,29] Finally, AF may be another mechanism by which heart failure patients experience cognitive decline. AF is a common cause of cardio-embolism, and silent infarction is known to be a risk factor for cognitive decline.[30,31] Anticoagulation use in theory should also help prevent silent ischemia, or ischemic stroke which also leads to cognitive decline. In our cohort, there was no difference in the prevalence of AF or anticoagulation use by either NYHA class or mean LVEF (results not shown). We recognize that subclinical AF may not have been fully captured in our cohort and so the overall prevalence of AF may be underreported, which could be a limitation in our work.

While the findings of this study provide unique insight into cognitive performance and CBFV of patients with CHF, there are several limitations. The results are from a single center study and from a small cohort size that lack a non-CHF control group. A 1-year time frame for TTE was chosen as these patients have established decompensated heart failure, so we assumed that most patients in our cohort would have stable findings within this time frame. We may have not captured all potential sources of confounding, and because we were interested in several different cognitive domains, it is possible that the interpretation of the data was impacted by multiple comparisons. Furthermore, this analysis only captures one point in time during the time course of CHF, a dynamic and complex disease. We utilized CBFV as a surrogate measure of cerebral blood flow, and differences in anatomical changes in cerebral arteries, such as diameter, that are associated with age, sex, race, and disease can influence CBFV even if CBF remains similar.[32,33] We did not have cerebral imaging data to provide the burden of ischemic white matter disease or other silent cerebral infarcts, which may be potential mechanisms of cognitive decline in heart failure patients, in our study cohort. However, this study is not a mechanistic study and thus did not seek to determine mechanisms but rather to suggest potential associations between features of CHF and cognitive function that might be hypothesis-generating.

Conclusion

We did not find that severity of heart failure, as measured by stage of heart failure and TTE measures of heart function, is associated with cognitive performance nor with CBFVs. We did find singular associations between heart failure characteristics and performance on a cognitive test and between heart failure characteristics and CBFV. Our results support that future work with larger sample sizes and leveraging a control group with no CHF are needed to determine the etiology of underlying elevated CBFV in CHF and whether this elevation contributes to the reported cognitive decline in CHF.

Author contributions

S.K. contributed to study design, study execution, statistical analysis, writing, and proofreading support; E.G. contributed to technical assistance, study execution, and proofreading support; N.W. contributed to study execution and proofreading support; R.G. contributed to study execution and proofreading support; and M.J. contributed to study design, statistical analysis, writing, and proofreading support.

Ethical policy and institutional review board statement

This study was reviewed and approved by the Johns Hopkins Medicine Institutional Review Board (IRB00287444) on May 25th, 2021. The study was conducted in accordance with ethical standards specified in the Helsinki Declaration of 1975 (revised in 2000). All participants provided informed consent.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Conflicts of interest

M.C.J serves as Associate Editor for Stroke. All other authors declare no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary Table 1: Multivariable linear regression models demonstrating the association between left atrial diameter and cognitive performance among congestive heart failure patients

Left atrial diameter β (95% CI) (*n*=111)	Letter number sequence (*n*=99)	Trial making A (*n*=125)	Trail making B (*n*=114)	RCF copy (*n*=127)	RCF immediate recall (*n*=126)	RAVLT immediate recall *n*=137)	RAVLT delayed recall (*n*=137)	Global cognitive score* (*n*=98)
Model A[a]	0.003 (−0.25–0.26)	−0.03 (−0.25–0.2)	0.15 (−0.1–0.4)	0.07 (−0.13–0.27)	0.11 (−0.11–0.32)	−1.08 (−7.55–5.39)	4.89 (−15.33–25.1)	0.26 (−0.33–0.86)
Model B[b]	0.06 (−0.17–0.28)	−0.01 (−0.23–0.22)	0.17 (−0.07–0.41)	0.11 (−0.09–0.3)	0.12 (−0.1–0.34)	−1.9 (−8.51–4.72)	−0.49 (−20.04–19.07)	0.38 (−0.17–0.92)

*Z-scores of the LNS, RAVLT immediate recall, and RAVLT delayed recall tests were summed to create a global cognitive score to assess multiple cognitive domains, [a]Adjustment Model A adjusted for participant age, sex, race (black vs. other), and education (years), [b]Adjustment Model B further adjusted for CCI and smoking status. RAVLT: Rey Auditory Verbal Learning Test, RCF: Rey Complex Figure, LNS: Letter-Number Sequencing, CCI: Charlson Comorbidity Index, CI: Confidence interval