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Cerebral Perfusion is Associated with White Matter Hyperintensities in Older Adults with Heart Failure

Michael L. Alosco, B.A.[1], **Adam M. Brickman, Ph.D.**[2], **Mary Beth Spitznagel, Ph.D.**[1,3], **Sarah L. Garcia, B.A.**[1], **Atul Narkhede, M.S.**[2], **Erica Y Griffith, B.S.**[2], **Naftali Raz, Ph.D.**[4], **Ronald Cohen, Ph.D.**[5], **Lawrence H. Sweet, Ph.D.**[6], **Lisa H. Colbert, Ph.D.**[7], **Richard Josephson, M.S., M.D.**[8,9,10], **Joel Hughes, Ph.D.**[1,3], **Jim Rosneck, M.S.**[3], and **John Gunstad, Ph.D.**[1,3]

[1]Department of Psychology, Kent State University, Kent, OH [2]Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Department of Neurology, College of Physicians and Surgeons, Columbia University, New York, NY [3]Department of Psychiatry, Summa Health System, Akron City Hospital, Akron, OH [4]Institute of Gerontology, Wayne State University, Detroit, MI [5]Departments of Neurology Psychiatry and the Institute on Aging, Center for Cognitive Aging and Memory, University of Florida [6]Department of Psychology, University of Georgia, Atlanta, USA [7]Department of Kinesiology, University of Wisconsin, Madison, WI [8]University Hospitals Case Medical Center and Department of Medicine, Cleveland [9]Harrington Heart & Vascular Institute, Cleveland, OH [10]Case Western Reserve University School of Medicine, Cleveland, OH

Abstract

Cognitive impairment is common in heart failure (HF) and believed to be the result of cerebral hypoperfusion and subsequent brain changes including white matter hyperintensities (WMH). The current study examined the association between cerebral blood flow and WMH in HF patients and the relationship of WMH to cognitive impairment. Sixty-nine patients with HF completed the mini mental state examination (MMSE), echocardiogram, transcranial Doppler sonography (TCD) for cerebral blood flow velocity of the middle cerebral artery and brain magnetic resonance imaging (MRI). Multivariable hierarchical regression analyses controlling for medical and demographic characteristics as well as intracranial volume showed reduced cerebral blood flow velocity of the middle cerebral artery was associated with greater WMH ($\beta = -.34$, $p = .02$). Follow up regression analyses adjusting for the same medical and demographic factors in addition to cerebral perfusion also revealed marginal significance between increased WMH and poorer performance on the MMSE ($\beta = -.26$, $p = .05$). This study suggests that reduced cerebral perfusion is associated with greater WMH in older adults with HF. Our findings support the widely proposed mechanism of cognitive impairment in HF patients and prospective studies are needed to confirm our findings.

Keywords

Cardiovascular disease; cerebral blood flow; cognitive function; heat failure; white matter hyperintensities

Address Correspondence to: Michael Alosco, B.A., Department of Psychology, Kent State University, Kent OH USA 44242; Phone 203-417-1892; Fax 330-672-3786; Malosco@kent.edu.

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1. Introduction

Heart failure (HF) is a chronic disease that affects nearly six million Americans and is associated with significant economic burden,[1] recurrent hospitalizations,[2] and elevated mortality risk.[3] Heart failure patients are also at risk for conditions like Alzheimer's disease, and up to 75% exhibit deficits on neuropsychological tests assessing attention, executive function, memory, and language.[4–7] Past work has identified medical and clinical contributors to cognitive impairment in older adults with HF. For instance, hypertension can be found in up to 75% of HF patients and has been linked with impairments in attention/executive function in HF.[1,8] Other common comorbid conditions in HF such as depression, obesity, and diabetes have also been shown to negatively impact cognition in this population.[9–11]

Recent work shows that structural brain changes, including the development of white matter hyperintensities (WMH), are important contributors to cognitive impairment in HF. Indeed, WMH are associated with decline in global cognition as well as increased risk for depression, anxiety, cerebrovascular events, and mortality in cardiac and cognitively impaired populations.[12–13] Heart failure patients also have more severe WMH relative to healthy and cardiac controls and such white matter damage has been linked with cognitive dysfunction in this population.[14–15] There is extant evidence that demonstrates the adverse effects of WMH on cognitive outcomes in cardiovascular disease and aging populations.[12, 16–19]

It is hypothesized that WMH—and resulting cognitive impairment—in HF is a manifestation of cerebral hypoperfusion and subsequent ischemia secondary to the effects of reduced cardiac pumping efficiency and comorbid medical conditions.[20–21] Past findings showing cerebral hypoperfusion is common in this population (i.e., reduced by as much as 30%) and associated with impairments in global cognitive functioning[22–25] support this hypothesis. In addition, reduced cardiac function, as measured by ejection fraction and/or cardiac output, has also been shown to be related to increased WMH in other cardiac populations.[20, 26–27] Moreover, cerebral hypoperfusion quantified with neuroimaging techniques has been linked with WMH in healthy elderly and patients with type 2 diabetes.[28–30]

Despite these findings, past work examining the relationship between cerebral blood flow and WMH in HF has mainly relied on measures of cardiac function to operationalize cerebral perfusion. Thus, the objective of the current study was to examine the association between cerebral perfusion measured by transcranial Doppler sonography (TCD) and WMH among older adults with HF. We further sought to investigate the independent association between WMH and global cognitive status in this sample of HF patients.

2. Methods

2.1 Participants

The sample consisted of 69 consecutively enrolled persons with HF from an ongoing study that examines neurocognitive outcomes in HF patients. Patients included in the study were between the ages of 50–85 years of age, native English speakers, and had an established diagnosis of New York Heart Association (NYHA) class II or III at the time of enrollment. NYHA is comprised of four classes, including Class I: no symptoms associated with ordinary activity and no limitation of physical activity; Class II: slight limitation of physical activity, though comfortable at rest; Class III: marked limitation of physical activity, but remains comfortable at rest; Class IV: inability to perform physical activity without discomfort and symptoms of cardiac insufficiency or chest pain at rest.

The exclusion criteria were history of significant neurological disorder (e.g. dementia, stroke), head injury with more than 10 minutes loss of consciousness, severe psychiatric disorder (e.g. schizophrenia, bipolar disorder), history of substance use, renal failure, and sleep apnea. Participants were also excluded for any contraindications to magnetic resonance imaging (MRI) (e.g., pacemaker). Participants averaged 68.55 (SD = 8.07) years of age, were 36.2% female, and 85.4% Caucasian. As ascertained through a medical record review, the sample exhibited an average left ventricular ejection fraction (LVEF) of 42.39 (13.77). Refer to Table 1 for sample demographic and medical characteristics.

2.2 Measures

2.2.1 Neuroimaging—Whole-brain T2 and FLAIR images were acquired on a Siemens Symphony 1.5Tesla scanner to quantify WMH. For the T2-weighted images, twenty-one 5-mm thick slices were acquired with a 230 × 100 mm field of view with TR = 2910 and TE = 134. For the FLAIR images, twenty-one 5-mm slices were acquired with TR = 8500, TE = 115, and FOV = 220 × 75.

Total WMH volume was derived by a three-step operator-driven protocol that has been described in detail previously.[31–32] Briefly, in Step 1, a threshold was applied to each FLAIR image to label all voxels that fell within the intensity distribution of hyperintense signal. In Step 2, gross regions-of-interest (ROI) were drawn manually to include WMH but to exclude other regions (e.g., dermal fat) that have similar intensity values. In Step 3, a new image is generated that contains the intersection of voxels labeled in Step 1 and those labeled in Step 2. The resulting image contains labeled voxels that are common in Step 1 and Step 2. The number of resulting voxels is summed and multiplied by voxel dimensions to derive a total volume score. We have shown the validity and reliability of this approach previously.[31]

2.2.2 Cerebral Blood Flow—We used TCD ultrasonography through an expanded Stroke Prevention Trial in Sickle Cell Anemia (STOP) protocol.[33] 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. The current study chose to assess mean cerebral blood flow velocity (CBF-V) of the Middle Cerebral Artery (MCA). The MCA irrigates the frontal, temporal, and the parietal cerebrum and has been shown to reliably reflect changes in cerebral blood flow and exhibit higher blood flow velocity compared to other TCD measured arteries (e.g., ACA, PCA).[34–35] Furthermore, relative to healthy controls persons with HF have been shown to demonstrate significant reductions in CBF-V of the MCA.[36]

2.2.3 Global Cognitive Status—The Mini Mental State Examination (MMSE) was used to assess global cognitive function. It is a brief screening measure that assesses aspects of attention, orientation, memory, language, and calculation.[37] Scores on the MMSE range from 0–30 with higher scores reflective of better cognitive function. The dependent variable used in the current study was the participants' raw MMSE score.

2.2.4 Estimated Intelligence—To estimate intelligence, the American National Adult Reading Test (AMNART) was administered to all participants. The AMNART is a reliable estimate of intellect in medical populations.[38–40] The AMNART requires the participant to read a 45-item list of irregularly pronounced words out loud. Errors in pronunciation are scored and an estimated IQ score is calculated using Grober and Sliwinski's formula.[41]

AMNART IQ estimates are converted to standard scores (i.e., a mean of 100 and a standard deviation of 15) with higher scores reflective of better performance.

2.2.5 Depressive Symptoms—The BDI-II is a commonly used checklist that assesses depressive symptoms with good psychometric properties in medical populations (e.g., test retest reliability of $r = .93$ to $r = .96$).[42–43] BDI-II scores range from 0–63 with increased scores indicative of greater depressive symptomatology. Participant's raw BDI-II score was included in the current analyses.

2.2.6 Demographic and Medical Characteristics—Participant demographic and medical characteristics were obtained through self-report and medical record review. Specifically, information regarding participants' age, sex, education, race, cardiac function (i.e., left ventricular ejection fraction), and diagnostic history of diabetes, hypertension, and thyroid abnormalities were obtained.

2.3 Procedures

The local Institutional Review Board (IRB) approved the study procedures and all participants provided written informed consent prior to study enrollment. A medical chart review was performed for all participants. Participants height and weight were then measured and demographic, medical and psychosocial self-report measures were completed. Finally, upon enrollment all HF patients underwent neuroimaging and TCD.

2.4 Statistical Analyses

A square root transformation of WMH was performed to correct for the positively skewed distribution of this variable. Multivariable hierarchical regression analysis was then conducted to examine whether CBF-V of the MCA was associated with WMH after controlling for demographic and medical factors. Medical and demographic characteristics were entered in block 1, including age, sex (1 = male; 2 = female), premorbid intelligence, depressive symptoms (as assessed by the BDI-II), body mass index (BMI), diagnostic history of hypertension, diabetes, and thyroid abnormalities (1 = positive diagnostic history; 0 = negative diagnostic history) and intracranial volume. These medical and demographic variables were included as covariates in order to account for their established influence on neurocognitive outcomes. CBF-V of the MCA was then entered in block 2 to determine its predictive validity over medical and demographic characteristics. A final regression analysis controlling for the same medical and demographic characteristics as above in addition to CBF-V of the MCA was conducted to determine the independent influence of WMH on MMSE scores.

3. Results

Cerebral Blood Flow Velocity and WMH

Older age was associated with increased WMH ($\beta = .29$, $p = .03$). After controlling for age, sex, premorbid intelligence, depressive symptoms (as assessed by the BDI-II), BMI, diagnostic history of hypertension, diabetes, and thyroid abnormalities, and intracranial volume, decreased CBF-V was associated with increased WMH ($\beta = -.34$, $p = .02$). Table 2 displays a full summary of regression analyses.

WMH and Cognitive Function

Reduced cognitive function was common in this sample with an average MMSE score of 27.62 (SD = 1.91) and 27.5% of the sample scoring below a 27. After adjustment for age, sex, premorbid intelligence, depressive symptoms (as assessed by the BDI-II), BMI,

diagnostic history of hypertension, diabetes, thyroid abnormalities, CBF-V of the MCA, and intracranial volume, greater WMH was associated with lower scores on the MMSE (β = −.26, p = .05). See Table 3.

4. Discussion

Past work suggests that cognitive impairment in HF is a manifestation of cerebral hypoperfusion and subsequent cerebral structural damage (e.g., WMH). Previous investigations of these proposed mechanisms in HF and other cardiac samples are limited due to use of indirect perfusion measures (e.g., indices of cardiac function). In the current study, we found that lower TCD measured cerebral perfusion of the MCA was associated with higher WMH volume in a sample of older adults with HF.

Although brief changes in cerebral blood flow are maintained in healthy individuals through autoregulatory mechanisms, such mechanisms can become compromised in the presence of chronic hypoperfusion that results from HF.[21, 24, 36] This pattern of decreased cerebral blood flow is theorized to produce WMH through declines in oxygenation and subsequent ischemic injury.[21,44] Indeed, WMH are believed to reflect ischemic related injury, including axonal loss, rarefaction of myelin, gliosis, spongiosis, and fiber loss.[45–46] The strong relationship between vascular risk factors common to HF patients that impact cerebral hemodynamics, such as reduced cardiac output, hypertension, atherosclerosis, and reduced endothelial functioning, and WMH provides further evidence for their ischemic nature.[26, 44, 47–51]

Contrary to the findings of the current study, Vogels and colleagues[36] did not find a significant relationship between cerebral blood flow velocity and WMH in HF patients. The exact reason for the discrepancy between our findings and Vogels et al.[36] is not entirely clear. One possible explanation involves the possibility of a threshold effect. On average, the sample in Vogels et al.[36] exhibited rather preserved levels of cerebral blood flow velocity relative to the sample in the current study. Thus, cerebral perfusion might need to fall below a certain level to disrupt autoregulatory mechanisms and produce subsequent insult. Some evidence for this notion may be found in the Vogels et al.,[36] study in that a relationship between cerebral blood flow and WMH emerged in the subset of most severe HF patients in their sample but not in the overall, generally healthier, sample. Prospective studies in larger samples with a wide range of HF severity are needed to clarify the relationship between cerebral perfusion and WMH in HF.

Finally, the current study found that greater WMH was independently associated with reduced global cognitive status in HF patients. White matter hyperintensities are prevalent in vascular populations and associated with increased dementia risk and reduced performance on cognitive testing among aging and cardiovascular disease populations.[12, 15, 52] It seems likely that WMH may also serve as a sensitive predictor of cognitive test outcomes in HF patients. Prospective studies are needed to clarify the predictive validity of WMH to cognitive impairment in HF, including risk for dementia.

Our findings are limited in several ways. First, although past work in other populations supports the directionality of our findings,[53–54] the current study consisted of cross-sectional analyses and prospective studies are needed to confirm our findings. Future studies with larger samples are also needed to determine whether WMH mediate the relationship between cerebral hypoperfusion and cognitive impairment. In addition, the current study also did not utilize a healthy control or comparison group and case-controlled studies are also needed to confirm the association between reduced cerebral blood flow, WMH, and neurocognitive outcomes in HF. If our findings are replicated with the above limitations addressed, interventions that modify cerebral blood flow (e.g., cardiac rehabilitation) in HF

may lead to better neurocognitive outcomes in this population. Support for this hypothesis may be found in the concept of cognitive reserve. For instance, recent work shows that higher cognitive reserve mitigates the effects of HF on cognitive abilities such as attention, executive function, and language.[55] These findings may in part be explained by the protective effects of greater brain reserve on altered cerebral hemodynamics.[56]

Several other limitations warrant further discussion. Although TCD is a valid measure of cerebral blood flow,[34] it does not directly assess perfusion within the brain and blood flow velocity may be compromised by conditions that negatively impact the arterial diameter (e.g., artheroscelorosis). Thus, future studies should also examine WMH and cerebral perfusion using other methods that assess cerebral blood flow (e.g., arterial spin labeling (ASL) magnetic resonance imaging or positron emission tomography (PET) imaging). Specifically, ASL MRI imaging has become increasingly popular to assess cerebral blood flow because it is non-invasive and associated with decreased patient risk.[57] More importantly, ASL provides a direct measure of cerebral blood flow through the use of an endogenous tracer that consists of magnetically-labeled arterial blood water.[57,58] Consistent with this notion, the current findings may also be limited by the MRI parameters implemented. For instance, the use of a slice thickness of 5 mm slice may have underestimated white matter lesion load relative to thinner slices.[59] Finally, future work should examine the association between cerebral blood flow and WMH with cognitive function using comprehensive neuropsychological test batteries that assesses attention, executive function, memory, and language.[6] Such work would help to clarify the possibility of differential effects of WMH on cognition in HF.

In brief summary, the current study suggests that reduced cerebral perfusion is associated with greater WMH in HF. These findings may in part explain the high rates of cognitive impairment observed in HF populations. Prospective studies are needed to confirm our findings using additional measures of cerebral blood flow (e.g., ASL from MRI, PET scan imaging).

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Table 1

Demographic, Medical, and Cognitive Characteristics of 69 Older Adults with Heart Failure ($N = 69$)

Demographic Characteristics		**Range**
Age, mean years (SD)	68.55(8.07)	52 to 82
Years Education, mean (SD)	13.93(2.75)	9 to 23
AMNART, mean (SD)	110.87 (16.10)	10.31 to 129.72
Female (%)	36.2	--
Race (% Caucasian)	85.4	--
Medical Characteristics		
BDI-II, mean (SD)	5.97(6.12)	0 to 38
Body mass index, mean (SD)	30.35(6.80)	19.19 to 47.92
Diabetes (% yes)	27.5	--
Hypertension (% yes)	71.0	--
Thyroid (% yes)	20.3	--
White Matter Hyperintensities, mean (SD) mm^3	13.16 (11.73)	.69 to 62.66
MCA CBF-V, mean (SD) cm/s	42.86 (14.32)	8.63 to 85.08 cm/s
Global Cognitive Status		
MMSE	27.62 (1.91)	21 to 30

AMNART = North American Adult Reading Test; BDI-II = Beck Depression Inventory-II; MCA CBF-V = Cerebral Blood Velocity of the MCA; WMH = White matter hyperintensities; MMSE = Mini Mental State Examination

Table 2

Cerebral Perfusion Independently Predicts WMH in Older Adults with Heart Failure ($N = 69$)

Variable	WMH β (*SE b*)
Block 1	
Age	.29(.02)*
Sex	.26(.44)
AMNART	−.10(.01)
BMI	.05(.03)
BDI-II	.11(.03)
Hypertension	− .07(.40)
Diabetes	.07(.42)
Thyroid	−.18(.47)
Volume	.26(.00)
R^2	.16
F	1.25
Block 2	
CBF-V	−.34(.01)*
R^2	.23
F for ΔR^2	5.57*

Note.

* denotes $p \leq 0.05$

Abbreviations: β – standardized regression coefficients, SE – standard error; AMNART = North American Adult Reading Test; BMI = Body Mass Index; BDI-II = Beck Depression Inventory-II; Volume = Intracranial Volume; CBF-V = Cerebral Blood Velocity of the MCA

Table 3

White Matter Hyperintensities Independently Predict Cognitive Function in Older Adults with Heart Failure ($N = 69$)

Variable	MMSE β(*SE b*)
Block 1	
Age	−.18(.03)
Sex	.29(.61)
AMNART	.13(.02)
BMI	−.09(.04)
BDI-II	−.03(.04)
Hypertension	−.09(.57)
Diabetes	.13(.59)
Thyroid	−.04(.66)
Volume	.32(.00)*
CBF-V	−.13(.02)
R^2	.17
F	1.15
Block 2	
WMH	−.26(.18)*
R^2	.22
F for ΔR^2	3.89*

Note.

* denotes $p \leq 0.05$

Abbreviations: β – standardized regression coefficients, SE – standard error; AMNART = North American Adult Reading Test; BMI = Body Mass Index; BDI-II = Beck Depression Inventory-II; Volume = Intracranial Volume; CBF-V = Cerebral Blood Velocity of the MCA; WMH = White matter hyperintensities; MMSE = Mini Mental State Examination