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Reduced Cerebral Perfusion Predicts Greater Depressive Symptoms and Cognitive Dysfunction at a One Year Follow-up in Patients with Heart Failure

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Abstract

Objective—Cerebral hypoperfusion is common in heart failure (HF) and believed to underlie poor neurocognitive outcomes in this population. Up to 42% of HF patients also exhibit depressive symptomatology that may stem from reduced cerebral blood flow. However, no study has examined this possibility or whether reduced brain perfusion increases risk for future cognitive dysfunction in older adults with HF.

Methods—100 HF patients underwent transcranial doppler ultrasonography to quantify global cerebral blood flow velocity (CBF-V) and were administered a cognitive test battery to assess global cognition, attention/executive function, and memory abilities. All participants then completed the Beck Depression Inventory-II to assess depressive symptomatology. These procedures were performed at baseline and a 12-month follow-up.

Results—Repeated measures revealed CBF-V declined over the 12-month period. Regression analyses showed reduced baseline CBF-V predicted worse performances in attention/executive function ($p < 0.05$ for all) and a trend for memory ($p = 0.09$) in addition to greater depressive symptomatology ($p < 0.05$) at the 12-month follow-up, even after controlling for baseline factors and medical and demographic variables.

Conclusions—Cerebral perfusion declined over time and was associated with poorer cognitive function and greater depressive symptoms at a 1-year follow-up in HF. Prospective studies with long-term follow-ups that employ neuroimaging are needed to examine whether cognitive dysfunction and depression in HF stems from the adverse effects of cerebral hypoperfusion on the cerebral structure.

Keywords

Cerebral blood flow; cognitive function; depression; heart failure

INTRODUCTION

Heart failure (HF) accounts for nearly 1 million hospitalizations each year due to the many health consequences associated with cardiac dysfunction (Gheorghiade *et al.*, 2013). Aging and vascular processes in HF are also known to adversely affect the brain, including altered cerebral hemodynamics (Jefferson, 2010; de la Torre, 2012). As an example, 31% of HF patients exhibit reduced cerebral blood flow relative to controls, with greater hypoperfusion linked to increasing HF severity (Loncar *et al.*, 2011; Gruhn *et al.*, 2001).

Neurological symptoms commonly manifested in HF patients are theorized to be a result of cerebral hypoperfusion and subsequent ischemic-related brain injury (Gheorghiade *et al.*, 2013; Alosco *et al.*, 2013). Supporting this notion is the vast evidence in HF showing impairments in mental abilities (e.g., attention/executive function) mediated by brain regions sensitive to decreased oxygenation (e.g., frontal lobes) (Pressler *et al.*, 2010). Adverse brain changes reflective of ischemic injury are also well documented in this population, including white matter hyperintensities and reduced axonal integrity (Vogels *et al.*, 2007; Kumar *et al.*, 2011).

The effects of HF also extend into psychological symptoms, with as many as 42% of patients exhibiting clinically meaningful levels of depressive symptomatology (Skotzko *et al.*, 2000). Depression in HF is associated with greater risk for hospitalizations, cardiac events (Kato *et al.*, 2012), and heightened risk for mortality (Rutledge *et al.*, 2006). As with the cognitive impairment described above, there is reason to believe that the etiology of depression in HF may be at least partly attributable to cerebral hypoperfusion. For example, rapidly growing evidence links depression with neurological changes in older adults with HF, including cognitive impairment (Garcia *et al.*, 2011). Moreover, relative to non-depressed HF patients, cross-sectional work shows that depressed HF patients demonstrate greater reductions in cerebral blood flow, including to brain regions that mediate emotion regulation (Alves *et al.*, 2006; Alves *et al.*, 2005), and depression and cerebral hypoperfusion also interact to exacerbate cognitive impairment in this population (Alosco *et al.*, in press). In addition to these findings in HF, past work in elderly samples suggests that age-related disruptions in cerebral blood flow to brain regions that help regulate emotions might lay the foundation for later life depression (Chen *et al.*, 2006; Dotson *et al.*, 2009; Tiemeir *et al.*, 2002; Willeumier *et al.*, 2011).

Despite these findings, changes in cerebral perfusion over time in HF are poorly understood and no study to date has examined whether reduced cerebral blood flow increases risk for cognitive dysfunction or depression in this population. The goal of the current study was to determine whether reduced cerebral blood flow predicts cognitive dysfunction and depression 12-months later in older adults with HF. Based on past work, we hypothesized that decreased cerebral blood flow would predict reduced cognitive function and greater depressive symptomatology at the 12-month follow-up.

METHODS

Participants

A total of 145 patients with HF were recruited for participation in a larger longitudinal National Institutes of Health (NIH) funded research study examining neurocognitive

function in older adults with HF over a 12-month period. However, the sample size for the current study was reduced to a total of 100 following exclusion of participants due to attrition and/or those participants with any missing data. HF patients were lost to attrition across the 12-month period due to factors such as failure to meet exclusion criteria at the follow-ups ($n = 2$), death ($n = 4$), poor health ($n = 4$), drop-outs ($n = 8$), lost to follow-up ($n = 3$), and/or failure to complete follow-up in a reasonable amount of time ($n = 2$). Participants excluded were not significantly different from the remaining sample in terms of age ($t(142) = -0.18, p = 0.86$), gender ($\chi^2(N = 145) = 3.31, p = 0.07$), or HF severity ($t(137) = -0.65, p = 0.52$).

All HF participants were recruited from outpatient cardiology clinics and are representative of patients at a large community hospital. Strict inclusion/exclusion criteria were implemented as part of the larger study's protocol in order to minimize confounds that impact neurocognitive outcomes. For inclusion, participants must have been between the ages of 50–85 years, English speaking, and had a diagnosis of New York Heart Association (NYHA) HF class II, III, or IV at the time of enrollment. Potential participants were excluded for a history or current diagnosis of a significant neurological disorder (e.g. dementia, stroke), head injury with >10 minutes loss of consciousness, severe psychiatric disorder (e.g. schizophrenia, bipolar disorder), substance abuse/dependence, and/or stage 5 chronic kidney disease.

Measures

Cerebral Blood Flow—Transcranial doppler (TCD) ultrasonography assessed cerebral blood flow velocity (CBF-V) using an expanded STOP protocol (Bulas *et al.*, 2000). The protocol assesses blood flow velocity in the major brain arteries, including the Middle Cerebral Artery (MCA), the Anterior Cerebral Artery (ACA), and the Posterior Cerebral Artery (PCA). TCD measured cerebral blood flow velocity has been shown to reliably reflect changes in cerebral flow (Bishop *et al.*, 1986) and are significantly associated with direct measures of brain perfusion (i.e., arterial spin labeling) (Sorond *et al.*, 2010). Moreover, past work shows TCD is sensitive to neurocognitive outcomes in HF populations (Gruhn *et al.*, 2001) and depressive symptomatology in elderly samples (Tiemeir *et al.*, 2002). In the current analyses, a global cerebral blood flow velocity (CBF-V) index composite was computed that consisted of the mean blood flow velocity of the ACA, MCA, and PCA. These arteries irrigate nearly all aspects of the cerebrum, including the frontal, temporal, parietal, and occipital lobes.

Cognitive Function—All participants were administered a brief neuropsychological test battery to assess global cognitive status and multiple sub-domains of cognitive function, including attention/executive function and memory. Specifically, the Mini Mental Status Examination (MMSE) was used to provide an estimate of global cognitive function. It is a brief (5–10 minute) screening measure that taps into aspects of attention, orientation, memory, language, and calculation (Folstein *et al.*, 1975). Higher score on the MMSE is reflective of better global cognitive functioning (Folstein *et al.*, 1975). The psychometric properties of the MMSE are strong (Folstein *et al.*, 1975). A cut score of 27 has been shown to be sensitive to the detection of cognitive impairment and was used to reflect cognitive dysfunction in the current sample (O'Bryant *et al.*, 2008).

Several measures were also administered to more fully examine attention/executive function in the current sample, including Trail Making Test A and B (Reitan, 1958), and the Frontal Assessment Battery (FAB) (Dubois *et al.*, 2000). Long delayed free recall and total recognition hits from the California Verbal Learning Test-Second Edition (Delis *et al.*, 2000) were also used to examine memory abilities in this sample. All cognitive tests have

been shown to demonstrate excellent psychometric properties and are sensitive to deficits observed in HF populations.

Depressive Symptomatology—The Beck Depression Inventory-II (BDI-II) was used to assess depressive symptoms in the current sample. The BDI-II is a widely used assessment of affective and somatic depressive symptoms that demonstrates strong psychometric properties in community dwelling older adults and persons with medical conditions (Arnau *et al.*, 2001; Segal *et al.*, 2008). Cronbach's alpha of the BDI-II items in the current sample was 0.88. BDI-II scores range from 0–63 with higher scores reflective of greater depressive symptomatology.

HF Severity—The 2-minute step test (2MST) served as a HF severity proxy in the current sample. It is a brief assessment of physical fitness that requires participants to march in place lifting his/her knees to a marked target set on the wall set at the midpoint between the kneecap and crest of the iliac for a 2-minute period (Jones and Rikli, 2002). Greater step count is associated with better physical fitness. The 2MST is a valid measure of physical fitness (Garcia *et al.*, 2013). Average step count for females between the ages of 50–85 ranges from 71–115, while males range from 60–107 (Jones and Rikli, 2002).

Demographic and Medical History—Demographic and medical characteristics were ascertained through participant self-report and corroborated by medical record review. Common cardiac medications were also obtained through medical record review and medication lists provided by the participants. Medications were categorized into categories as according to the American Heart Association, namely: diuretics, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, and statins.

Procedures

The local Institutional Review Board (IRB) approved the study procedures and all participants provided written informed consent prior to study enrollment. All participants completed identical study procedures at baseline and a 12-month follow-up. During each assessment time point, participants were administered a brief neuropsychological test battery, performed the 2MST, and completed demographic and psychosocial self-report measures, including the BDI-II. During a separate study visit and within 2-weeks of the cognitive assessment, participants also underwent TCD ultrasonography at both baseline and the 12-month follow up.

Statistical Analyses

Raw scores from neuropsychological measures examining attention/executive function and memory were transformed to T-scores using normative data correcting for age, and both age and gender in the case of the CVLT-II. Composite indexes were computed for attention/executive function and memory that consisted of the means of the neuropsychological measures that comprise their respective domains. In the case of missing data on individual variables that comprise CBF-V (i.e., MCA, ACA, PCA) and/or the cognitive domains, the average for these cases was based on values from the remaining variables (N = 100). For follow-up analyses examining the individual CBF-V components, the sample size was reduced to 87 due to missing data on the individual indices at the baseline and/or 12-month time point.

Repeated measures analysis of variance (ANOVA) examined changes in CBF-V, cognitive function in each domain (e.g., global cognition, attention/executive function, and memory), and depressive symptomatology (as assessed by the BDI-II) from baseline to the 12-month

follow-up. Exploratory analyses were conducted to examine whether changes in CBF-V over time corresponded to changes in depressive symptoms and cognitive function. Specifically, change scores for each cognitive domain, the BDI-II, and CBF-V were calculated and bivariate correlations examined the association among the change scores for CBF-V with the BDI-II, and MMSE, attention/executive function, and memory.

For the primary analyses, a series of hierarchical regression analyses were conducted to examine whether baseline CBF-V predicted 12-month cognitive test performance on the MMSE, attention/executive function, and memory. For each regression model, baseline cognitive test performance and demographic and medical characteristics were controlled for and entered in block 1 of the regression model, including age, sex (1 = male; 2 = female), and diagnostic history of hypertension, diabetes, and sleep apnea (1 = positive diagnostic history; 0 = negative diagnostic history). Baseline CBF-V was entered in block 2 to determine its incremental predictive validity on cognitive function above and beyond medical and demographic characteristics.

The same procedures described above were utilized to determine whether baseline CBF-V predicts 12-month depressive symptomatology. For analyses examining 12-month BDI-II scores as the dependent variable, baseline BDI-II scores and the above listed demographic and medical characteristics were controlled for and entered in block 1 of the regression model. Total BDI-II score was entered in block 2. These same analyses were conducted to examine the differential effects of CBF-V of the ACA, MCA, and PCA on 12-month BDI-II.

RESULTS

Sample Medical and Demographic Characteristics

See Table 1 for a full summary of participant demographic and medical characteristics. Medical record review revealed that the sample had an average left ventricular ejection fraction of 42.74 (SD = 15.60), 40.6% had an LVEF < 40, and 81.0% were classified as NYHA Class II at baseline. Based on 2MST performances, repeated measures analysis showed that the sample demonstrated relatively stable HF severity from baseline to the 12-month follow-up ($F(1,82) = 0.72, p = 0.40$). Comorbid medical conditions were also prevalent at the baseline and 12-month time points, particularly hypertension and type 2 diabetes. Participants were also commonly prescribed cardiac medications, including diuretics (56.6%), ACE inhibitors (55.6%), beta-blockers (80.9%), angiotensin II receptor blockers (31.3%), and statins (10.1%). Of note, five cases exhibited missing data for complete medication status.

Change in CBF-V, Cognitive Function, and BDI-II Over Time

In terms of CBF-V, repeated measures analysis showed that the sample exhibited significant reductions in CBF-V from baseline to the 12-month follow-up ($F(1, 99) = 4.34, p = 0.04$). Follow-up analyses among the sample size of 87, showed specific decreases in CBF-V of the PCA ($p < 0.05$) and a trend for the MCA ($p < 0.10$) over time were noted. See Table 3. Bivariate correlation analyses revealed no significant associations between change in CBF-V with change in any of the cognitive domains or BDI-II scores over time ($p > 0.05$ for all).

The average baseline MMSE score of the current sample was 27.59 (SD = 1.80) and scores on this test significantly improved over time ($F(1,99) = 10.82, p < 0.01$). Specifically, at baseline, 28.0% of the sample exhibited a score < 27 on the MMSE relative to 15.0% at the 12-month follow-up. Similar to this pattern, performances in memory abilities fell within the average range at baseline and improved over the 1 year period ($F(1,99) = 24.53, p < 0.001$). Performance on attention/executive function measures also generally fell within the average

range, with the exception of low average baseline FAB performances. However, no significant changes in attention/executive function were found over time ($F(1, 99) = 0.43, p = 0.52$). See Table 2.

In terms of depressive symptoms, the sample exhibited an average baseline BDI-II score of 7.30 (SD = 6.56). Of the sample, 87.0% fell in the minimal range, 7.0% mild, 4.0% moderate, and 2.0% as severe. With a mean 12-month BDI-II score of 7.23 (6.60), no significant changes in BDI-II scores over time were found ($F(1, 99) = 0.02, p = 0.89$) (see Table 3).

Baseline CBF-V Predicts 12-Month Cognitive Function

Refer to Table 4 for hierarchical regression analyses examining the effects of baseline CBF-V on 12-month MMSE score, attention/executive function, and memory. After controlling for baseline test performance and medical and demographic variables, baseline CBF-V predicted 12-month performances in attention/executive function ($\beta = 0.24, p < 0.01$), and a trend for memory ($\beta = 0.15, p = 0.085$). In each case, despite the improvements in cognitive function at the group level, decreased baseline CBF-V predicted poorer cognitive function at the 12-month follow-up. Baseline CBF-V did not demonstrate significant effects on 12-month MMSE performances ($\beta = 0.14, p = 0.11$).

Baseline CBF-V Predicts 12-Month BDI-II Scores

Table 5 presents a full summary of hierarchical regression analyses examining the predictive validity of baseline CBF-V on 12-month depressive symptomatology. Block 1 with baseline BDI-II scores and demographic and medical characteristics demonstrated significant association with 12-month BDI-II scores ($F(6, 93) = 16.78, p < 0.001$). Baseline CBF-V demonstrated significant incremental predictive validity for 12-month BDI-II scores above and beyond medical and demographic variables ($\beta = -0.16, p = 0.04$). Specifically, reduced baseline CBF-V predicted greater depressive symptomatology at the 12-month follow-up. Among the sample of 87 patients with HF, follow-up regression analyses controlling for baseline BDI-II and medical and demographic variables showed that reduced baseline CBF-V of the MCA predicted greater depressive symptomatology at the 12-month follow-up ($\Delta F(1, 79) = 8.40, R^2 = 0.67, \beta = -0.21, p < 0.01$). No such pattern emerged for the CBF-V of the ACA or PCA ($p > 0.05$ for all).

HF Severity and 12-Month Cognitive Function and Depressive Symptoms

Additional regression analyses were performed to determine the possible effects of HF severity on 12-month cognitive function and depressive symptoms. Using the above described regression models, NYHA class did not predict 12-month attention/executive function, memory, or BDI-II scores ($p > 0.05$ for all), suggesting the current findings are not completely accounted for by HF severity.

DISCUSSION

Cerebral hypoperfusion is prevalent in HF and a significant correlate of cognitive impairment in this population. Depression is also common in patients with HF and past work in aging samples suggests depression may be a neuropsychiatric consequence in HF stemming from reduced brain perfusion. The current study is the first to show that cerebral blood flow predicts both cognitive function and depression at a later time point in a sample of older adults with HF. These findings warrant further discussion.

The current study found that reduced cerebral blood flow predicted decreased attention/executive function and memory abilities at the 1-year follow-up. These findings are

consistent with past cross-sectional work (Alves *et al.*, 2005) and provide further evidence for cerebral hypoperfusion as an important contributor to cognitive impairment in this population. HF patients with significantly reduced cardiac function may be at greatest risk for adverse brain changes and future cognitive decline and/or dementia. For instance, brain hypoperfusion has been shown to predict cognitive decline and conversion from mild cognitive impairment to dementia (Chao *et al.*, 2010). Moreover, cerebral hypoperfusion is a known contributor to WMH (Pressler *et al.*, 2010) and such insult to the cerebral structure has been directly correlated with reduced cognitive test performance in this population (Beer *et al.*, 2009). In-turn, future work is needed to determine whether cerebral hypoperfusion underlies increased risk of neurological conditions in HF, including Alzheimer's disease.

We also found that reduced cerebral blood flow predicted greater depressive symptomatology at a 1-year follow-up in patients with HF. Specifically, decreased blood flow velocity of the MCA was found to be the most important contributor to greater levels of depressive symptoms 1 year later. These findings support the notion that depression in older adults with HF is at least partly due to the adverse effects of cerebral hypoperfusion on the brain. Such proposed mechanisms have been theorized to underlie geriatric depressive syndromes and is widely known as the "vascular depression" hypothesis (Alexopoulos *et al.*, 1997; Alexopoulos, 2006). Specifically, physiological processes associated with aging alter cerebral hemodynamics (Ajmani *et al.*, 2000), which in-turn, underpin depressive symptoms due to ischemic related injury to brain networks responsible for emotions (e.g., frontolimbic structures) (Willeumier *et al.*, 2011; Bulas *et al.*, 2000; Alexopoulos *et al.*, 1997; Alexopoulos, 2002). HF patients may be at elevated risk for depression in light of the additive effects of cardiac dysfunction on cerebral perfusion levels and resulting brain damage in this population (Loncar *et al.*, 2011). For instance, relative to their non-depressed counterparts and healthy controls, depressed HF patients exhibit greater reductions in cerebral blood flow of the middle temporal lobe regions (Alves *et al.*, 2006). Cerebral hypoperfusion is indeed associated with greater WMH in patients with HF (Alosco *et al.*, 2013) and WMH have been identified as a significant contributor to depressive symptomatology in this population (Almeida *et al.*, 2005). Lastly, atrophy of brain regions that modulate emotions has recently been shown to be associated with increasing depressive symptoms over a two-year period in older adult HF patients (Almeida *et al.*, 2013). Fortunately, cerebral perfusion in HF may be partially reversible through improved cardiac function (Gruhn *et al.*, 2001) and future studies should examine whether structured exercise programs (e.g., cardiac rehabilitation) can improve brain perfusion and attenuate depressive symptomatology.

Interestingly, based on our findings, depression and cognitive impairment in HF may occur simultaneously through similar mechanisms (e.g., cerebral hypoperfusion and subsequent ischemia) (Alosco *et al.*, 2013). Depression and cognitive impairment are independent contributors to mortality risk in HF (Rutledge *et al.*, 2006; Zuccala *et al.*, 2003) and their simultaneous onset and decline could exacerbate poor outcomes in this population. Prospective studies are needed to examine the differential etiologies and interactive effects of depression and cognitive impairment in HF.

Although cerebral blood flow significantly declined over the 1-year period in this sample of HF patients, cognitive function improved and depressive symptoms remained stable. The exact etiology of this pattern is unclear and requires further study. A possible explanation for this finding involves the known subgroups of neurocognitive outcomes in persons with HF (Miller *et al.*, 2012). Most likely, only a subgroup of individuals exhibit meaningful decline in cognitive function and mood during the 12-month period and such individuals are driving the significant analyses. Consistent with this notion, HF severity indices remained stable during the study period on average. Regardless, given the pattern of decreased cerebral

blood flow over 12-months, future risk of cognitive decline and worsening of depressive symptoms is likely due to continue disruptions of cerebral hemodynamics and studies with extended follow-ups (e.g., 2–5 years) should examine this possibility in addition to interventions that can attenuate deteriorating cerebral perfusion.

Several limitations of the current study warrant brief discussion. First, the current study did not employ a control or comparison group and future case-controlled studies with larger sample sizes are needed to confirm our findings. However, it is noted that past work shows HF patients exhibit greater reductions in cerebral perfusion and cognitive function in addition to increased depressive symptoms relative to healthy controls (Pressler *et al.*, 2010; Gruhn *et al.*, 2001; Almeida *et al.*, 2013). It is also possible that the current findings are largely driven by a subset of the unhealthiest HF patients and future studies should explore the aims of the current study while controlling for factors such as HF and/or treatment duration. The current study also examined depressive symptomatology using a self-report instrument. Although the BDI-II is widely used and well-validated in older adult and medical populations (Arnau *et al.*, 2001), there are inherent biases associated with self-report in medical populations at-risk for cognitive impairment and future studies should examine the current study's aims using more objective assessments of depressive symptomatology (e.g., semi-structured interviews). Similarly, TCD ultrasonography is also a validated assessment of cerebral blood flow (Bishop *et al.*, 1986), though future work that employs direct assessments of brain perfusion (e.g., arterial spin labeling) are needed to confirm the association between cerebral hypoperfusion and depression in HF and also help identify the regional effects of reduced brain perfusion (e.g., frontolimbic structures) on depressive symptomatology. Such studies should also investigate the association between cerebral perfusion and cerebral morphometry and WMH to elucidate the exact mechanisms that underlie cerebral hypoperfusion and cognitive impairment and depression in HF.

Conclusion

In brief summary, the current study suggests that reduced cerebral blood flow is a significant predictor of poorer cognitive function and greater depressive symptomatology at a 1-year follow-up in older adults with HF. Such findings suggest that depression in HF may be a neuropsychiatric consequence stemming from the adverse effects of cerebral hypoperfusion on the brain. Prospective studies with long-term follow-up that employ neuroimaging are needed to examine whether the negative impact of cerebral hypoperfusion on the brain corresponds to neuropsychiatric changes and cognitive decline.

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Key Points

- Cerebral blood flow declines over time in patients with heart failure
- Reduced brain perfusion increases future risk for depressive symptoms and cognitive impairment
- Cognitive dysfunction and depression in HF may stem from the adverse effects of cerebral hypoperfusion on the brain

Table 1**Demographic and Clinical Characteristics**

Demographic Characteristics	Baseline	12-Months
Age, mean (SD)	69.49 (9.56)	70.26 (9.75)
Years of Education, mean (SD)	13.71 (2.65)	--
Female (%)	31.0	--
Race (% Caucasian)	91.0	--
Medical and Clinical Characteristics		
NYHA Class (% II, III)	84.0; 16.0	--
Diabetes (% yes)	31.0	31.0
Hypertension (% yes)	66.0	70.0
Sleep Apnea (% yes)	21.0	6.0
2MST, mean (SD)	61.62 (21.64)*	64.37 (24.62)**

NYHA = New York Heart Association; 2MST = 2-minute step test;

*
N = 92;

**
N = 87

Table 2

Baseline and 12-Month Neuropsychological Test Performance

	Baseline Mean (SD)	% T-score < 35	12-month Mean (SD)	% T-score < 35	F-statistic
<i>Global Cognition</i>	27.59 (1.80)	--	28.12 (1.61)	--	10.82**
MMSE	27.59 (1.80)	--	28.12 (1.61)	--	10.82**
<i>Attention/Executive Function (T-scores)</i>	47.64 (11.17)	14.0	48.23 (11.24)	12.0	0.43
TMTA	51.78 (8.92)	6.0	51.29 (11.31)	10.1	0.37
TMTB	47.69 (12.03)	12.0	47.63 (13.79)	14.1	0.00
FAB	43.55 (20.25)	21.0	45.64 (15.23)	23.0	1.21
<i>Memory</i>	45.75 (10.38)	13.0	50.15 (9.67)	7.0	24.53**
CVLT LDFR	47.80 (10.50)	7.0	52.25 (10.90)	3.0	25.81**
CVLT Recognition Hits	43.70 (13.14)	19.0	48.05 (12.06)	9.0	12.85**

Note.

**
 $p < 0.01$

Abbreviations—MMSE = Mini Mental State Examination; TMTA = Trail Making Test A ($N = 99$); TMTB = Trail Making Test B ($N = 99$); FAB = Frontal Assessment Battery; CVLT = California Verbal Learning Test; LDFR = Long Delay Free Recall

Table 3

BDI-II and CBF-V Descriptive Statistics

	Baseline mean (SD)	12-Month mean (SD)	F-statistic
CBF-V			
MCA	41.72 (12.08)	39.58 (13.79)	2.79 ($p = 0.099$)
ACA	35.46 (15.85)	35.75 (10.49)	0.05
PCA	28.86 (8.46)	26.50 (6.33)	6.52 *
Global CBF-V	34.61 (9.79)	33.13 (9.15)	4.34 *
Depressive Symptomatology			
BDI-II	7.30 (6.56)	7.23 (6.60)	0.02

Note. Sample sizes for MCA, ACA, and PCA = 87; MCA = middle cerebral artery; ACA = anterior cerebral artery; PCA = posterior cerebral artery;

*
 $p < 0.05$

Table 4

Predictive Validity of Baseline CBF-V on 12-Month Cognitive Function

	MMSE		Attention/Executive Function		Memory	
	β	SE b	β	SE b	β	SE b
Block 1						
Age	-.23*	.02	-.05	.09	.06	.09
Sex	.13	.29	.04	1.84	.01	1.70
Hypertension	.07	.30	.03	1.90	.09	1.76
Diabetes	-.03	.30	.02	1.93	.01	1.76
Sleep Apnea	.01	.35	-.09	2.22	-.07	2.07
Baseline Test Performance***	.46**	.08	.67**	.08	.62**	.08
R ²	.33		.43		.35	
F	9.10**		13.55**		9.78	
Block 2						
CBF-V	.14	.01	.24**	.09	.15	.09
R ²	.34		.48		.36 ψ	
F for ΔR^2	2.65		9.91**		3.03	

Note.

* $p < 0.05$;

** $p < 0.01$;

ψ $p = 0.085$;

Baseline test performance of the 12-month dependent variable was entered as a covariate

Abbreviations: MMSE = Mini Mental State Examination; CBF-V = Cerebral blood flow velocity

Table 5

Predictive Validity of Baseline CBF-V on 12-Month Depressive Symptomatology

	12-Month BDI-II	
	β	SE b
<i>Block 1</i>		
Age	.09	.05
Sex	-.02	1.03
Hypertension	-.04	1.06
Diabetes	.10	1.07
Sleep Apnea	.13	1.24
Baseline BDI-II	.68	.07**
R^2	.49	
F	16.78**	
<i>Block 2</i>		
CBF-V	-.16*	.05
R^2	.51	
F for ΔR^2	4.25*	

Note.

* $p < 0.05$;** $p < 0.01$

Abbreviations: BDI-II = Beck Depression Inventory-II; CBF-V = cerebral blood flow velocity