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Vascular and cognitive functions associated with cardiovascular disease in the elderly

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Abstract

This study examines the relationship between systemic vascular function, neurocognitive performance, and structural brain abnormalities on magnetic resonance imaging (MRI) among geriatric outpatients with treated, stable cardiovascular disease and no history of neurological illness ($n = 88$, ages 56–85 years). Vascular function was assessed by cardiac ejection fraction and output, sequential systolic and diastolic blood pressures, flow mediated brachial artery reactivity (BAR), and carotid intima media thickness (IMT). White matter hyperintensities (WMH) on MRI were quantified and examined relative to cognitive and vascular function. Principal component analysis revealed two primary vascular components: one associated with cardiac function, the other with atherosclerotic burden/endothelial dysfunction. Both factors were significantly associated with cognitive function and WMH volume. Reduced systolic variability and increased IMT were most strongly related to reduced attention, executive function, and information-processing speed. These findings suggest the possibility that systemic vascular indices may provide proxy measures of cerebrovascular dysfunction and reinforce the importance of achieving greater understanding of interaction between systemic vascular disease and brain dysfunction among elderly people with cardiovascular disease.

Keywords

Cardiovascular disease; Cerebrovascular disease; White matter hyperintensities; Magnetic resonance imaging; Flow mediated dilatation intima lamina thickness; Blood pressure variability; Cardiac output; Cognition; Attention; Executive function; Psychomotor function

Vascular cognitive impairments (VCI) occur on a continuum ranging from mild deficits among patients with vascular risk factors such as cardiovascular disease (CVD) to the severe cognitive dysfunction characteristic of vascular dementia (Bowler, Steenhuis, & Hachinski, 1999; Rockwood, 2002; Roman, Erkinjuntti, Wallin, Pantoni, & Chui, 2002). Cardiovascular disease was once thought to convey little risk to the brain given its capacity for vascular autoregulation and sustained cerebral perfusion even under adverse hemodynamic conditions (Lassen, 1964). Brain dysfunction secondary to cardiovascular disease was usually attributed to acute stroke during cardiac surgery (Newman et al., 2001), or in response to cardiac events (e.g., arrhythmia). Yet, patients with severe cardiovascular disease frequently exhibit cognitive problems in the absence of clinically identified stroke (Moser et al., 1999; Paul et al., 2005), particularly in cases of heart failure (Bennett & Sauve, 2003; Bornstein, Starling, Myerowitz, & Haas, 1995), presumably reflecting the impact of reduced cardiac function on the aging brain (Roman, 2004). We have previously shown that both cognitive dysfunction and structural brain abnormalities on magnetic resonance imaging (MRI) are associated with reduced cardiac output among patients with severe cardiovascular disease (Jefferson, Poppas, Paul, & Cohen, 2007a; Jefferson et al., 2007b) and abnormalities of systemic vascular function (Gunstad et al., 2006a; Gunstad et al., 2005; Gunstad et al., 2006b; Haley et al., 2007a; Haley et al., 2007b; Hoth et al., 2007).

It seems intuitive that cerebral hypoperfusion secondary to impaired cardiac function should contribute to CVD-associated cognitive impairments, particularly among patients with heart failure. Yet, not all patients with CVD-associated cognitive problems have heart failure, nor do all patients with heart failure experience brain dysfunction. Therefore, other factors beyond cardiac output must also play a role. CVD-associated brain dysfunction is greatest among the elderly (Rastas et al., 2006; Verhaegen, Borchelt, & Smith, 2003). There is now considerable evidence that the homeostatic mechanisms involved in maintaining hemodynamic regulation break down as people reach advanced age (Bakker et al., 2004; Murkin, 2002; Serrador, Milberg, & Lipsitz, 2005). This is a significant problem as the cerebrovascular system must adapt to momentary changes in hemodynamic state to insure sustained cerebral perfusion of the brain. A variety of pathophysiological processes contribute to a breakdown of cerebral hemodynamic function among the elderly with CVD, including factors that affect endothelial function and smooth muscle reactivity (Kathiresan et al., 2006; Serrador et al., 2005; Verma, Buchanan, & Anderson, 2003). Reduced vasodilatory responses to drug challenge (e.g., nitroglycerin, verapamil) or mechanically induced ischemia provides evidence of endothelial dysfunction that occurs in association with both advanced age and vascular disease (Adams et al., 1998; Bank & Kaiser, 1998; Bank et al., 1995). Dyslipidemia and associated atherosclerosis also play an important role (Claus et al., 1996), as cardiovascular disease is known to contribute to structural changes in cerebral blood vessels, including thickening of the intima media and a breakdown in smooth muscle function (Akopov, Sercombe, & Seylaz, 1996; Tentolouris et al., 2004, 2006; Vita, 2005; White, Deane, Vallance, & Markus, 1998). Chronic blood pressure abnormalities also have detrimental mechanical effects on cerebral hemodynamics (Birns, Markus, & Kalra, 2005; Lorberboym, Lampl, Kesler, Sadeh, & Gadot, 2001; Schmidt et al., 2004). In sum, CVD-associated brain dysfunction among the elderly, without a clinical history of acute stroke, likely depends on a complex interaction of impaired cardiac and cerebral hemodynamic factors. Structural changes of both small and large cerebral vessels occur as the result of atherosclerosis and associated thickening of the intima media. These changes are

amplified when there has been a breakdown of endothelial function and vascular reactivity, particularly in the context of chronic blood pressure disturbance.

Past studies have examined the influence of specific risk factors and pathophysiological processes on the development of brain dysfunction. For example, chronic hypertension is known to contribute to microvascular abnormalities, which has been shown to underlie structural white matter damage and reduced cognitive function in large epidemiological studies (Birkenhager, Forette, Seux, Wang, & Staessen, 2001; de Leeuw et al., 2004; den Heijer et al., 2005; Vermeer, Koudstaal, Oudkerk, Hofman, & Breteler, 2002). We previously examined the influence of specific cardiac and systemic vascular factors on cognitive function and MRI brain abnormalities among the elderly with cardiovascular disease (Gunstad et al., 2005; Haley et al., 2007a; Haley et al., 2007b; Hoth et al., 2007; Jefferson et al., 2007a; Jefferson et al., 2007b; Paul et al., 2005). Yet, to date few studies have examined the simultaneous relationships among cardiac output, blood pressure, and systemic hemodynamic function and measures of brain function and structure. Past studies have investigated these relationships primarily by examining the prevalence of specific risk factors in an epidemiological context (Claus et al., 1996; DeCarli et al., 1999; de Leeuw et al., 2004; Vermeer et al., 2003). Most elderly people with cardiovascular disease have a variety of underlying risk and etiological factors (Martins e Silva & Saldanha, 2007; Terry et al., 2005; Tranche, Galgo, Mundet, & Sanchez-Zamorano, 2005). Accordingly delineating the basis of brain disturbances secondary to cardiovascular disease, in the absence of large vessel stroke, requires simultaneous consideration of multiple biomarkers of cardiac and systemic vascular function and structure. This motivated the current study to explore the relative contributions of cardiac function (cardiac output and systolic blood pressure) and systemic hemodynamic function to cognitive dysfunction and the brain abnormalities in cardiovascular disease patients.

We hypothesized that cognitive performance and MRI brain abnormalities would vary as a function of both cardiac and systemic vascular function among elderly people with cardiovascular disease with no prior history of acute stroke or other neurological brain disease. Patients with both impaired cardiac function (reduced cardiac output, systolic variability) and systemic hemodynamic dysfunction on brachial artery response (BAR) and thickening of the carotid intima media (IMT) would show the weakest cognitive functioning and greater structural abnormality on brain imaging. We studied 88 cardiovascular disease patients to test the hypothesis that neurocognitive dysfunction secondary to cardiovascular disease is associated with two primary vascular factors (cardiac function and systemic vascular health). Patients underwent a vascular assessment that included measures of cardiac output, blood pressure variability, carotid IMT, and BAR. In addition to the vascular assessment, a subset of participants underwent structural brain MRI to assess the severity of white matter hyperintensities (WMH), a proxy measure of cerebrovascular disease. The goal was to determine which vascular factors were most strongly associated with cognitive status and MRI brain abnormalities.

Method

Clinical sample

Participants in the study consisted of 88 elderly patients (age: 70.0 ± 7.7 years) with CVD, recruited from the cardiology services at the Rhode Island Hospital and the Miriam Hospital in Providence, RI. The majority of participants were identified from patients undergoing noninvasive cardiovascular assessment for coronary heart disease and from the Rhode Island Hospital Heart Failure Clinic (A.P.). Demographic and clinical characteristics of the sample are presented in Table 1. Briefly, participants included 47 males (53%) and 41 females (47%) who were clinically treated for cardiovascular disease. Racial/ethnic composition included 76.6% Caucasians, 9.4% African-American, and 1.8% Hispanic. The majority of the

participants were married (65.8%), while 7.9% were divorced, 15.8% widowed, 10.5% never married.

All participants had a documented history of cardiovascular disease including at least one of the following: coronary artery disease (CAD: 73.4%), myocardial infarction (42.9%), heart failure (22.8%), chronic hypertension (76.0%), or cardiac arrhythmia (17.5%). A subset of patients had previously undergone revascularization procedures: angioplasty (19.3%), stenting (14.0%), coronary artery bypass graft (CABG: 32.8%). Determination of cardiovascular risk factors were based on the self-report of all patients during the medical history interview, with independent verification of the presence of specific risk factors derived from medical records and/or discussion with the patients' physicians when possible. Pertinent risk factors and medical histories of the sample included: 76.0% hypertension (76.0%), hypercholesterolemia (59.3%), Type 2 diabetes (22.2%), and smoking (53.2%). A total of 36% of participants endorsed one risk factor, 38% endorsed two, 20% endorsed three, and 6% had all four factors. All participants were receiving ongoing treatment by a cardiologist and were diagnosed as having moderate to severe cardiac disease. The mean New York Heart Scale severity <http://www.hcoa.org/hcoacme/> was 1.86 ($SD = 0.73$). Medication information for the sample was as follows: 88% antihypertensives, 68% aspirin/antithrombotics, 75% lipid lowering agents, 63% vitamins, 42% gastric acid inhibitors, 16% hypoglycemics, 18% vasodilators, and 15.9% psychiatric medications.

Exclusion criteria included a history of neurological disease (e.g., stroke, seizure disorder, Parkinson's disease, traumatic head injury with loss of consciousness for >10 minutes, diagnosis of dementia), substance abuse, and major psychiatric illness (e.g., schizophrenia, bipolar disorder). The study received local institutional review board approval, and all patients gave signed informed consent prior to participation. All participants received monetary compensation for their participation in the study.

Vascular assessment

Participants were asked to refrain from taking vasoactive medications (e.g., calcium channel blockers, ACE inhibitors, and beta blockers), caffeinated beverages, and smoking for 6 hours before the vascular assessment. Furthermore, all participants fasted for 6 hours prior to the assessment. Prior to initiating vascular interrogation, patients remained supine for 15 minutes in a quiet room.

Echocardiogram—A complete, transthoracic echocardiogram was obtained from each participant according to standards put forth by the American Society of Echocardiography. From these data, cardiac output (CO) was derived. CO is the amount of blood in liters per minute that is pumped from the heart to perfuse the systemic circulation. Because the flow is pulsatile, CO is a function of stroke volume and heart rate. Stroke volume is a function of mean velocity of blood flow from the left ventricle multiplied by the area of left ventricular outflow tract measured from the 2D echo image: $CO = (TVI \times CSA) \times HR$, where TVI = time velocity integral, CSA = cross-sectional area, and HR = heart rate. It is recorded with Doppler echocardiography. While this method reflects a noninvasive procedure for obtaining CO, previous research has shown that data generated from such noninvasive procedures strongly correlate with invasive measures of CO (Moulinier et al., 1991).

Blood pressure—An automatic noninvasive blood pressure monitor Press-Mate 8800 (Colin Medical Instruments Corp, San Antonio, TX) was used to assess blood pressure (BP) serially over the course of the vascular assessment. With the participant resting in the fasted state in a quiet, darkened room, BP was measured in the left arm every 10 minutes for 2 hours. Eight BP indices used in past studies were generated, including average resting pressure,

standard deviation, and coefficient of variability (standard deviation divided by average resting pressure) for both systolic and diastolic blood pressure. Pulse pressure and mean arterial pressure were also collected. Mean diastolic and systolic pressures across the sequential blood pressure samples were analyzed, along with the systolic and diastolic variability measures.

Carotid intima media thickness (IMT)—High-resolution B-mode carotid ultrasonography was performed using a 7.5-MHz transducer and an Agilent 5500 machine (Agilent, Andover, MA). IMT was calculated using scans of the far wall of the left common carotid artery approximately 1 cm proximal to the carotid bulb. IMT was defined as the distance between the luminal-endothelial interface and the junction between the media and the adventitia. Automated, objective edge detection software was developed to measure IMT thickness based on a validated technique described previously (Stadler et al., 1996).

Brachial artery flow-mediated dilatation—Peripheral vascular autoregulation and associated endothelial function were assessed by flow-mediated brachial artery vasodilatation using well-established methods (Corretti et al., 2002; Stadler, Ibrahim, & Lees, 1997). High-frequency B-mode ultrasound was used to visualize the brachial vessel. A Hewlett Packard 5500 ultrasound system, equipped with a linear array vascular (7.5-MHz) transducer was used to acquire 2D and Doppler flows of each participant's left arm. Images were obtained in longitudinal orientation approximately 5 cm above the antecubital fossa; straight segments, at least 10 mm, were targeted for optimal assessments. Blood pressure was measured with an automated Datascope accutor 3SAT (Paramus, NJ) in the contralateral arm after more than 10 minutes of rest in the supine position prior to the initiation of any vasoactive maneuvers.

To assess endothelial function, hyperemic (flow-mediated) vascular responses were assessed. First, baseline images of brachial artery diameter and blood flow velocity were recorded for one minute (sequential images, captured and digitized on each R-wave). Thereafter, a 4-cm cuff (positioned on the mid-forearm) was inflated to 40 mm above the baseline systolic blood pressure for 5 minutes so that mechanical ischemia was induced. The same brachial segment was interrogated for 3 minutes after the cuff was deflated (the period of hyperemic flow). An investigator who was blinded to participant characteristics performed analyses of the digital images. Arterial diameter was determined using a validated software algorithm that automatically calculates the average diameter over the selected segment (Yamauchi, Fukuda, & Oyanagi, 2002). Flow-mediated vasodilatation was calculated as the percentage change in diameter from baseline to the maximum diameter induced by reactive hyperemia.

A total of 10 minutes after the hyperemic brachial assessment was completed, endothelial independent-vascular function was assessed by measuring the same portion of the brachial artery, before and 5 minutes after the administration of 0.3 mg sublingual nitroglycerin, a time corresponding to peak vasodilatory responses to nitroglycerin. Nitroglycerin-mediated vasodilation was calculated as the percentage change in arterial diameter from the prenitroglycerine baseline to the diameter after nitroglycerin.

Neurocognitive assessment

All participants completed an extensive neuropsychological assessment including measures of global cognitive functioning, language, memory, attention, executive functioning, psychomotor speed, and visual-spatial ability. The battery included standard neuropsychological instruments with known established reliability and validity (see Table 2) (Yamauchi et al., 2002). All tests were administered and scored by trained research assistants under the supervision of a licensed clinical neuropsychologist (R.A.C.), using standardized procedures. The research assistants who administered the tests were blind to other clinical data

from the vascular and neuroimaging assessments. The testing session was approximately 2 hours in duration.

Neuropsychological test measures were grouped into one of five cognitive domains: (a) *global cognitive functioning*, (b) *language functions*, (c) *visual-spatial abilities*, (d) *learning and memory functions*, and (e) *attention-executive-psychomotor functions*. The following test scores were included in each domain: (a) global: Mini-Mental State Examination (MMSE), Dementia Rating Scale (DRS); (b) language: Boston Naming Test (BNT) total, Animals total; (c) visual-spatial: Block Design total, Hooper Visual Organization Test (HVOT) total, Rey Complex Figure Test (CFT) copy total; (d) memory: California Verbal Learning Test (CVLT) sum of Trials 1–5, total immediate recall, delayed recall, and discrimination, CFT total immediate and delayed recall and discrimination, Brief Visual Memory Test–Revised (BVMTR) sum of Trials 1–3, delayed recall and discrimination; (e) attention-executive-psychomotor functions: Stroop Interference trial time, Trail Making A & B time, Controlled Oral Word Association Test (COWAT) total, Letter Search total time, Digit Symbol Coding total, Digit Span total, and Pegs-D time. The assignment of tests to particular cognitive domains was based on the way these tests have been typically conceptualized in clinical neuropsychology (e.g., Lezak, 1995) and to maintain consistency with our previous studies of cardiovascular disease. Given expectation of greatest cardiovascular disease effects on frontal-subcortical systems, the battery was designed to assess attention and executive functioning using multiple measures. Raw test scores were converted to *z*-scores using sample means and standard deviations. For measures on which the dependent measure was time for task completion (e.g., Trail Making), *z*-scores were multiplied by -1.0 to correct for the fact that a shorter duration indicates better performance. This correction equated the direction of effects for all measures, enabling us to average across the individual *z*-scores to derive a composite index score for each domain. Five composite cognitive domain *z*-scores were calculated for each participant by averaging the *z*-scores of all tests within that domain. Missing individual tests scores were replaced by 0, the mean *z*-score of the sample. Demographic characteristics such as age, education, and gender were entered into analyses as covariates to control for their potential influence on effects.

Cardiac disease risk severity was coded (0 = no risk; 1 = one risk factor; 2 = two risk factors; etc.) based on medical history of hypertension, hypercholesterolemia, diabetes, and tobacco use. Coronary artery disease (CAD) was coded as present if any one of the following conditions was evident from the medical history: myocardial infarction, angina pectoris, coronary artery bypass graft (CABG), or angioplasty/stent placement.

Brain MRI and WMH quantification

Brain MRI was obtained using a Siemens Symphony 1.5 Tesla unit. Sagittal T1-weighted (TR/TE = 500/30) and T2-weighted (TR/TE = 2500/80) conventional spin-echo localizer images and axial T1-, T2-, and fluid-attenuated inversion recovery (FLAIR; TR/TE = 6000/105, slice thickness = 5-mm/2-mm gap) images were obtained for each participant. We used the FLAIR sequence because of its ability to suppress cerebrospinal fluid (CSF) signal and the sensitivity to visualize WMH, as described our previous studies (R. A. Cohen et al., 2002).

The FLAIR images were used to quantify WMH utilizing semiautomated threshold methods with good intra- and interrater reliability. The intraclass correlations were conducted in order to help us feel confident that the technicians were performing the semiautomatic brain measurements in the same way each time. Each rater produced two traces for each of the MRI indices in a small sample of participants ($n = 10$) at two different points in time. Intraclass correlation (ICC) coefficients were determined using SPSS-14 (Shrout & Fleiss, 1979). The derived Kappa correlation coefficients were consistently $>.85$, indicating that brain regions were being measured by each rater in a consistent manner.

The raw FLAIR imaging data was imported into the commercially available Mayo Clinic software program ANAYLZE® (Biomedical Imaging Resource, Rochester, MN) where the skull was stripped and the brain stem and cerebellum removed leaving only the total cerebral brain parenchyma (WBV). Second, using the ANAYLZE® threshold tool, WMH in areas of surrounding parenchyma were isolated for each patient. The total number of pixels reflecting WMH was summed across the slices. Finally, WBV was calculated similarly using threshold histogram values that were consistent with brain parenchyma. The WBV was used as a correction factor for each of the hyperintensity values, and this ratio was the primary imaging variable for this study. It also allows for a more direct comparison between patients controlling for variability in brain size and generalized atrophy as the result of aging. We examined the relationship of WBV to the vascular and cognitive indices.

Data analysis

Descriptive statistics were performed to characterize the sample with respect to demographic and clinical characteristics, neurocognitive performance, and the vascular indices. Pearson correlation coefficients were then calculated between each vascular and cognitive measure. Composite *z*-scores were derived for each cognitive measure based on the study sample. Cognitive domain index scores were then computed by summing across corrected *z*-scores for all tests in a particular domain. Attention-executive, memory, language, and visual integrative composite index scores were derived.

The eight vascular indices (cardiac output, ejection fraction, mean systolic and diastolic blood pressures, systolic and diastolic variance, flow mediated BAR, and IMT) were analyzed by principal component analysis (PCA) and a maximum likelihood factor analysis (FA), with subsequent confirmatory factor analysis based on structural equation modeling using Amos in SPSS-14.0 (2007) used to test for goodness of fit (χ^2). Three methods were used to determine the optimal number of components or factors (Scree test, and Parallel Analysis, PA, and minimum average partial, MAP, procedures). Loadings between retained components and individual vascular indices $>.40$ were considered as statistically significant.

Hierarchical multiple regression analyses were then performed using SPSS 14.0. Analysis of the association between the vascular measures and cognitive function was conducted by domain. The *a priori* hypothesis underlying this study was that significant associations would be observed for the domain of attention, executive functioning, and information-processing speed relative to the vascular indices, whereas that other cognitive domains would not strongly associate with vascular function. These hypotheses led to planned set of regression analyses, with the primary analysis of interest being the analysis of vascular function relative to neurocognitive function. Vascular relationships with the other cognitive domains were analyzed to provide comparison with the executive-attention domain. Accordingly, the examination of associations between vascular function and the other cognitive domains were conducted primarily as a contrast to this primary analysis, and effects were not expected for these domains, alleviating the need for correction for multiple comparisons.

As hypothesized, many of the measures of attention and executive and psychomotor functioning correlated significantly with the individual vascular indices (see Table 3). Accordingly, hierarchical regression analyses were first conducted relative to the attention-executive domain (entry criteria: $p < .05$; removal criteria: $p < .10$), in which age, years of education, Beck Depression Inventory (BDI) score, cardiovascular disease risk score, CAD status, and medication classes were entered in the first step, followed by seven vascular indices (average systolic blood pressure, BP, systolic variability, average diastolic BP, diastolic variability, BAR, IMT, cardiac output). BAR to reactive hyperemia was entered into the analyses, but not BAR in response to the nitroglycerine condition in order to avoid colinearity. The composite indices for each cognitive domain were entered as dependent measures in a

series of five separate regression analyses (attention/executive, learning/memory, language, visual integration). The two vascular component scores from the PCA analysis were then entered in a hierarchical regression with the executive index as the dependent measure and the same covariates as those described above.

In a similar manner, the two MRI indices (WMH, WBV) were treated as dependent measures in subsequent regression analyses, first with the individual vascular entered as independent measures, and then in a second analysis using the two vascular component scores from the PCA. Given that, as hypothesized, the vascular indices were associated with the attention-executive index, a series of subsequent analyses were conducted in which the vascular measures were examined in relation to individual tests from this domain (e.g., Stroop, Trail Making, etc.). A total of 23 cardiovascular disease patients both underwent MRI brain imaging and completed all of the vascular and the neurocognitive tests. Others either chose not to participate in this procedure or were excluded because of medical factors (e.g., pacemakers). In a final set of analyses, the derived components from the PCA were examined by regression analysis relative to each of the composite cognitive factors (Z-scores) and the MRI indices.

Results

Vascular function

Cardiovascular disease patients in the sample exhibited a relatively wide range of findings on the cardiac and vascular indices as shown in Table 1. Older patients (age >75 years) did not differ from younger patients (age <75 years) on most vascular indices, so that we did not stratify patients based on age. Instead age was entered as a covariate in subsequent analyses.

Both the PCA and FA analyses of the eight vascular indices revealed two primary vascular components. The varimax-rotated patterns of variable loadings for the PCA and FA yielded near identical results, strongly supporting a two-component solution. As shown in Table 4, Component 1 was significantly associated with cardiac output, ejection fraction, and systolic variance. Component 2 was most significantly associated with BAR, IMT, and diastolic variance. This two-factor solution accounted for 72% of the overall variance of the vascular indices. The reliability of three indices comprising the cardiac factor (Component 1) as measured by Chronbach coefficient (α) statistic was .83, while the reliability of the three indices comprising the hemodynamic factor (Component 2) was .89.

A confirmatory FA analysis using structural equation modeling was conducted. The three variables associated with the cardiac factor were allowed to load on Component 1, while the other three variables were allowed to load on Component 2. A correlation was estimated between latent constructs and each vascular variable's error variance. This analysis indicated that a significant goodness of fit was the factor structure derived from the PCA and FA analyses, $\chi^2(5) = 22.6, p < .01$.

Vascular and attention-executive functioning—Correlations between the five vascular indices and the neuropsychological measures of attention, executive, and psychomotor functioning, as well as the overall attention-executive index are provided in Table 3. Three of the five vascular indices (IMT, BAR, systolic BP variance) were significantly associated with the attention-executive index and also with various measures from this cognitive domain. Cardiac output approached a significant correlation with the overall attention-executive index ($p = .06$). Diastolic variance did not correlate with the executive index or any of the attention-executive measures.

Stepwise hierarchical regression analysis in which the five vascular indices were entered as independent measures and the attention-executive index was entered as the dependent measure

revealed a significant association, $R = .45$, $F(3, 80) = 7.30$, $p = .001$. Three vascular indices were retained as significant correlates (systolic variance: $\beta = .33$; IMT: $\beta = -.29$; BAR: $\beta = .09$). For this analysis, age, BDI severity, and medication class were not found to be significantly associated with the attention-executive index.

Vascular functioning was significantly associated with each of the individual cognitive measures in the executive index measures. Trail Making A performance, $R = .46$, $F(1, 82) = 6.13$, $p < .02$, was most significantly associated with systolic BP variance ($\beta = .33$) and BAR ($\beta = .15$). Trail Making B performance, $R = .46$, $F(2, 81) = 9.92$, $p < .02$, was most significantly associated with systolic BP variance ($\beta = .43$) and IMT ($\beta = .23$). Letter Cancellation performance, $R = .39$, $F(2, 81) = 4.91$, $p = .01$, was most significantly associated with IMT ($\beta = .30$) and systolic BP variance ($\beta = .22$). Digit Span performance, $R = .46$, $F(2, 81) = 5.23$, $p = .01$, was most significantly associated with IMT thickness ($\beta = -.28$) and systolic BP variance ($\beta = .26$). Stroop performance, $R = .33$, $F(2, 81) = 5.25$, $p = .01$, was most significantly associated with BAR ($\beta = -.20$) and systolic BP variance ($\beta = -.20$). Digit Symbol Coding performance, $R = .36$, $F(2, 81) = 4.77$, $p = .01$, was most significantly associated with IMT thickness ($\beta = -.26$) and cardiac output ($\beta = -.21$). Psychomotor speed on the Grooved Pegboard, $R = .25$, $F(1, 82) = 5.23$, $p = .01$, was most strongly associated with IMT ($\beta = .25$). In summary, the vascular indices were significantly associated with all of the individual measures of attention and executive and psychomotor functioning. IMT and systolic BP variance were the vascular measures that tended to associate with most of the performance measures.

Vascular components and attention-executive function—The two vascular components derived from the PCA were then entered into a similar set of hierarchical regression analyses in which age and the other clinical variables were treated as covariates, and the executive index was treated as the dependent variable. A highly significant association between vascular function and performance on the executive index was found, $R = .67$, $F(1, 82) = 12.30$, $p < .001$. Both Component 1 (cardiac: $\beta = .37$) and Component 2 (systemic vascular: $\beta = .47$) were retained as contributing to this association and together best accounted for the variance in attention-executive function.

Vascular and other cognitive functions—The overall relationships between the eight vascular indices and the other cognitive domain scores (language, visual, memory) were not found to be statistically significant. In sum, BP variability, IMT, BAR, and cardiac output were not strongly associated with cognitive functioning outside the domain of executive functioning, attention, and psychomotor speed. The two component scores from the PCA analyses were entered as independent measures in a similar set of hierarchical regression analyses using the same covariates, though neither vascular component loaded on the other index scores for the other cognitive domains.

Vascular function and structural brain findings—As shown in Table 3, several of the vascular biomarkers significantly correlated with the structural brain MRI indices. Given that a subset of the total sample completed both the MRI and vascular assessments, analyses were conducted to determine whether the patients who underwent MRI differed from those who did not. Patients in this subsample did not differ from those who did not undergo MRI scanning on any demographic characteristics. The two groups did not differ with respect to age, education, or gender. Cognitive function also did not differ between the groups on multivariate analysis of variance (MANOVA; $p > .10$). Furthermore, cardiac disease severity as measured by the New York Heart Scale (NYHS) did not differ between groups, nor did rates for most risk and etiological factors. Patients undergoing MRI assessment had a lower rate of cardiac arrhythmia ($p < .05$), attributable to the exclusion of patients with pacemakers from MRI assessment.

BAR during the reactive hyperemia condition showed the strongest association with both total WMH volume and also with corrected WMH volume (WMH/WBV, where WBV is whole brain volume). Stepwise regression analysis revealed a strong association between the vascular indices and total WMH volume, $R = .77$, $F(2, 20) = 26.09$, $p = .0001$. The vascular factors contributing most significantly to this association were BAR during the reactive hyperemia condition ($\beta = -.74$), though cardiac output was also retained as contributing some variance ($\beta = -.41$). Whole brain volume (WBV) was also significantly associated with vascular function, $R = .67$, $F(2, 19) = 6.87$, $p = .01$, with IMT ($\beta = -.54$) and systolic BP variance ($\beta = .42$) most strongly associated with WBV.

Regression analysis conducted with the vascular component scores from the PCA analysis also revealed significant associations with each of the MRI indices. With respect to WMH, a significant association was found, $R = .78$, $F(1, 20) = 8.32$, $p < .01$. Component 2 was most strongly loaded on WMH volume ($\beta = -.56$) whereas Component 1 showed a weaker loading ($\beta = -.36$). For WBV, a significant association was also found, $R = .56$, $F(1, 20) = 6.25$, $p < .05$, with both components loading on WBV (Component 1: $\beta = .42$; Component 2: $\beta = .40$).

Discussion

The present study demonstrates that cardiovascular and systemic vascular functioning is associated with cognitive performance and structural brain abnormalities on MRI in patients with CVD. This is the first study to date to simultaneously examine measures of cardiac function (cardiac output, systolic variability), along with measures of systemic vascular health (BAR, IMT, diastolic variability) in relationship to measures of cognitive function and brain MRI. These findings provide compelling evidence that cardiovascular disease patients with the greatest systemic vascular dysfunction also have greater cognitive problems and structural brain alterations, independent of any clinical evidence of stroke. These findings provide support for current theories regarding the development of VCI in the absence of acute stroke (Bowler et al., 1999; Rockwood, 2002).

This study was motivated by the hypothesis that brain dysfunction among cardiovascular disease patients without prior history of acute stroke is a byproduct of chronic cerebral hypoperfusion (Roman, 2004), which in turn may be influenced by the interaction of two important vascular pathophysiological factors: (a) impaired cardiac output (Jefferson et al., 2007a; Jefferson et al., 2007b); and (b) systemic hemodynamic dysfunction affecting cerebrovascular autoregulation (Knopman, Mosley, Catellier, & Sharrett, 2005; Launer, Feskens, Kalmijn, & Kromhout, 1996; Messier, Awad, & Gagnon, 2004; Messier & Teutenberg, 2005; Moser et al., 2004; Serrador et al., 2005; Wong, Molyneaux, Constantino, Twigg, & Yue, 2006). Simultaneous examination of cardiac output, blood pressure variability, carotid IMT, and flow-mediated BAR in relationship to neurocognitive and MRI indices provided a method for testing this hypothesis. As hypothesized these vascular indices were strongly associated with cognitive function and MRI abnormalities. Furthermore, both cardiac and systemic hemodynamic factors had significant influence on these effects.

The PCA analysis revealed a two-component solution, which was validated by several methods. This result provides strong evidence that both impaired cardiac output and systemic hemodynamic dysfunction is important in this cohort. The underlying vascular indices examined in this cohort loaded on a cardiac factor and a systemic vascular factor. Furthermore, the vascular indices loaded on these two factors as expected, with cardiac output, ejection fraction, and systolic variability loading on the first "cardiac factor," and IMT, BAR, and diastolic variability loading on the second "systemic vascular factor," providing construct validity. The indices loading on Component 1 are all vascular measures known to be strongly influenced by cardiac function, while those loading on Component 2 are known to relate

strongly to systemic hemodynamic function. While the systemic hemodynamic indices are not direct measures of cerebral vascular disturbance, the fact that they are significantly associated with neurocognitive and MRI abnormalities suggests that they have the potential to serve as proxy measures of cerebrovascular health. Wall thickening of the carotid artery (IMT), decreased vascular reactivity on tests of flow-mediated dilation (BAR), and, more generally, vessel stiffening provides evidence of diminished integrity of systemic vascular structure and function, including the possibility of endothelial or vascular smooth muscle dysfunction (Andresen, Shari, & Bryan, 2006; Hassan et al., 2004; Lavi, Gaitini, Milloul, & Jacob, 2006; Panza, Casino, Kilcoyne, & Quyyumi, 1993). Among people with severe CVD, the effects of these systemic abnormalities on the brain would be compounded in the context of diminished or unstable cardiac function. For example, a patient with heart failure who has greatly diminished cardiac output would experience even greater adverse brain effects if they are unable to sustain stable cerebrovascular hemodynamic function and autoregulation relative to changes in their cardiac output. Conditions associated with rapid fluctuations in perfusion would also likely contribute to further cerebrovascular damage due to mechanical effects of flow changes.

Average diastolic and systolic blood pressures were not significantly associated with cognitive function. This may seem a bit surprising given the association observed in past studies between elevated blood pressure, cerebrovascular disease, and cognitive dysfunction. However, with closer examination these findings are not too surprising, given that all patients in this sample had significant cardiovascular disease, and the majority had a history of hypertension. The sample was obtained from outpatient clinical settings, and all patients were being treated for CVD. The majority were taking antihypertensive medications, and the sample had mean diastolic and systolic blood pressures that were within the average range, though a small proportion of patients remained hypertensive despite being treated. Past studies that have found that associations between hypertension and cognition either have tended to involve large community samples in which the majority of people were healthy or have involved comparisons of hypertensive versus nonhypertensive patients (Elias, D'Agostino, Elias, & Wolf, 1995; Elias, Sullivan, Wolf, & D'Agostino, 2003; Farmer et al., 1990; Lawlor et al., 2005). The current findings suggest that blood pressure taken at the time of the assessment may prove less useful in understanding vascular effects on the brain than are other vascular indices among people being actively treated for their CVD. The fact that systolic blood pressure variability was found to be positively associated with cognitive function is noteworthy. This finding provides further support for the idea that capacity for hemodynamic reactivity is essential for maintaining healthy brain function among cardiac patients with controlled hypertension (HTN).

The fact that the vascular indices were associated not only with cognitive function but also with brain MRI indices is significant, as it supports the hypothesis that vascular dysfunction secondary to cardiovascular disease may cause structural brain alterations. For the most part, the relationships with respect to the cognitive and MRI were theoretically consistent as one would expect attention, executive, and psychomotor function to be most affected in patients with greater WMH (Almeida et al., 2005; Bakker et al., 1999; Breteler et al., 1994; Chalela, Wolf, Maldjian, & Kasner, 2001; R. Cohen, 1993; R. A. Cohen et al., 2002; DeCarli et al., 2001; Deicken, Reus, Manfredi, & Wolkowitz, 1991; de Leeuw et al., 1999; Fernando & Ince, 2004; Gunstad et al., 2005; Knuiman, Folsom, Chambless, Liao, & Wu, 2001; Lazarus, Prettyman, & Cherryman, 2005; R. H. Paul et al., 2005; Roman et al., 2002; Yamauchi et al., 2002). Yet, the findings with respect to the brain MRI indices were somewhat more complicated, although not altogether surprising. Peripheral vascular reactivity measured by flow-mediated dilatation of the brachial artery, was significantly associated with greater volume of brain WMH corrected for WBV, suggesting a possible linkage between cardiovascular disease, diminished endothelial health, and brain changes. Yet, carotid IMT and

cardiac output were associated with WBV, but not WMH, and systolic variability was actually significantly associated with both corrected WMH volume and WBV. Therefore, vascular brain effects may not be limited to white matter damage traditionally associated with microvascular disease, but may relate to cortical atrophy as well. This possibility needs to be explored in future studies examining cortical and subcortical morphometry in relationship to cardiovascular disease vascular dysfunction in larger samples.

Several studies by our group have shown relationships between individual vascular indices and brain functioning in CVD. For example, cardiac output was found to be associated with executive functioning and attention performance (Jefferson et al., 2007a; Jefferson et al., 2007b). BP variability was also found to be associated with cognitive function (Gunstad et al., 2005). Diminished vascular reactivity on BAR to both pharmacological manipulation and reactive hyperemia (Hoth et al., 2007; Moser et al., 2004) and vessel wall thickness as measured by carotid IMT (Haley et al., 2007a) were also found to be associated cognitive functioning and structural brain abnormalities in CVD. These findings suggest that in addition to cardiac function, endothelial health may be important to preservation of cognitive function in the context of cardiovascular disease in the elderly. Our previous analyses suggest that relationships between endothelial function and brain WMH are significant even after controlling for the effects of age and hypertension (Hoth et al., 2007), suggesting that endothelial dysfunction was associated with the presence of structural brain abnormalities beyond these other vascular risk factors. Also, endothelial-dependent vasodilatation is influenced by multiple factors in addition to hypertension, such as hypercholesterolemia and obesity. Therefore, systemic indices, such as BAR and IMT that are sensitive to vascular wall thickening and stiffness, may provide integrated measure of large conduit systemic vascular autoregulation and atherosclerotic burden (Celermajer, Sorensen, Bull, Robinson, & Deanfield, 1994; Corretti et al., 2002).

Consistent with our past studies of vascular dementia (R. A. Cohen et al., 2002; Moser et al., 2001) and also cardiovascular disease (Haley et al., 2007a; Hoth et al., 2007; Paul et al., 2006), the relationship of the vascular and MRI indices to cognitive function was almost entirely observed on timed tasks requiring rapid processing speed. In contrast, there were few effects observed for tasks without processing-speed demands. Accordingly, the current findings suggest that processing speed is the function most associated with abnormalities of systemic vascular function and also with white matter abnormalities on MRI. This finding fits with expectation given that cerebral microvascular abnormalities associated with severe cardiovascular disease are known to have the greatest effects on the white matter of the brain and frontal-subcortical systems (Paul, Cohen, Ott, & Salloway, 2004). It does not appear that these processing-speed effects are primarily attributable to motor speed disturbances for several reasons. Performance on the Grooved Pegboard Test was less strongly associated with vascular function than some of the other attention-executive measures. Also, findings from our recent functional brain imaging studies of cardiovascular disease patients indicate that the vascular indices used in the current study were strongly associated with processing speed related to working-memory performance and associated brain activation on a 2-back task having minimal motor demands (Haley et al., 2007b).

The study has some limitations that warrant mentioning. By study design, the sample was composed of patients whose cardiovascular disease severity ranged from mild to severe, with some heterogeneity in etiology. For example, patients with severe cardiovascular disease tended to have greater heart failure. Most patients had histories of HTN, atherosclerosis, and other cardiovascular disease risk factors, though the exact mix of these factors varied across individuals. A study of this type without sufficient sample heterogeneity would not be feasible, as patients would not differ sufficiently on the vascular variables of interest. By including patients with cardiovascular disease heterogeneity and a range of severity, we were able to

observe a broad range of disturbance across the vascular indices, enabling simultaneous examination of the contribution of multiple vascular factors. While this heterogeneity has a cost of reducing some experimental control achievable with a more homogeneous group, it has the benefit of making our sample representative of the population of elderly cardiovascular disease patients in the real world. Accordingly, sample heterogeneity offers many advantages when trying to account for relative effects of multiple risk and etiological influences typical in cardiovascular disease.

Another limitation stems from the fact that the majority of patients in the sample were actively being treated with medications for their CVD, most notably drugs to control hypertension. Since it is not realistic to take patients off of their medications, it would be impossible to completely eliminate this potential confound. Yet, there appears to be little systemic influence of particular medications based on analyses conducted by comparing cognitive performance by medication class and also when medications were treated as covariates. Also, this study examined the association among vascular factors, neurocognitive function, and structural brain abnormalities at a single point in time. While this enabled tests of specific hypotheses, it does not permit conclusions regarding causality. Future prospective longitudinal studies are needed with experimental designs aimed at examining the influence of specific vascular factors on the development of brain dysfunction.

Findings regarding the relationship between the vascular function and structural MRI brain abnormalities were based on a subset of patients, raising the possibility that this subgroup was not representative of the full sample. Yet, patients who underwent MRI did not differ from the group as a whole with respect to demographic, neurocognitive, cardiac disease severity, or most vascular risk and etiological factors, mitigating against the smaller sample size for the MRI analyses being a significant concern. Furthermore, associations among systemic vascular function, structural brain abnormalities, and neurocognitive performance were entirely consistent with a priori hypotheses.

In summary, the current findings suggest that cardiac and systemic hemodynamic dysfunction likely contribute to the development of brain dysfunction among cardiovascular disease patients without prior evidence of stroke or other neurological brain disease. The results point to the possible involvement of atherosclerotic load and endothelial and vascular smooth muscle function as factors that may underlie systemic and ultimately cerebral hemodynamic function. However, these findings must be viewed as an initial step in understanding these relationships, as the causal bases of these vascular effects cannot be fully ascertained from this cross-sectional analysis. Future large-scale prospective studies will be important to determine the direction of this relationship. The findings underscore the potential importance of interventions to improve systemic vascular function, given the possible deleterious effects of cerebrovascular changes. Future research combining measures of vascular function, neuroimaging, and functional outcomes in longitudinal experimental designs will help to clarify the relative roles of diminished cardiac and systemic vascular function, including endothelial health, in the development of VCI and associated structural and functional brain abnormalities.

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TABLE 1
Characteristics of sample

	Mean	Range
Demographic-clinical variables		
Age (years)	72.2 (7.7)	56–85
Education (years)	14.3 (2.7)	9–20
Mini Mental Status Exam Score	28.8 (1.1)	26–30
Beck Depression Inventory	4.2 (2.5)	1–9
Vascular indices		
Systolic BP variability: Mean (mm Hg)	129.3 (19.5)	87.2–186.8
Systolic BP: Standard deviation (mm Hg)	8.3 (5.7)	0.0–28.6
Diastolic BP variability: Mean (mm Hg)	68.5 (10.1)	52.2–90.4
Diastolic BP: Standard deviation (mm Hg)	5.8 (3.2)	0.0–15.2
Ejection fraction	0.62 (0.13)	0.25–0.80
Cardiac output (l/m)	4.6 (1.2)	2.5–9.6
IMT (mm)	0.88 (0.13)	0.61–1.19
BAR–reactive hyperemia	5.9 (4.5)	0–14.6
BAR–nitroglycerine (% increase)	15.6 (6.8)	3.5–25.7
Brain MRI indices ($n = 23$)		
WMH/WBV (ratio)	0.68 (1.22)	0.02–5.47
WBV (mm ³)	1226.8 (155.9)	886.9–1574.9

Note. Standard deviations in parentheses. BP = blood pressure. IMT = intima media thickness. BAR = brachial artery response. WMH = white matter hyperintensities. WBV = whole brain volume.

TABLE 2

Neuropsychological performance among cardiovascular disease patients

Test measures by domain	Mean (SD)	Range
Global cognitive functioning		
MMSE	28.4 (1.7)	23–30
DRS	137.3 (5.3)	116–144
Language		
BNT	54.7 (5.1)	36–60
Animals	19.8 (5.3)	8–36
Visual-spatial		
HVOT	23.5 (3.5)	17–30
CFT–Copy	30.6 (5.6)	13–36
Block Design	32.1 (11.1)	10–60
Memory		
CVLT Long Delay	8.9 (3.5)	0–10
CFT–Delay	14.2 (7.3)	0–34
BVMT-R Delay	7.1 (3.1)	0–12
Attention-executive-psychomotor		
Trail Making A	39.0 (12.9)	16–93
Trail Making B	100.9 (53.0)	34–300
Letter Cancellation	92.9 (25.8)	49–200
Stroop Interference Trial	30.9 (9.5)	10–72
COWAT	40.1 (12.7)	12–75
GPB-dominant	93.9 (25.1)	56–206
Digit Span	17.5 (3.7)	8–28
Symbol Coding	54.9 (14.5)	18–98

Note. Tests included in the neuropsychological battery are listed along with the mean and standard deviation and range of raw scores for the total sample. MMSE = Folstein Mini-Mental State Examination; DRS = Dementia Rating Scale-2; WAIS-III FSIQ = Wechsler Adult Intelligence Scale-III Full Scale Intelligence Quotient; BNT = Boston Naming Test; Animals = Category Fluency-Animal Naming; HVOT = Hooper Visual Organization Test; CFT = Rey Complex Figure Test; Block Design = Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) Block Design; CVLT = California Verbal Learning Test; BVMT-R = Brief Visual Memory Test-Revised; COWAT = Controlled Oral Word Association Test; GPB = Grooved Pegboard; Digit Span and Digit Symbol = WAIS-III subtests. As indicated by the range of scores for most tests, CVD patients differed rather dramatically in their performance across the sample.

TABLE 3

Associations among vascular, cognitive, and MRI indices

Cognitive	IMT	Systolic variability	BAR	CO	Diastolic variability
Executive index	-.34 ^{***}	.19 [*]	.19 [*]	.13 [#]	.07
COWAT	-.20 [*]	-.06	.28 ^{**}	-.19 ^{**}	-.06
Digit Span	-.26 ^{***}	-.04	.21 [*]	.04	.05
GPB	.23 ^{**}	.10	-.12	.06	.09
Letter Cancellation	.33 ^{***}	.15 [*]	-.18 [*]	-.15 [*]	.02
Stroop	-.29 ^{**}	-.16 [*]	.25 ^{**}	-.09	.06
Coding	-.31 ^{***}	-.12 [#]	.17 [*]	-.12 [#]	-.09
TMT A	.14 [#]	.14 [*]	.04	.07	.07
TMT B	.32 ^{***}	.16 [*]	.06	.10	-.03
Language index	.08	.03	.08	.02	.01
Visual index	.09	.07	.04	.08	.07
Memory index	.10	.11	.05	.10	.07
MRI					
Total WMH	-.63 ^{**}	.22	-.14	.01	-.15
WMH/WBV	-.49 ^{**}	.28	.18	.01	-.14
WBV	.26	-.29 [*]	-.35 ^{**}	-.32 [*]	-.23 [#]

Note. Statistically significant associations are reported in **bold**. Columns are in the order of their strength of association with the attention-executive index (sum of Z-scores for each measure in this domain). COWAT = Controlled Oral Word Association Test. GPB = Grooved Pegboard. TMT A = Trail Making Test A. TMT B = Trail Making Test B. MRI = magnetic resonance imaging. WMH = white matter hyperintensities. WBV = whole brain volume.

* $p < .05$.

** $p < .01$.

*** $p < .001$.

[#] Effect approached statistical significance ($p = .06-.08$).

TABLE 4

Principal component analysis of vascular indices

Vascular measure	Component 1 (Cardiac)	Component 2 (Systemic vascular)
CO	.86	—
Systolic variance	.76	—
Ejection fraction	.56	—
IMT	—	.80
Diastolic variance	—	.68
BAR: Flow mediated	—	.48
Systolic BP: mean	—	—
Diastolic BP: mean	—	—

Note. CO = cardiac output. IMT = intima media thickness. BAR = brachial artery response. BP = blood pressure.