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Vascular Health and Cognitive Function in Older Adults with Cardiovascular Disease

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Abstract

Background—We hypothesized that changes in vascular flow dynamics resulting from age and cardiovascular disease (CVD) would correlate to neurocognitive capacities, even in adults screened to exclude dementia and neurological disease. We studied endothelial-dependent as well as endothelial-independent brachial responses in older adults with CVD to study the associations of vascular responses with cognition. Comprehensive neurocognitive testing was used to discern which specific cognitive domain(s) correlated to the vascular responses.

Methods—Eighty-eight independent, community-dwelling older adults (70.02+7.67 years) with mild to severe CVD were recruited. Enrollees were thoroughly screened to exclude neurological disease and dementia. Flow-mediated (endothelial-dependent) and nitroglycerin-mediated (endothelial-independent) brachial artery responses were assessed using 2-d ultrasound. Cognitive

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functioning was assessed using comprehensive neuropsychological testing. Linear regression analyses were used to evaluate the relationships between the endothelial-dependent and endothelial-independent vascular flow dynamics and specific domains of neurocognitive function.

Results—Endothelial-dependent and endothelial-independent brachial artery responses both correlated with neurocognitive testing indices. The strongest independent relationship was between endothelial function and measures of attention-executive functioning.

Conclusions—Endothelial-dependent and endothelial-independent vascular responsiveness correlate with neurocognitive performance among older CVD patients, particularly in the attention-executive domain. While further study is needed to substantiate causal relationships, our data demonstrate that brachial responses serve as important markers of risk for common neurocognitive changes. Learning and behavior-modifying therapeutic strategies that compensate for such common, insidious neurocognitive limitations will likely improve caregiving efficacy.

Keywords

Cardiovascular Disease; vascular function; age; endothelium; neurocognitive performance

Introduction

Many studies have demonstrated a prominent role of vascular health in normal systemic physiology[1-3]. However, age[4], cardiovascular risk factors[5], and cardiovascular disease[6] adversely affect vascular health. Associated changes in endothelial-mediated and endothelial-independent vascular flow dynamics diminish blood delivery throughout the vascular tree and often lead to cardiovascular events[7-10]. Consistently, abnormal vascular flow responses have been demonstrated to predict increased cardiovascular morbidity and mortality[11-13]. In particular, non-invasive assessments of brachial artery, both flow-mediated (endothelial-dependent) and nitroglycerin-mediated (endothelial-independent) dilation are popular techniques that can be used to gauge systemic vascular responses and thereby predict increased cardiovascular risk[14].

In this study, we hypothesized that vascular flow dynamics that underlie increased susceptibility to cardiovascular events among older adults may correlate with vascular-mediated neurocognitive capacities. We analyzed older adults with cardiovascular disease (CVD) particularly because both age and CVD affect vascular physiology[15] and might thereby constitute compounding risks for insidious neurocognitive sequelae. Likewise, while management for CVD in older adults typically centers on lifestyle modifications and medications, such options presume that older adults have sufficient cognitive capacities to grasp complex instructions and/or behavior-modifying goals. Our study explores whether age and cardiovascular disease correlate to neurocognitive changes that may undermine such therapeutic and management objectives.

Multiple studies have demonstrated the role of vascular health in determining cognitive function[16-24], ranging from mild cognitive impairment to vascular dementia. In two earlier studies, investigators used invasive techniques to distinguish endothelial vascular responses in elderly patients with atherosclerosis and to analyze correlations to global cognition[25, 26]. In contrast to these investigations, we employed brachial flow-mediated dilation, a more convenient non-invasive measure of endothelial function, to analyze vascular responses and cognition. We also analyzed brachial artery responses to nitroglycerin, an endothelial-independent vascular response, to see if extra-endothelial factors (e.g., smooth muscle responsiveness, vessel stiffness) also correlated to cognition. Furthermore, we used comprehensive neurocognitive testing, a more discriminating assessment of cognition,

enabling us to isolate the specific cognitive domains that correlated with differences in endothelial-mediated and non-endothelial-mediated vascular responses.

We recruited older independent, community-living adults with no prior histories of neurological disease or dementia, but with a broad range of antecedent cardiovascular diseases. Whereas the two previously mentioned studies by Moser et al. enrolled only patients with atherosclerotic disease[25, 26], we enrolled older adults with hypertension, heart failure, arrhythmia, as well as atherosclerosis, because all are highly prevalent with aging[15] and we wanted to study vascular flow responses and cognition in a population of typical elderly adults.

Methods

Clinical sample

Participants between the ages of 55 and 85 were recruited from cardiology outpatient clinics, cardiac rehabilitation programs, and community fliers in Providence, RI and vicinity. Volunteers were screened for participation if they had a documented history of at least one of the following: diagnosis of coronary artery disease (CAD), angina pectoris, previous myocardial infarction (MI), heart failure, cardiac surgery, arrhythmia or hypertension. Patients were excluded from the study if they had a history of neurological disease (i.e., large vessel stroke, seizure disorder, Parkinson's disease, clinically significant traumatic brain injury, multiple sclerosis, brain infection/meningitis, or diagnosed dementia), major psychiatric illness (e.g. schizophrenia, bipolar disorder), substance abuse (i.e., diagnosed abuse and/or previous hospitalization for substance abuse), or if they scored below the cut off for dementia (total score < 24) on the Mini Mental Status Exam (MMSE)[27].

Of over 300 screened volunteers, 176 fit the cardiac disease and age profile. Five participants were excluded for low MMSE scores. Brachial assessments and complete cognitive test data were available on 86 participants. Demographic and clinical characteristics of the study population are presented in Table 1. Briefly, participants included 46 males (53%) and 40 females (47%), with mean age 70.0 ± 7.7 years. Racial/ethnic composition consisted of Caucasian (76.6%), African-American (9.4%), and Hispanic (1.8%) participants. While the majority of the participants were currently married (65.8%), 7.9% were divorced, 15.8% widowed, and 10.5% had never married.

All participants had a documented history of cardiovascular disease including at least one of the following: coronary heart disease (73.4%), myocardial infarction (42.9%), heart failure (22.8%), chronic hypertension (76.0%), or cardiac arrhythmia (17.5%). A subset of patients had been revascularized: angioplasty (19.3%), stenting (14.0%), and coronary artery bypass surgery (32.8%).

Pertinent risk factors and medical histories of the sample included: systolic or diastolic hypertension (76.0%), hypercholesterolemia (59.3%), Type II diabetes (22.2%), and smoking history (53.2%). Thirty-two percent of participants described having one risk factor, 40% described having two, 12% had three, and 8% had all four risk factors.

Medication usage included: antihypertensives (88%), aspirin/antithrombotics (68%), lipid lowering agents (68%), vitamins (48%), gastric acid inhibitors (44%), hypoglycemics (12%), vasodilators (8%), and psychoactive medications (8%). The study received local institutional review board approval and written informed consent was completed and documented for all participants.

Brachial Artery Flow-Mediated Dilation

Peripheral vascular autoregulation and associated endothelial function were assessed by flow-mediated brachial artery vasodilation[14]. Participants were asked to hold vasoactive medications (i.e., calcium channel blockers, ACE inhibitors and beta blockers), smoking, food, and drinks for 6 hours before the vascular assessment. Immediately prior to vascular assessments, patients remained supine for 15 minutes in a quiet room. Blood pressure was measured with an automated Datascope Accutorr 3 SPA (Paramus NJ) on the right arm and vascular measures were obtained using the left arm.

High frequency B-mode ultrasound was used to visualize the brachial artery. A Hewlett Packard 5500 ultrasound system, equipped with a linear array vascular (7.5 MHz) transducer was used to acquire 2-D and Doppler flows of the left arm. Images were obtained in longitudinal orientation approximately 5 cm above the antecubital fossa; straight segments, at least 10 mm were interrogated, providing optimal assessments.

To assess endothelial function, hyperemic (flow-mediated) endothelium-dependent vascular responses were elicited. 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 mg above the baseline systolic blood pressure for 5 minutes, inducing mechanical ischemia. The cuff was then deflated and the same brachial segment was imaged for the next 3 minutes (the period of hyperemic flow).

Ten minutes after the endothelial-dependent hyperemic brachial assessment was completed, endothelial independent-vascular function was also assessed at the same portion of the brachial artery. Ultrasound images were obtained before and 5 minutes after the administration of 0.3mg sublingual nitroglycerin, a time corresponding to peak vasodilatory responses to nitroglycerin.

Vascular measurements of digitized ultrasound images were completed by an investigator who was blinded to subject characteristics. Arterial diameter was determined using a validated software algorithm that automatically calculates the average diameter over the selected segment[28]. Flow-mediated and nitroglycerin-mediated vasodilation indices were calculated as the percentage changes in diameter from baseline to the maximum diameters induced by reactive hyperemia and nitroglycerin respectively.

Neurocognitive Assessment

All participants completed a comprehensive neurocognitive battery including measures of global cognition, language, memory, attention, executive functioning, psychomotor speed, and visual-spatial ability. The battery included standard instruments with established reliability and validity [27, 29-40] (see Table 2). All tests were administered and scored by a trained research assistant under the supervision of a licensed clinical psychologist, using standardized procedures. Testing sessions were approximately two hours long.

Neurocognitive test measures were grouped into five cognitive domains: 1) *global cognitive functioning*; 2) *language*; 3) *visual-spatial abilities*; 4) *learning and memory functions*; and 5) *attention-executive-psychomotor functions*. The following test indices were collected in each domain: 1) *global*: Mini-Mental State Examination (MMSE)27, Dementia Rating Scale (DRS)29,30; 2) *language*: Boston Naming Test (BNT)31, Categorical Fluency for Animals32; 3) *visual-spatial*: Hooper Visual Organization Test (HVOT)33, Rey Complex Figure-Copy (CFT-copy)32, Wechsler Adult Intelligence Scale (WAIS)-III Block Design Subtest34; 4) *learning and memory*: California Verbal Learning Test –Revised (CVLT-R)35, total immediate recall, delayed recall, and discrimination, Complex Figure Test

(CFT)32-total immediate and delayed recall and discrimination, Brief Visuospatial Memory Test-Revised (BVMT-R)36 delayed recall and discrimination; 5) *attention-executive-psychomotor functions*: Trails A & B37, Stroop[38], Controlled Oral Word Association test (COWAT)[39], Letter Search34 total time and errors, Digit-Symbol Coding total34, Digit-Span total34, and Pegs-D[40] time.

Cardiovascular disease risk was stratified using a simple score. Past medical history of hypertension (systolic or diastolic), hypercholesterolemia, diabetes, and/or tobacco abuse were each assigned one point, with the CVD risk score (0 to 4) used to grade the relative magnitude of CVD risk on vascular performance. Similarly, coronary heart disease (CHD) was stratified using a simple CHD score. Past medical history of myocardial infarction, angina, CABG, or angioplasty / stent placement were each assigned one point, with a CHD score (0 to 4) used to grade the relative magnitude of CHD on vascular performance. These scores, along with both systolic and diastolic blood pressures were treated as covariates in subsequent analyses to determine whether associations between the brachial responses and cognitive domains existed beyond the influence of these CVD-associated factors.

Data Analysis

Descriptive statistics were performed to characterize the sample with respect to demographic and clinical characteristics, neurocognitive performance and the brachial responses. Analyses of variance (ANOVA) were conducted to compare the brachial responses as a function of gender and race.

Vascular responses constituted the primary independent measures for all subsequent analyses, and indices of cognitive performance were the dependent measures. Pearson correlation coefficients were calculated for each of the brachial response measures relative to each of the individual neurocognitive domains, the cognitive indices comprising the executive-attention index, and also the demographic and clinical variables, including individual CVD risk factors and medications. Regression analyses were performed to examine the strength of association between the brachial flow-mediated and nitroglycerin-mediated brachial responses and the composite z-score index for each cognitive domain. The dependent cognitive indices were organized as composites of tests, with groups oriented to 1. attention-executive function; 2. language; 3. visual integration; 4. learning/memory; and 5. global cognitive functioning.

Cognitive domain indices were created by deriving the transformed z-score for each test included in a particular domain, and then summing the across z-scores, such that negative z-scores on a particular test always indicated poorer performance. The following composite cognitive indices were derived: 1) Attention-executive index = Digit Span Backwards + COWAT + Stroop Interference Trial + Stroop Color Naming + Symbol Coding + Letter Cancellation + Trail Making A + Trail Making B + Grooved Pegboard; 2) Language = Vocabulary + Boston Naming + Animal Naming + Comprehension; 3) Visual = Block Design + Hooper Visual Organization Test + Complex Figure Copy; 4) Learning/Memory = CVLT-Total + CVLT-Long Delay + CVLT-Discrimination + BVMT-Total Recall + BVMT Delayed Recall + BVMT Discrimination + CFT-Delayed recall + Logical Memory II; and 5) Global = FSIQ + DRS-Total + MMSE. Based on our previous work[20], we hypothesized that the attention-executive performance would be the cognitive domain most affected by vascular properties. Nonetheless, regression analyses were also conducted to assess the relationship between vascular performance and other cognitive domains, insuring that we would underscore the relationship of vascular performance on attention-executive capacities, and also discern any unanticipated relationships between vascular performance and other cognitive domains.

Separate stepwise multiple regression analyses with backwards removal of variables were then performed using SPSS 14.0 (SPSS Inc., Chicago, IL) to examine the relationship of the brachial responses (flow- and nitroglycerin-mediated brachial responses grouped together) and each of the five cognitive domains. Clinical and demographic measures were entered in the regression analysis, including age, gender, race, years of education, Beck Depression Inventory (BDI) score, diastolic and systolic blood pressures (means), CVD risk factors score, CHD severity index, and medications used by the patients. Medications were coded by class (Beta-blockers, ACE-inhibitors, Other Vasodilators, NSAIDS, Psychiatric medications) and entered as binary values based on whether or not a patient was taking that drug class. The two brachial indices (flow-mediated and nitroglycerin-mediated) were entered along with the demographic and clinical variables in the regression. A significance level $p < 0.10$ was required for independent measures to be included in the regression model. Measures were retained as significant associates of cognitive function if they met a significance level of $p < 0.05$. This regression approach was conducted in an identical manner for each cognitive domain.

Results

Overall, flow-mediated (endothelial-dependent) brachial responses were significantly associated with nitroglycerin-mediated (endothelial-independent) brachial responses ($r = .34$, $p<.01$) (Table 3), and neither correlated with age, gender, education, or race. Similarly, T-tests comparing brachial responses relative to gender and race did not demonstrate significant differences.

In contrast, severity of coronary artery disease, as measured by the CAD index was significantly correlated with nitroglycerin-mediated brachial responses ($r = -.22$, $p<.05$), but not with flow-mediated brachial responses. Similarly, the CVD risk score ($r = -.20$, $p<.05$) and diabetes history ($r = -.20$, $p<.01$) correlated with nitroglycerin-mediated vascular responses but not to endothelial-mediated responses. Among other CVD risk factors, current smoking was strongly associated with both nitroglycerin- ($r = -.34$, $p<.01$) and flow-mediated ($r = -.45$, $p<.01$) brachial responses. None of the other CVD risk and etiological factors correlated with the brachial response indices.

Brachial Responses and Cognitive Function

Many of the individual tests comprising the Attention-Executive composite index significantly correlated with both brachial responses to both flow- and nitroglycerin-mediated brachial responses (see Table 3).

In stepwise regression analysis, the two brachial response assessments (brachial flow- and nitroglycerin-mediated responses) were entered simultaneously along with the clinical and demographic indices (age, gender, education, race, systolic and diastolic blood pressure, CVD risk score, and CAD index), with the Attention-Executive composite index as the dependent measure (Table 4). A highly significant association was demonstrated ($R = .64$, $F(2, 66) = 14.20$, $p<.0001$), and the brachial flow-mediated responses were retained as the factor most strongly associated with attention-executive performance ($\beta = .59$, $p<.001$). The endothelial-dependent brachial flow-mediated responses accounted for 29.9% of the variance in this cognitive domain. Race was the only other clinical or demographic variable retained in the regression analysis as relating to attention-executive performance ($\beta = -.34$, $p=.01$), though it accounted for only 10% added variance above the brachial flow-mediated effect.

Similar regression analyses were conducted with the other four cognitive domains (Learning-Memory, Language, Visual, and Global Cognition). These analyses failed to

reveal significant relationships between cognitive performances across these domains to either brachial flow- or nitroglycerin-mediated responses. In contrast, age, education, and gender were significantly associated with performance on Global Cognitive ($r = .46$, $p < .01$), Memory ($r = .42$, $p < .01$), and Language ($r = .33$, $p < .05$).

In a secondary analysis, the independent association between brachial nitroglycerin-mediated dilation and attention-executive function was examined using stepwise regression analysis, with flow-mediated assessments removed from the analysis. These endothelial-independent responses were significantly associated with performance on the Executive-Attentional Index ($R = .32$, $F(1, 67) = 7.31$, $p = .01$). However, the association was relatively weaker than the combined (flow- and nitroglycerin-mediated) vascular assessments; nitroglycerin-mediated responses accounted for only 10% of the variance in cognitive performance. No other clinical or demographic variables were retained as significantly associated with the Attention-Executive Index in this analysis.

Reanalysis of the data was also completed with exclusion of patients who had been revascularized (stent or CABG). However, this did not yield any significant changes in the results, i.e. the correlations between vascular responses and cognitive changes are not attributable to iatrogenic effects of revascularizaton procedures.

Discussion

Endothelium-dependent, flow-mediated brachial artery dilation was found to be significantly associated with attention, executive functioning, and processing speed in elderly patients with antecedent cardiovascular disease. Our data build upon previous findings that established a link between peripheral vascular reactivity and brain functioning[25,26]. Moser and colleagues studied elderly individuals with atherosclerotic vascular disease and demonstrated that diminished peripheral small vessel reactivity following infusion of vasoactive drugs was associated with decreased global cognition. Our analyses extend these results, demonstrating vascular-cognition interrelationships in a broader patient population, even those who are community-dwelling, independent, and considered neurologically stable. We also extended Moser et al's findings, by substituting prior reliance on a broad scale of cognitive function (the Repeatable Battery for the Assessment of Neurophyschological Status or RBANS) with more comprehensive neuropsychological testing that enabled us to show that the vascular-cognition relationships were strongest for attention-executive functioning (and processing speed), domains typically associated with CVD, even in the absence of stroke. We also utilized a more familiar non-invasive technique of endothelial assessment, i.e., brachial flow-mediated dilation.

Our work also extends upon previous analyses from our own laboratory[20], i.e., broadening upon our assessments between endothelial-mediated brachial responses and MRI-based brain imaging[20]. In that prior investigation, we demonstrated brachial flow-mediated responses correlated to white matter hyperintensities in brains of older adults with cardiovascular disease[20]. Data from this study demonstrate that brachial responses correlate specifically to neurocognitive changes in the attention-executive domain, i.e., capacities of rapid processing speed, but not with language, visual-spatial abilities, or memory. Such neurocognitive attributes correspond to frontal lobe function, and is consistent other studies that have described relationships between CVD and frontal lobe changes[25,26,41].

Susceptibility of attention and executive functioning to CVD may result from several factors. Cerebral hypoperfusion secondary to CVD may preferentially affect subcortical white matter pathways[42] reducing information processing speed and efficiency. Frontal-

subcortical systems are thought to be particularly susceptible to cerebrovascular effects, as evident in patients with vascular dementia [18, 42].

None of patients in our study population had a diagnosis or clinical evidence of dementia or other neurological brain disease. Therefore our findings suggest that vascular-mediated attention-executive abnormalities are widespread even among independent, community dwelling adults who are considered neurologically healthy. Confounding issues of CVD risk factors abnormality (e.g., hypertension (systolic or diastolic), smoking, diabetes, hypercholesteremia) did not alter our observed relationship, nor did prior history of CAD or revascularization. The data imply that endothelial dependent and endothelial-independent peripheral vascular reactivity, as a composite measure of vascular health, is more closely related to cerebral/cerebrovascular capacities that influence neurocognitive performance than any risk factor considered individually or as composite risk factor score. Consistently, our results suggest that vascular reactivity is an independent determinant of specific aspects of cognition, above and beyond the presence of these conditions.

Notably, the magnitude of the relationship between endothelium-dependent, flow-mediated dilation to cognitive function was greater than that of nitroglycerin-mediated vasodilation. While causality cannot be inferred on the basis of correlations, the relative strength of the observed effects suggests that endothelial-mediated vascular dynamics have relatively more impact on cerebral blood supply and neurocognition. However, our data also demonstrate that nitroglycerin-mediated vasodilation (endothelial-independent) correlate to cognition, suggesting that vascular-cognitive relationships are complex. Correlation of cognition to endothelial-independent indices is consistent with the conclusions demonstrated by Moser et al[26] as well as Scuteri et al's assessments of vascular stiffness23, 24.

A variety of vascular components may lead to endothelial-independent influences of vascular performance on cognition. Age and cardiovascular disease both lead to vessel wall fibrosis and stiffening. Medial calcification deposits, elastic breakdown, collagen cross-linking, and intimal-medial thickening confer predominant vascular stiffening[46, 15, 43, 44], i.e., changes that can hinder the normal ventricular-vascular coupling dynamics and can contribute to progressive impedance and progressive potential for peripheral hypoperfusion[6]. Oxidative stress may compound propensity for endothelial-independent vascular abnormalities[45, 46]. Accumulating free radicals with age and disease can interrupt normal smooth muscle vasodilatory mechanisms, i.e., diminishing vasodilatory responses to exogenous as well as endogenous nitrates. Ultimately, endothelium-dependent and endothelium-independent vascular abnormalities both likely compound one another, i.e., diminished auto-regulation due to the limiting effects of intrinsic vessel stiffening, smooth muscle changes, and endothelial changes[47].

Evidence of a general relationship between vascular regulation and cognition has been known for many years in the field of psychophysiology[48]. Heart rate, blood pressure, and autonomic physiological responses have been shown to be associated with attention, learning, and other cognitive operations[49]. In this study we broaden the vascular physiological-cognitive paradigm with demonstration that endothelial- and nitroglycerin-mediated brachial responses also correlate to cognition.

While our analyses were potentially limited by confounding effects of vasoactive medications (to insure patient safety, we only held medications on the morning of vascular assessments, i.e., time that may have been insufficient to fully mitigate medication effects), we controlled for medication effects statistically (specifically factoring in the effects of beta blockers, ACE inhibitors, calcium channel blockers, nitrates, anti-inflammatory medications, and psychiatric medications). We found that medications did not influence our primary

results. Likewise, as noted above, whether or not patients had been revascularized (with PCI or CABG) did not change the results.

Another limitation of this study is its relatively small size and lack of neurovascular imaging data to substantiate that changes in cerebral blood flow are specifically linked to neurological pathology in a causal relationship. While we used careful methodology to try to clarify the relationship between peripheral vascular responses and cognition, residual confounders may have influenced vascular perfusion and neurocognition, and may have affected our assessments Therefore, further investigations are essential, particularly prospective studies specifically analyzing cerebrovasular flow and neuroanatomic sequelae, to confirm and better characterize causality. Nonetheless, in this study we clearly demonstrate that brachial responses (particularly, endothelial-mediated dilation) are markers of risk for cognitive impairment, and we underscore a premise that CVD may contribute to these neurocognitive changes.

Of note, African American race was also retained in the regression analysis in relation to attention-executive performance (β =-.34, p=.01). This is intriguing, especially given data from the African American Heart Failure Trial (A-HeFT)50 and related studies51 that indicate that race affects endothelial-mediated vascular responsiveness. Nonetheless, in this study, race accounted for only a modest variance above the brachial flow-mediated effect, and since relatively few African American patients were enrolled (N=7) further analysis is necessary to fully delineate the impact of race on vascular-cognition relationships.

Clinical implications

Overall, this investigation suggests beyond affecting cardiovascular outcomes, vascular disease may have systemic effects that influence the ability of older adults to achieve with optimal cognitive function. Therefore, learning and behavior-changing objectives pertinent to compliance and self-care among today's burgeoning population of CVD patients may be enhanced by strategies that compensate for common and insidious attention-executive limitations that are associated with the cardiovascular disease process. Furthermore, one might infer that steps to enhance vascular health may also help forestall and perhaps even reverse risks for cognitive decline among elderly cardiovascular patients. Consistently, recent reports highlight the benefits of statin therapy and lifestyle modifications on cerebral perfusion, mitigating injury of ischemic strokes[52,53] and even dementia[54].

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On behalf of the research team, Dr. Forman vouches for the integrity of these data.

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Table 1

Clinical Characteristics of Patient Population

	Frequency	Mean (SD)
Age (years)		70.0 (7.7)
Education		14.35 (2.9)
Risk Factors		
Hypertension	76.0%	
Hypercholesterolemia	59.3%	
Diabetes: Type 2	22.2%	
Smoking	37.1%	
CVD Etiologies		
Coronary Heart Disease	89.5%	
Myocardial Infarction	9.5%	
Heart Failure	19.3%	
Arrhythmia	15.9%	
Procedures		
CABG	32.8%	
Angioplasty	19.3%	
Stent	14.0%	
Mental Status		
MMSE Score		28.4 (1.1)
DRS Total Score		136.9 (5.8)
Beck Depression Inventory Score		4.5 (2.3)
Vascular Indices		
Systolic BP, mm Hg		132.5 (22.3)
Diastolic BP, mm Hg		67.5 (10.7)
% endothelial mediated brachial dilation		5.8 (4.8)
% endothelial independent brachial dilation		14.8 (7.8)

Table 2

Neurocognitive Assessment

Test Measures by Domain	Abbreviation	Reference
Global Cognitive Functioning		
Mini Mental Status Exam	MMSE	25
Dementia Rating Scale	DRS	27,28
Language		
Boston Naming Test	BNT	29
Category Fluency for Animals	Animals	30
Visual-Spatial		
Hooper Visual Organization Test	HVOT	31
Complex Figure Test, copy	CFT-copy	30
WAIS-III Block Design Subtest	Block Design	32
Learning and Memory		
California Verbal Learning Test-Revised	CVLT-R	33
Complex Figure Test	CFT	30
Brief Visual Memory Test – Revised	BVMT-R	34
Attention-Executive-Psychomotor		
Trail Making Tests A & B	Trails	35
Letter Search	Letter Search	32
Stroop Test	Stroop	36
Controlled Oral Word Association Test	COWAT	37
Grooved Pegboard, dominant hand	Pegs-D	38
WAIS-III Digit Span Subtest	Digit Span	32
WAIS-III Symbol Coding Subtest	Coding	32

Table 3

Simple Correlations between Flow Mediated Dilatation and Executive Attention and Psychomotor Measures.

	Flow-induced % in vessel diameter	Nitroglycerin-induced % in vessel diameter
Demographics		
Age	-.13	-.02
Gender	.08	.14
Education	-.09	-.04
Race	.14	-.11
CVD Risk and Etiological Factors		
Angina	-.14	-.17
Angioplasty	-.09	-.17
CABG	-.05	-.05
CAD	-.01	.01
Diabetes	-.09	**-.20**
Heart Failure	-.09	.02
Hypertension	.01	-.09
Hypercholesteremia	.00	-.06
Myocardial infarction	.01	-.12
Smoking	**-.45**	**-.34**
CVD Risk Score	-.09	**-.20**
CAD Index	.15	**-.22**
Tasks		
COWAT	**.30**	.12
Digit Span	**.21**	.03
GPB-Dominant	-.12	**-.21**
GPB-Non-dominant	**-.19**	**-.28**
Letter Cancellation	**-.18**	-.05
Stroop Interference	**.25**	**.21**
Symbol Coding	**.17**	**.17**
Trail Making A	.04	.03
Trail Making B	.06	.03
Global Function Index	.07	-.05
Memory Index	.09	.03
Language Index	.07	.06
Visual Spatial Index	.11	.13
Attention-Executive Index	**.45**	**.35**

Note: Statistically significant associations are reported in bold ($p<.05$).

CVD= Cardiovascular Disease; CAD = Coronary Artery Disease; CABG = Coronary Artery Bypass Graph; COWAT = Controlled Oral Word Association Test; GPB = Grooved Pegboard.

Table 4

Variables entered and retained in regression of brachial responses relative to the Attention-Executive Index.

Variable Entered	Standardized β coefficients*
Age	-0.17
Gender	0.15
Race	**-0.29**
Years of Education	0.14
BDI	-0.11
CVD Risk Index	-0.04
CAD Severity Index	-0.06
Systolic BP (mean)	-0.07
Diastolic BP (mean)	-0.08
Beta-Blockers	-0.10
ACE Inhibitors	0.04
Vasodilators	0.06
NSAIDs	0.03
Psychiatric Medications	0.04
FMD	**0.54**
NTG-mediated dilation	0.13

Note: Statistically significant beta coefficients between clinical variables retained in the hierarchical regression and the attention-executive index are reported in **bold**.

*Partial correlations are given for variables not retained as statistically significant in stepwise regression. BDI = Beck Depression Inventory total score. NSAIDS = non-steroidal anti-inflammatory drugs. FMD = Flow mediated dilation of the brachial artery (endothelial-mediated brachial response); NTG-mediated=Brachial artery response to nitroglycerin (endothelial independent brachial responses).