Neuropsychological Performance Is Associated With Vascular Function in Patients With Atherosclerotic Vascular Disease

David J. Moser, Robert G. Robinson, Stephanie M. Hynes, Rebecca L. Reese, Stephan Arndt, Jane S. Paulsen, William G. Haynes

Objective—We previously reported preliminary data (N=14) demonstrating a significant and positive relationship between forearm vascular function and neuropsychological performance in individuals with atherosclerotic vascular disease (AVD). The current study was conducted to confirm and extend those findings in a much larger, nonoverlapping sample.

Methods and Results—Participants were 82 individuals with AVD, with no history of stroke, cardiac surgery, or dementia. Forearm vascular function was measured before and after brachial artery infusion of vasoactive agents (acetylcholine, nitroprusside, verapamil). Neuropsychological functioning was assessed with the Repeatable Battery for the Assessment of Neuropsychological Status. Statistical analysis included multiple regression and partial correlations, controlling for education. Vascular function was significantly and positively associated with neuropsychological performance \( R^2 = 0.116, F_{\text{change}} (3,74) = 3.72, P = 0.015 \). Follow-up analyses indicated that smooth muscle function was the aspect of vascular function most strongly associated with neuropsychological performance. Individual vascular risk factors were not significantly associated with neuropsychological performance when controlling for vascular function.

Conclusions—Better vascular function is significantly associated with better neuropsychological performance in individuals with AVD. It is possible that this relationship exists in healthy elderly individuals as well, although this cannot be determined based on the existing data, because a healthy comparison group was not studied. With additional research, measures of vascular function might be useful in the early identification of individuals who are at greatest risk for developing vascular cognitive impairment. (Arterioscler Thromb Vasc Biol. 2007;27:141-146.)

Key Words: atherosclerosis □ vascular cognitive impairment □ vascular function

Atherosclerotic vascular disease (AVD) is a progressive and generalized process involving the accumulation of lipid-rich plaque in the arterial wall. It is by far the single leading cause of morbidity and mortality in the United States and most other industrialized countries, through its primary role in myocardial infarction, stroke, and other occlusive vascular diseases.\(^1\) In addition to its tremendous impact on the medical, financial, and quality of life status of the general population, the effects of AVD are particularly devastating among the elderly. Atherosclerosis and related cerebrovascular ischemia have been shown to cause mild to severe cognitive dysfunction,\(^2\) and it has been estimated that vascular pathology causes or significantly contributes to at least half of all cases of dementia, regardless of specific dementia subtype.\(^3\)

Although it is well-established that individuals with vascular disease are at increased risk for developing cognitive impairment, such individuals represent an extremely heterogeneous group, with widely varying risk factors such as hypertension, hyperlipidemia, obesity, and a host of others. This makes it difficult to examine the relationship between one or more vascular variables and cognitive functioning, while having to account for the effects of many other potentially confounding variables. For this reason there is a growing body of research aimed at finding more effective ways to assess overall vascular condition, regardless of risk factor profile, and examine its association with cognitive function.

In 2004, we conducted a preliminary study (N=14) of elderly patients with atherosclerotic disease who had no history of stroke, coronary artery bypass grafting, or dementia, and reported the first published evidence of a significant and positive relationship between forearm vascular function and cognition.\(^4\) Vascular function was chosen as the single
variable representing overall vascular condition for several reasons. Importantly, this measure has been shown to decline very early in the development of AVD, before the onset of atherosclerotic plaques. Furthermore, all known risk factors for AVD are also associated with impaired vascular function. Lastly, forearm vascular function has been shown to be associated with coronary artery function. Taken together, these facts suggest that forearm vascular function is reflective of more general vascular health and might be used as an integrated measure of overall atherosclerotic risk factor burden to be examined in relation to other aspects of health, including cognition.

The current study was conducted to examine the association between vascular function and cognition in an entirely new, much larger sample that would allow for more rigorous study of this relationship. Specifically, we sought to confirm the previous finding that there is a significant and positive relationship between vascular function and cognition, to determine whether this relationship would remain when more traditional vascular variables were controlled, to examine which aspects of vascular function were most strongly associated with cognition, and to explore which aspects of cognitive performance were most strongly associated with vascular function. In keeping with our preliminary findings, it was hypothesized that better vascular function would be significantly associated with better cognitive performance and that this relationship would be much stronger than the relationship between cognition and individual vascular risk factors.

Materials and Methods
This study was approved by the University of Iowa Institutional Review Board and signed informed consent was obtained from all participants.

Participants
Eighty-two elderly individuals (35 women, 47 men; mean age=68 years, SD=7.7; mean education=14.5 years, SD=3.2) were recruited from the University of Iowa Heart and Vascular Care Clinic and also from newspaper advertisements. All participants were age 55 or older, with an unequivocal diagnosis of AVD and a history of one or more of the following: angina pectoris, myocardial infarction, percutaneous transluminal coronary angioplasty, placement of coronary artery stent, and peripheral vascular disease (claudication). The numbers of participants taking various medications were as follows: antihypertensives=79, statins=59, non-steroidal anti-inflammatory=73, angiotensin-converting enzyme inhibitors=36, beta blockers=61, aspirin=70. Additionally, 4 women were taking an estrogen supplement. Exclusion criteria included coronary artery bypass grafting, valve replacement, carotid endarterectomy, stroke, head injury with loss of consciousness >30 minutes, other neurological disorder or systemic illness unrelated to vascular disease that is likely to affect cognition, focal neurological sign, diagnosis of dementia, and current or past severe psychiatric illness (eg, bipolar affective disorder, schizophrenia). All subjects underwent thorough history and physical examinations conducted by a physician, including neurological examination, ECG, and fasting blood draw/analysis.

Neuropsychological Assessment
As in our previous study, The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) was used to assess level of neuropsychological functioning. This widely used battery consists of 12 subtests and yields an age-corrected Total Scale Score that indicates level of global neuropsychological functioning, in addition to 5 age-corrected domain scores including Immediate Memory, Delayed Memory, Attention, Language, and Visuospatial Constructual. The Symptom Checklist 90-Revised (SCL-90-R) was used to assess psychological symptoms. The SCL-90-R is a well-established self-report measure that asks participants to rate the extent to which they are bothered by particular psychological symptoms, along a continuum from 0 (not at all) to 4 (extremely). It provides an overall T-score measuring level of general psychological distress (Global Severity Index) as well as T-scores for nine individual domains, including depression.

Vascular Function Assessment
Beginning the night before testing, subjects fasted and refrained from taking any medication until all study procedures were completed the next morning. Forearm blood flow was measured in both arms before and after infusion of vasoactive agents using venous occlusion plethysmography with mercury-in-silastic strain gauges. This technique is currently the gold standard for measuring resistance vessel function in the forearm, requires virtually no subjective judgment on the part of the technician, and has been shown to yield highly reproducible results in our laboratory. During this procedure, the left brachial artery was cannulated under local anesthesia with a 27-gauge steel needle attached to an 18-gauge epidural catheter. Baseline forearm blood flows were obtained during infusion of 0.9% saline (1 mL/min) for 30 minutes. Acetylcholine (3 to 30 μg/min), nitroprusside (1 to 10 μg/min), and verapamil (10 to 100 μg/min) were then infused separately into the left arm, with each dose infused for 6 minutes. The order of acetylcholine and nitroprusside was randomized, but verapamil was always administered last because of its longer duration of action.

The rationale for using these 3 vasoactive agents was as follows: intra-arterial acetylcholine causes vasodilation through stimulation of endothelial cell muscarinic receptors, thereby activating endothelial nitric oxide synthase and increasing nitric oxide production, which then relaxes underlying vascular smooth muscle, resulting in resistance vessel dilatation. Nitroprusside, however, is a direct nitric oxide donor, causing vascular smooth muscle relaxation without involvement of endothelial cells. Verapamil acts directly on vascular smooth muscle cells, causing relaxation without altering endothelial cell function or generation of nitric oxide. For these reasons, vasodilation that occurs as the result of acetylcholine administration is often referred to as “endothelium-dependent” and that which occurs in response to nitroprusside and verapamil is described as “endothelium-independent.” It should be noted, however, that examining response to acetylcholine alone does not yield a truly specific index of endothelial-dependent vasodilation. For example, even if vascular smooth muscle dysfunction occurred alone, vasodilation in response to acetylcholine would still be impaired, despite the fact that endothelial function would be normal. Therefore, the most robust parameter for endothelium-dependent vasodilation is obtained by assessing vascular response to acetylcholine and correcting that for dilatation that occurs in response to a vascular smooth muscle specific dilator. In this study, we chose to accomplish this by using simple acetylcholine response/nitroprusside response and acetylcho line response/verapamil response ratios.

With each drug, forearm blood flow was measured during the last three minutes of each 6-minute dose. Saline was infused for at least 12 minutes between drugs to allow blood flow to return to basal levels. Blood flows were measured in the noninfused (control) arm at time points identical to those in the infused arm so as to provide a contemporaneous control for random fluctuations in flow.

The single outcome measure for each drug was the mean percent increase in forearm blood flow in the infused arm after infusion of the 3 doses of that drug, relative to baseline, adjusted for changes in blood flow in the noninfused arm. Higher values indicated better vascular function. Neuropsychological assessment and blood vessel testing were conducted by separate individuals, each of whom was blind to the other’s data.
TABLE 1. Vascular Function and Related Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Δ in Blood flow with acetylcholine</td>
<td>150</td>
<td>104</td>
<td>3–512</td>
</tr>
<tr>
<td>% Δ in Blood flow with nitroprusside</td>
<td>173</td>
<td>97</td>
<td>18–548</td>
</tr>
<tr>
<td>% Δ in Blood flow with verapamil</td>
<td>166</td>
<td>97</td>
<td>6–529</td>
</tr>
<tr>
<td>Body mass index</td>
<td>31</td>
<td>7</td>
<td>18–54</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>136</td>
<td>22</td>
<td>87–199</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>72</td>
<td>11</td>
<td>46–100</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>170</td>
<td>41</td>
<td>111–282</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>51</td>
<td>16</td>
<td>14–126</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>90</td>
<td>30</td>
<td>40–173</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>116</td>
<td>32</td>
<td>83–286</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>143</td>
<td>71</td>
<td>29–490</td>
</tr>
<tr>
<td>Homocysteine, μM/L</td>
<td>12.00</td>
<td>4.22</td>
<td>5.30–33.84</td>
</tr>
<tr>
<td>C-reactive protein, mg/L</td>
<td>4.29</td>
<td>4.60</td>
<td>0.06–16.77</td>
</tr>
</tbody>
</table>

Blood flow Δ is the percent increase in forearm blood flow in response to intra-arterial infusion of drug, adjusted for changes in blood flow in the noninfused arm (higher values indicate better function).

HDL-C indicates high-density-lipoprotein cholesterol; LDL-C, low-density-lipoprotein cholesterol.

Statistical Analysis

Data were analyzed using multiple regression and partial correlations, as discussed. Level of education was included in all analyses, as this variable was significantly correlated with global neuropsychological test performance, as measured by RBANS Total Scale Score (r = 0.338, P = 0.002). Age was not used as a covariate because the neuropsychological scores used in these analyses had already been corrected for age before being subjected to analysis. Furthermore, it was confirmed using Pearson correlation that age was not associated with RBANS Total Scale Score.

To test the overall association between vascular function and neuropsychological performance, education was entered into a multiple regression as a first independent variable, followed by the three vascular-related variables shown in Table 1, and also with the Global Severity Index and Depressive Scale scores from the SCL-90-R. Finally, when it was found that 2 of the individual vascular-related variables shared a significant correlation with neuropsychological performance, 2 partial correlations were conducted to determine whether these relationships remained significant when controlling for vascular function.

Results

Descriptive statistics for vascular function, vascular-related variables, and neuropsychological scores are shown in Tables 1 and 2.

Multiple regression results indicated a significant association between vascular function and RBANS Total Scale Score, after controlling for education [R² change = 0.116, F change (3,74) = 3.72, P = 0.015]. Partial correlations, controlling for education, indicated significant associations between all 3 measures of vascular function and RBANS Total Scale Score (acetylcholine: partial r = 0.333, P = 0.002; nitroprusside: partial r = 0.380, P < 0.001; verapamil: partial r = 0.277, P = 0.014). Additionally, vascular function was positively related to neuropsychological performance across 4 of the 5 RBANS domains that contribute to the Total Scale Score, particularly Delayed Memory and Language. Vascular function was not associated with performance on the Visuospatial/Constructional domain (Table 3).
Partial correlations calculated between the acetylcholine response/nitroprusside response ratio and RBANS Total Scale Score ($r=0.013$, $P=0.909$) and between the acetylcholine response/verapamil response ratio and RBANS Total Scale Score ($r=0.104$, $P=0.367$) were both nonsignificant (Figures 1 and 2).

Correlations calculated between RBANS Total Scale Score and the 10 vascular risk factors shown in Table 1 (controlling for education) yielded only 2 significant associations (glucose: partial $r=-0.262$, $P=0.018$; high-density lipoprotein cholesterol: partial $r=0.269$, $P=0.015$). Neither of these correlations remained significant when vascular function was controlled for in addition to education. RBANS Total Scale Score was not significantly associated with SCL-90-R Depression or Global Severity Index scores.

**Discussion**

These findings support our hypotheses and indicate that better vascular function is significantly associated with better neuropsychological performance in older patients with atherosclerotic vascular disease. They further indicate that the relationship between vascular function and cognition is much
stronger than that shared by neuropsychological performance and more conventional vascular variables. As such, this study serves to replicate our previously published findings, using a much larger, nonoverlapping sample that allowed for more scientifically rigorous testing of our hypotheses.

The importance of these findings is two-fold. First, they demonstrate a relationship between vascular disease and cognitive performance in a group of individuals who have not yet experienced moderate or severe vascular cognitive decline. This sample had no history of stroke or cardiac surgery and, as a group, performed in the average range across a battery of neuropsychological tests. Second, if longitudinal investigation reveals that vascular function is not only cross-sectionally related to neuropsychological performance but also predictive of cognitive decline across time, such measures will be useful in the early identification of those individuals who are at greatest risk for vascular cognitive decline, allowing for early intervention aimed at preventing or attenuating this process.

In addition to our own published findings, there are other recently published data to suggest that measures of peripheral vascular condition might become useful in such early detection. In a cross-sectional study that included healthy individuals and those with mild cognitive impairment, Alzheimer disease, or vascular dementia, Hanon et al demonstrated a relationship between arterial stiffness, measured with carotid–femoral pulse wave velocity, and cognitive dysfunction. Additionally, in a longitudinal analysis, Price et al have reported a very modest but significant relationship between baseline ankle brachial index, and cognitive performance at 10-year follow-up.

It is noteworthy that the relationship between vascular function and cognition in our study was much stronger than the relationship between cognition and the many other individual vascular-related variables that were analyzed. We again posit that this is due to the fact that vascular function serves as an integrated measure of total atherosclerotic risk factor burden in a given individual, regardless of that individual’s particular pattern and severity of specific risk factors. Of course, it has been shown that some individual factors such as hypertension are related to cognition, but this type of single-factor relationship has typically been difficult to demonstrate in general vascular disease samples, because of the enormous heterogeneity regarding risk factor profile among participants. It is the ability of measures such as vascular function to demonstrate the vascular-cognition relationship despite this heterogeneity that suggests that such measures might be useful in assessing risk for vascular cognitive decline in patients with a variety of vascular conditions.

While the main finding in this study concerns the relationship between vascular function and global neuropsychological performance (as measured by the RBANS Total Scale Score), the fact that the RBANS also provides individual domain scores allowed for more specific investigation of various aspects of cognition. As shown in Table 3, Delayed Memory and Language scores were particularly strongly associated with vascular function. Additionally, positive but more modest relationships were found between vessel function and RBANS Immediate Memory and Attention scores. It should be noted that the RBANS Attention and Language domains place demand on psychomotor processing speed and semantic fluency, respectively. The fact that these abilities were among the variables associated with vessel function is not surprising, given the well-established relationship between vascular disease and these aspects of cognitive function. It is perhaps surprising that memory scores were so strongly associated with vessel function in our sample, as this ability is not as consistently associated with severity of vascular disease, particularly in the early stages of vascular cognitive decline.

Regarding methodology, the fact that this sample was recruited primarily from a cardiology clinic represents both a weakness and a strength of the study. It could potentially limit the generalizability of the findings, given that participants had very well-monitored and treated vascular disease, as evidenced by their relatively normal values on many of the vascular variables that were collected. However, it is quite intriguing that this relationship between peripheral vascular function and cognition could be found in a sample of participants with such well-controlled disease. In this study sample, vascular function was associated with ~12% of the variance in cognition, above and beyond that which was associated with level of education. It is most plausible that this relationship would be even stronger in a sample of individuals with less well-controlled vascular disease and more severe cognitive dysfunction. Also regarding generalizability, given the lack of a nonvascular disease control group in this study, it cannot be determined with certainty whether these findings could apply to the general elderly population versus only those individuals with vascular disease.

The fact that all 3 measures (blood flow increase in response to acetylcholine, verapamil, and nitroprusside) were significantly associated with neuropsychological performance suggests that it is vascular smooth muscle function that was associated with cognition, as opposed to endothelial cell function. This finding was further validated by the fact that specific measures of endothelium-dependent functioning (acetylcholine response/nitroprusside response ratio, acetylcholine response/verapamil response ratio) were not correlated with neuropsychological performance. Larger-scale studies might allow for more specific examination of this issue, but the different measures of vessel function used in this relatively large sample were uniformly related to neuropsychological performance. It is plausible that forearm resistance vessel function and condition in the periphery is similar to that in the brain, and it is well-known that small vessel disease in the brain is associated with cognitive dysfunction (see Gunning Dixon 2004 for a review). However, demonstration of the relationship between peripheral and cerebral small vessel function will require additional investigation.

The findings from this study demonstrate a significant and positive relationship between forearm vascular function and cognition in a sample of older patients who have atherosclerotic vascular disease, but no history of stroke, cardiac surgery, or dementia diagnosis. Despite advances in medica-
tion and other forms of treatment, vascular disease remains the primary cause in 20% of all dementia cases,\textsuperscript{16} and is commonly a significant contributing factor in other neurodegenerative processes. This fact underscores the importance of finding new ways to identify and treat those individuals who are at greatest risk for developing vascular cognitive impairment. We consider the current findings to be an important early step in this process. Longitudinal intervention studies will be needed to determine whether improving vascular function can halt or attenuate the development of such impairment across time.

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Disclosures
None.

References
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