Blood Vessel Function and Cognition in Elderly Patients With Atherosclerosis

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Background and Purpose—Although a strong relationship has been established between vascular disease and cognitive decline, the current challenge is to identify vascular risk factors and mechanisms that are associated with cognitive function before the development of severe dysfunction (eg, vascular dementia). This study was conducted to determine the relationship between blood vessel function and cognition in elderly patients with atherosclerosis.

Methods—Participants were 14 elderly individuals with atherosclerotic vascular disease, who had no history of stroke, cardiac surgery, or dementia diagnosis. Forearm blood flow was measured before and after brachial artery infusion of 3 vasoactive agents (verapamil, acetylcholine, nitroprusside), and these measures of vessel function were then correlated with neuropsychological performance (total scale score on the Repeatable Battery for the Assessment of Neuropsychological Status).

Results—Positive correlations were found between neuropsychological performance and vasodilation in response to all 3 agents, with 2 reaching statistical significance (verapamil: \( r=0.78, P=0.001 \); nitroprusside: \( r=0.56, P=0.038 \)) and the third showing a strong trend toward significance (acetylcholine: \( r=0.49, P=0.076 \)). Correlations between neuropsychological performance and more conventional vascular-related variables were much weaker.

Conclusions—These data provide preliminary evidence of a relationship between resistance vessel function and neuropsychological performance. With further research, measures of vessel dysfunction may be useful in identifying individuals at risk for cognitive decline and vascular dementia. (Stroke. 2004;35:e369-e372.)

Key Words: cognition ■ dementia ■ neuropsychology ■ vascular diseases

In this study we sought to demonstrate a relationship between forearm blood vessel function and cognition in elderly individuals with atherosclerotic vascular disease (AVD). Changes in blood vessel function occur very early in the development of AVD, before the development of atherosclerotic plaques, and all known risk factors for AVD are also associated with impaired vessel function. Furthermore, forearm blood vessel function has been shown to be associated with coronary artery function, suggesting that forearm measures may serve as a useful surrogate marker of more general vascular function. Based on this, it is plausible that a sensitive measure of blood vessel function could provide an integrated measure of overall atherosclerotic risk factor burden and may be associated with cognitive function.

Materials and Methods
This study was approved by the University of Iowa Institutional Review Board and signed informed consent was obtained from all participants. Fourteen elderly individuals (7 women, 7 men; mean age, 73 years; SD, 6; mean education, 13 years; SD=3) were recruited by newspaper advertisement and from the Cardiology Clinic at the University of Iowa. All participants were age 65 years older, with an unequivocal diagnosis of AVD and a history of 1 or more of the following: angina pectoris, past myocardial infarction, percutaneous transluminal coronary angioplasty, placement of a coronary artery stent, and peripheral vascular disease (claudication). Thirteen were taking antihypertensives, 12 were taking aspirin or other antithrombotics, 7 were taking HMG CoA-reductase inhibitors, and 2 were taking hypoglycemics. 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 likely to affect cognition, any focal neurological sign, diagnosis of dementia, and current or past severe psychiatric illness (eg, schizophrenia, bipolar disorder). Participants fasted and refrained from taking any medication starting from the night before the study until procedures were completed the next morning.

Neuropsychological Assessment
Form A of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)\(^5\) was used to assess level of neuropsychological functioning across 5 cognitive domains (immediate and delayed memory, language, attention, and visuospatial/constructional skill). Depressive symptoms were assessed with the Beck Depression Inventory II.\(^6\)

Received August 2, 2004; final revision August 25, 2004, accepted September 1, 2004.
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Stroke is available at http://www.strokeaha.org
DOI: 10.1161/01.STR.0000145050.35039.51
Blood Vessel Function Assessment

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. The left brachial artery was cannulated under local anesthesia. 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 infused separately into the left arm, with each dose infused for 6 minutes. The order of administration was randomized for acetylcholine and nitroprusside, but verapamil was always administered last, because it has longer lasting effects than the other 2 drugs. In all cases, blood flow was allowed to return to baseline level before infusion of the next drug.

Acetylcholine was administered to measure endothelium-dependent vasodilation, nitroprusside was administered to measure endothelium-independent vasodilation, and verapamil was administered to measure smooth muscle function. Saline was infused between drugs to allow blood flow to return to basal levels. Blood flows were also measured in the noninfused arm to provide a contemporaneous control for random fluctuations in flow.

The outcome measure for each drug was the increase in the ratio of blood flow in the infused versus noninfused arms after infusion of a given drug, expressed as a percentage relative to what the ratio between flow in the 2 arms was at baseline. This measure has been widely used and it reflects the degree to which forearm resistance vessels can dilate when induced to do so, with higher values indicating healthier vessel function.

Statistical Analysis

Three Spearman correlations (1 for each vasoactive drug) were calculated to examine the association between blood vessel function and RBANS total scale score. These were then recalculated as partial correlations, controlling for age, then education, and then depression scores. Correlations were then calculated between RBANS total scale score and more conventional vascular-related variables. An alpha level of 0.05 was retained throughout the study because of its exploratory nature and the fact that only 3 main correlations were calculated. All additional correlations were calculated simply to ensure that other factors (eg, age, education, depression, and the additional vascular variables) were not as strongly associated with cognition as were the three measures of vessel function.

Results

Descriptive statistics are shown in Table 1. As shown in Table 2 and the Figure, all 3 measures of blood vessel function were positively associated with cognition (RBANS total scale score). Two of these correlations reached statistical significance (those involving verapamil: \( \rho=0.78, P=0.001, 95\% \text{ CI}=0.42 \) to 0.93; and nitroprussid-
Cognitive scores and drug-induced vasodilation. FBF indicates forearm blood flow; FBF values represent percent flow increase in the drug-infused arm, adjusted for changes in blood flow in the noninfused arm, with higher values indicating better vascular function.

Discussion

These findings provide evidence of a significant relationship between human resistance vessel function and neuropsychological performance, and suggest that this relationship may be stronger than that shared by neuropsychological performance and more conventional vascular-related variables. This suggests that vessel function may have served as an integrated measure of overall atherosclerotic risk factor burden, an assertion that is strengthened by the fact that all known risk factors for AVD are also associated with impaired vessel function. The particularly strong relationship between response to verapamil and cognition raises the possibility that vascular smooth muscle function may share a stronger relationship with neuropsychological status than does endothelial function, but additional investigation with larger samples will be needed to determine the specific sites and mechanisms of vascular dysfunction that are most strongly linked to cognitive decline. It is also possible that the verapamil results were affected somewhat by the fact that this agent was always administered last; however, this is quite unlikely because, as noted, blood flows were allowed to return to baseline between administration of the 3 vasoactive drugs.

This study was conducted using a relatively small sample and the findings should be considered preliminary. However, the aforementioned correlations were fairly consistent across all 3 vasoactive drugs and were only minimally changed when potential confounders were controlled. Therefore, we consider these results to provide support for continued research on the relationship between blood vessel function and cognition. Longitudinal studies and those that incorporate neuroimaging will be particularly important in elucidating this relationship. With additional investigation and technical advances in methodology, measures of blood vessel function could become useful in the identification of those patients who are in the
earliest stages of vascular cognitive decline and who are, therefore, at significant risk for development of conditions such as vascular dementia. This would allow for early medical intervention and lifestyle changes aimed specifically at improving vessel function and other aspects of vascular health.

Acknowledgements
This research was supported by grants from the National Institutes of Health, the National Heart, Lung, and Blood Institute, the American Federation for Aging Research, and the University of Iowa.

References