The contribution of cerebrovascular disease to development of dementia in the elderly remains a perplexing and unresolved issue with direct clinical implications. In the early part of the past century, the popular notion was that some type of vascular pathology (eg, “hardening of the arteries”) was a contributing factor. Yet, the idea that cerebrovascular disease plays a significant role in Alzheimer disease (AD) and related degenerative brain disorders was dismissed by a majority of dementia researchers, because AD pathology was found to be strongly related to specific neuronal abnormalities involving β-amyloid, τ protein, and disruption of cholinergic brain systems. Yet, clinical and experimental research conducted over the past several years suggests that cerebrovascular disease may play a greater role in degenerative dementia than was previously believed. Vascular disease is associated with increased risk for AD. Also, many of the biochemical processes involved in AD share common mechanisms with cerebrovascular disease factors (endothelial health, oxidative stress response, insulin metabolism, etc), suggesting possible convergence of underlying neuropathological mechanisms, at least among certain patients. There is a compelling need for studies aimed at achieving greater understanding about the relationship between vascular disease and the development of dementia in the elderly.

The diagnostic classification of vascular dementia (VaD) was developed to account for cases in which severe functional impairments could be unambiguously attributed to stroke or other well-defined vascular pathology. Unfortunately, the diagnosis of VaD is a clinical conundrum, because pure cases are more the exception than the rule, and also many of the cognitive and many of the clinical characteristics thought to differentiate VaD from AD (ie, stepwise progression, patchy cognitive profile, different cognitive presentations) have not held up in controlled studies. This diagnostic dilemma is most apparent for patients being assessed in memory disorder clinics for possible dementia, when there is clinical evidence of progressive decline in functioning suggestive of AD but also well-defined vascular risk factors, etiology, and neuroimaging findings pointing to possible cerebrovascular disease.

The effects of stroke on neuropsychological functions are well established with many identified syndromes associated with infarctions involving particular brain regions. Furthermore, VaD is relatively easy to diagnose in patients who have had multiple large cortical infarctions when changes in function can be linked to discrete events. Yet, a common scenario involves patients who present with cognitive problems along with clinical findings that suggest cerebrovascular disease secondary to cardiovascular or other chronic vascular conditions, but who have no clinical history of prior stroke. Often these cognitive problems are detected post hoc, when patients or family members notice subtle changes in functioning after a long period of illness, a cardiac event, or some surgical procedure. When significant quantities of white matter hyperintensities are detected on MRI, clinical findings are often attributed to microvascular pathology, though the development of cognitive problems in such cases is still not well understood. White matter findings of this type are usually attributed to multiple microvascular infarctions or the effects of chronic cerebral hypoperfusion. Yet, little is known about how these white matter abnormalities relate to the development of cortical brain abnormalities and VaD, or how cerebrovascular and AD processes interact to influence progressive brain degeneration.

In light of these considerations, it is essential that research be directed toward examining how specific vascular risk, etiological, and pathological factors relate to changes in cerebral perfusion, hemodynamic function and progressive cognitive dysfunction among patients without clinically recognized stroke. Such efforts depend on carefully assessing systemic vascular functions (eg, blood pressure, cardiac output, etc) while simultaneously examining cerebrovascular function and brain structure and function over time is particularly important. There is growing evidence that among elderly people without prior stroke, systemic vascular dysfunction is associated with both cognitive impairments and structural brain abnormalities, with worsening of brain structure and function among patients with the greatest vascular impairment. Reduced cardiac function together with alterations in peripheral endothelial function and atherosclerotic load in cerebral vessels seem to interact to affect cerebral hemodynamic conditions. However, to date there are few studies that have prospectively examined changes in cerebral hemodynamics over time as a function of specific vascular factors.
In this issue of Stroke, the study by Beason-Held et al takes an important step toward accomplishing this goal. Changes in cerebral blood flow measured by positron emission tomography (PET) were examined in relationship to hypertension (HTN) in the elderly. An association between HTN severity and dementia incidence is known to exist. Studies have shown that HTN is associated with functional brain measures tied to cerebral blood flow. Yet, there is a lack of data on long-term longitudinal change in functional brain response associated with chronic HTN. This study is the first to report on changes in resting CBF over 7 years as measured by PET. Collecting repeated PET data over this time period is commendable. Participants with HTN defined as 140/90 mm Hg showed decreased regional CBF (rCBF) over time across a number of cortical regions compared with healthy controls without HTN. This finding is significant given that the 2 groups were similar in other respects, and participants with HTN did not have clinical evidence of prior stroke or cerebrovascular disease, suggesting that HTN alone was the factor that accounted for reduced rCBF. The fact that reductions in rCBF were associated with HTN duration (ie, chronicity) further strengthens the significance of these findings. HTN effects appear to have been cumulative, rather than being linked to a single cerebrovascular event.

Although this study provides strong evidence that chronic HTN affects cerebral blood flow and perhaps cortical brain activation over time, caution must be taken to not over interpret the meaning of these findings. The study did not assess other vascular functions, such as cardiac output, endothelial function, or atherosclerotic load. It is possible that the effects observed are not occurring solely as a function of HTN, but rather that people in the HTN group have other risk factors that interact to reduce rCBF.

It is also noteworthy that the areas of greatest change over time included the prefrontal cortex and anterior cingulate cortex, and that motor areas and the globus pallidus also showed decreased responsiveness over time. These findings provide support for the notion that brain areas involved in attention and executive functioning or more broadly psychomotor and information processing speed are particularly vulnerable to the effects of vascular factors, such as HTN. However, the methodological approach used in this study limits some of the conclusions that can be made in this regard, as the rCBF metric reflects normalized blood flow data, which makes it difficult to interpret whether there was a more generalized reduction in blood flow across the entire brain among people with HTN.

The fact that cognitive performance did not decline over time in parallel with rCBF changes is a bit puzzling, because it raises the possibility that reductions in rCBF were physiologically significant from a hemodynamic standpoint, but perhaps not functionally significant with respect to cognitive function. However, it is also possible that the rCBF changes detected by PET over this time period were reflective of early pathological processes occurring before the development of cognitive impairments. Also, the relatively small sample size in this study makes it difficult to reach conclusions regarding how cognitive and vascular functions relate over time. It is also noteworthy that increased rCBF was found in certain cortical regions for both the HTN and control groups. This raises the possibility that compensatory brain activity was occurring in response to diminished activity in other areas, though the significance of these effects is difficult to determine from this study. Unfortunately, the reported findings were for resting CBF only, though apparently data were also obtained for a cognitive activation tasks. Examination of the brain activation during cognitive processing would help to answer the question about whether the CBF changes observed over time reflect early functional changes that are detectable on a sensitive challenge with functional imaging before impairments being evident on standard cognitive tests. Ultimately, this question will need to be resolved in future studies.

Consideration of these findings also raises many additional questions. For example, it is not clear whether the rCBF changes that were found map onto early structural brain changes that one might expect to see in patients with chronic HTN, such as white matter lesions apparent as hyperintensities on MRI. Besides increasing risk for stroke, HTN is thought to underlie the microvascular disease that causes white matter damage. Yet, the changes described in this study are occurring cortically. Are these changes linked either directly or indirectly to the processes involved in producing white matter lesions? If so, is diaschisis responsible? Diaschisis could result if damaged white matter pathways eventually lead to disruption of cortical regions to which they project, leading to impaired cortical rCBF activation in these regions. Alternatively, are white matter and cortical changes occurring simultaneously?

Despite some limitations in the conclusions that can be drawn, this study represents an early step in our understanding of how specific vascular risk factors affect the brain over time in the elderly. The findings provide a compelling argument for continued research aimed at understanding the linkage between systemic vascular disease, cerebral hemodynamic function, and vascular cognitive impairment.

Disclosures
None.

References

Key Words: cerebral blood flow  ■ hypertension  ■ vascular cognitive impairment

Ronald A. Cohen

Stroke. 2007;38:1715-1717; originally published online May 17, 2007;
doi: 10.1161/STROKEAHA.107.487165

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/38/6/1715

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/